NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

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Premeeting briefing

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Generalisability

Patients recruited to PEGASUS-TIMI 54 were those with a history of MI at least 12-36 months prior and at least one additional risk factor for subsequent atherothrombotic events. The UKCPA stated *'PEGASUS is not reflective of current UK practice, since we do not actively seek out patients post-event to restart or redefine treatment durations…the results of PEGASUS may not be applicable to the general 'real world' population that present with an ACS'*. How generalisable are the results from PEGASUS-TIMI to clinical practice in England?

Comparators

- Should clopidogrel in combination with aspirin be included as a comparator?

- The comparators listed in the final scope issued by NICE were aspirin monotherapy or clopidogrel in combination with aspirin. The company submission only included aspirin monotherapy as a comparator. The company argued that clopidogrel in combination with aspirin does not have a marketing authorisation in the population of interest, that is experienced a prior myocardial infarction between 1 and 2 years who also had 1 or more additional atherothrombotic risk factor.
- The ERG commented that NICE clinical guideline 172 recommends clopidogrel as a treatment option instead of aspirin in patients who have other cardiovascular disease and have either: had a myocardial infarction and stopped dual antiplatelet therapy, or had a myocardial infarction more than 12 months ago. The ERG commented that this recommendation indicates that clopidogrel may be used beyond 12 months post-myocardial infarction in some circumstances.

Clinical effectiveness

- The company focussed its clinical effectiveness submission on tigagrelor 60 mg in the population who had experienced a prior myocardial infarction between 1 and 2 years ago who also had 1 or more additional atherothrombotic risk factors based on a post hoc subgroup analysis of PEGASUS-TIMI 54 (8665/21,162, 41% of the total trial population). The study was not powered for this subgroup analysis. Is this analysis sufficiently robust to make a decision on the clinical effectiveness of ticagrelor?

Cost effectiveness

- PEGASUS-TIMI 54 was powered for the primary composite outcome. The study was not powered to consider component endpoints of cardiovascular (CV) death, MI or stroke. Individual patient data, collected from the 21,162 patients who entered the trial, were used to inform the risk equation for each component endpoint considered in cost effectiveness model in a competing risks framework. Is it appropriate to populate the model on component endpoints for which the study was not powered?

- The ERG reported that the majority of the time-to-event parameters used by the company in the economic modelling were based on the ITT population from PEGASUS-TIMI 54, and not adjusted for the company's 'label' or 'base case' population. The company claimed that this was to "maintain the level of precision" of the economic model and that its approach was conservative, however the ERG stated that they were unable to determine the magnitude and direction of the bias this may have caused. This was because the modelling of time to treatment discontinuation was unclear and may be incorrect. On which population from PEGASUS-TIMI 54 should the time-to-event parameters be based?
- The ERG was of the opinion that the company's probabilistic sensitivity analysis for the patient level simulation was not programmed correctly. As a result, the ERG based its base-case and additional analyses on the cohort simulation. The ERG commented that the probabilistic ICER from the cohort simulation may be an overestimation of the ICER as a result of it ignoring non-linearity in the model. Which probabilistic sensitivity analysis is more appropriate?
- The company's revised deterministic base case ICER for ticagrelor was £20,636 per QALY gained (based on the individual patient simulation). The company undertook a number of sensitivity and scenario analyses, none of which increased the ICER for ticagrelor above £30,000 per QALY gained. The ERG's probabilistic ICER for ticagrelor was £24,711 per QALY gained (based on the cohort simulation). The ERG's explorative analysis which assumed treatment duration of 3 years unless a non-fatal event or death occurred resulted in an ICER for ticagrelor of £33,676 per QALY gained. In the ERG's other explorative analyses, the ICER remained under £30,000 per QALY gained. What is the most plausible ICER for ticagrelor?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of ticagrelor within its marketing authorisation for the prevention of atherothrombotic events

in adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults who have had a myocardial infarction and are at increased risk of atherothrombotic events	Adults who have had a myocardial infarction between 1 and 2 years ago and are at increased risk of atherothrombotic events	This is a pre-specified subgroup within the limits of the marketing authorisation in this indication.	ERG agreed with the company that the subgroup specified represents the most relevant available evidence for the population in the final scope issued by NICE.
Int.	Ticagrelor co-administered with aspirin	Ticagrelor co-administered with aspirin	None	ERG agreed that the intervention is in line with the final scope issued by NICE.
Com.	• Aspirin • Clopidogrel in combination with aspirin	Aspirin 75 mg	Comparison with clopidogrel + aspirin is not presented • There is no head-to-head trial data and robust indirect comparison of pivotal trial outcomes is not feasible owing to important differences between studies • Clopidogrel + aspirin is not established NHS clinical practice in the population of interest Clopidogrel + aspirin does not have a licence in this indication	ERG agreed with the company that the differences in terms of design and characteristics of included patients between trials of ticagrelor plus aspirin versus placebo plus aspirin and trials of clopidogrel plus aspirin versus placebo plus aspirin were such that any indirect comparison would have been very difficult to interpret because of substantial heterogeneity between studies.

Out.	The outcome measures to be considered include: • non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary revascularisation • bleeding events • mortality • adverse effects of treatment • health-related quality of life.	The outcome measures considered include: • non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary revascularisation • bleeding events • mortality • adverse effects of treatment • health-related quality of life.	N/A	The ERG agreed that the outcomes considered are in line with the final scope issued by NICE.

2 The technology and the treatment pathway

2.1 Myocardial infarction (MI) is a cardiovascular disease (CVD) which may refer to cardiac disease, vascular diseases of the brain and peripheral arterial disease. MI is also known as acute coronary syndrome. It results from of atherosclerotic disease.

2.2 Activation of the coagulation system occurs during the acute phase of an acute coronary event; thrombin plays a key role in the coagulation cascade, leading to clot formation. Clot-bound thrombin remains activated and causes progression of the thrombus; this process can persist beyond the acute phase and can occur in patients up to 6 months following unstable angina or a MI. In general following an MI there is a risk of recurrent atherothrombotic events. Data suggest that the risk of an MI remains high for over a year. The main risk factors for recurrent atherothrombotic events include; diabetes mellitus, recurrent MI, multi-vessel coronary artery disease, chronic non-end stage renal disease and older age.

2.3 Ticagrelor is an oral, direct acting, selective and reversibly binding P2Y12 receptor antagonist that prevents platelet activation and aggregation. Ticagrelor co-administered with acetylsalicylic acid (ASA), has a marketing authorisation for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

2.4 The summary of product characteristics states that treatment with ticagrelor 90 mg is recommended for 12 months in patients with ACS unless discontinuation is clinically indicated. Ticagrelor 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Treatment may be started without interruption as continuation therapy after the initial one-year

treatment with ticagrelor 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in patients with ACS and with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.

2.5 NICE has already recommended ticagrelor in combination with low-dose aspirin for up to 12 months as a treatment option in adults with ACS (NICE technology appraisal guidance 236). The remit of this appraisal and therefore the focus of the company's submission is the use of ticagrelor for the prevention of atherothrombotic events in adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events (that is the 60 mg twice daily dose of ticagrelor).

Table 2 Technology and comparators

	Ticagrelor + aspirin	**Aspirin**
Marketing authorisation	Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.	Secondary prevention of thrombotic cerebrovascular or cardiovascular disease
Administration method	Ticagrelor 60 mg is taken orally twice daily combined with low dose aspirin once daily up 3 years after MI.	Low does aspirin is taken orally once daily
Cost	Ticagrelor 60 mg £56.40 for 56 pack (28 day supply) Aspirin 75 mg dispersible £0.81 for 28 pack (28 day supply)	Aspirin 75 mg dispersible £0.81 for 28 pack (28 day supply)
Average cost of a course of treatment	Average cost per course of 3 month treatment cycle estimated by the company based on the list price is £180.70	Average cost per course of 3 month treatment cycle estimated by the company based on the list price is £2.64
Abbreviations: ACS: Acute Coronary Syndrome; MI: Myocardial Infraction Source: British national formulary online (June 2016); European medicines agency; company's submission, table 105 See summary of product characteristics for details on adverse reactions and contraindications		

3 Comments from consultees (United Kingdom Clinical Pharmacy Association (UKCPA) – Cardiac Group)

3.1 Dual antiplatelet therapy (DAPT, aspirin + P2Y12 inhibitor) is the current standard of care for patients who present following an acute coronary syndrome and are treated either conservatively (medical management) or with mechanical reperfusion (percutaneous coronary intervention).

3.2 One in five patients who present with an acute coronary syndrome (ACS) will suffer a recurrent cardiac event secondary to residual disease after their index admission. The use of extended duration DAPT will therefore be of benefit in higher risk patient groups to mitigate against further major adverse cerebrovascular or cardiovascular events (MACCE).

3.3 An issue with regards to implementation will relate to how to define “stabilised high risk patients” and in particular those with a continued low risk of bleeding who are most likely to benefit from extended duration DAPT. The risk factors quoted in study for inclusion are, prior MI, diabetes, older age and patients with established atherosclerosis. Patients were excluded based on; concomitant long term anticoagulation, recent major surgery, ICH, recent active bleed or bleeding diathesis. The inclusion and exclusion criteria specified is not entirely reflective of “all-comers”/general population who may present with an ACS. Consideration should be given to whether long term administration of a P2Y12 inhibitor would provide any additional benefits or whether these benefits would be offset by the increase in bleeding risk that would inevitably be introduced.

3.4 There is significant variation in the uptake of the newer generation P2Y12 inhibitors and application of NICE treatment appraisal

guidance in clinical practice. The decision to prescribe one agent over another will be driven by the type of centre (e.g. Percutaneous Coronary Intervention capable) and individual clinical preferences.

3.5 European Society of Cardiology NSTEMI guidelines (2015) acknowledged the findings of recently published clinical trials in which the safety and efficacy of both short term and extended durations of P2Y12 inhibition plus aspirin have been investigated. The guideline does not make a definitive recommendation but summarises that treatment duration can be shortened (3-6 months) or extended (up to 30 months) in selected patients if required.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company conducted a systematic review and identified 1 randomised controlled trial (RCT), PEGASUS-TIMI 54, which it considered relevant to the decision problem. In addition, it presented 2 post-hoc subgroup analyses of the CHARISMA trial and the DAPT trial. The company considered whether a network meta-analysis or indirect treatment comparison was feasible given the available evidence (see Table 16 of the company submission), and concluded that it was not.

PEGASUS –TIMI 54

4.2 The PEGASUS-TIMI 54 trial was a randomised, double blind, RCT evaluating whether long-term therapy with ticagrelor plus low dose aspirin reduced the risk of atherothrombotic events compared with placebo plus low dose aspirin in patients who had experienced an MI 1 to 3 years before enrolment. Two different doses of ticagrelor (90 mg and 60 mg) were administered twice daily with low dose aspirin (75-150 mg). In total, 21,162 eligible patients were randomised in a 1:1:1 ratio to either ticagrelor group, or the placebo group. The

trial was conducted in 31 countries, 59% of the patient population considered were from Europe and South Africa. This document will primarily refer to the results from ticagrelor 60 mg as that is the focus of the company's submission.

ERG comments

4.3 The ERG considered that the company's systematic review of the literature was adequate, and that PEGASUS-TIMI 54 was the only relevant study. The ERG stated that the quality assessment of the trial showed a low risk of bias (ERG report Table 4.10).

Patient characteristics

4.4 Patients enrolled into PEGASUS-TIMI 54 were defined as people with high risk of atherothrombotic events, that is those who had experienced an MI 1 to 3 years before enrolment, were aged ≥50 years and had at least one of the following additional high-risk features: age ≥65 years, diabetes mellitus requiring medication, a second prior MI, multi-vessel CAD, chronic non-end stage renal dysfunction defined as an estimated creatinine clearance of <60 ml/min.

Clinical trial results

4.5 The primary outcome was event rate of the composite endpoint of cardiovascular death (CV death), MI, or stroke. The primary efficacy variable was time to first occurrence of any event after randomisation from the composite outcome. Secondary outcomes were the event rate of CV death and time to CV death. Additionally, the event rate of, and time to, all-cause mortality was a secondary outcome. The exploratory outcome of health-related quality of life was measured using the EuroQol 5 dimension questionnaire (EQ-5D). All efficacy analyses were performed according to an intention-to-treatment (ITT) principle for all patients randomised irrespective of protocol adherence or the duration of exposure to study treatment.

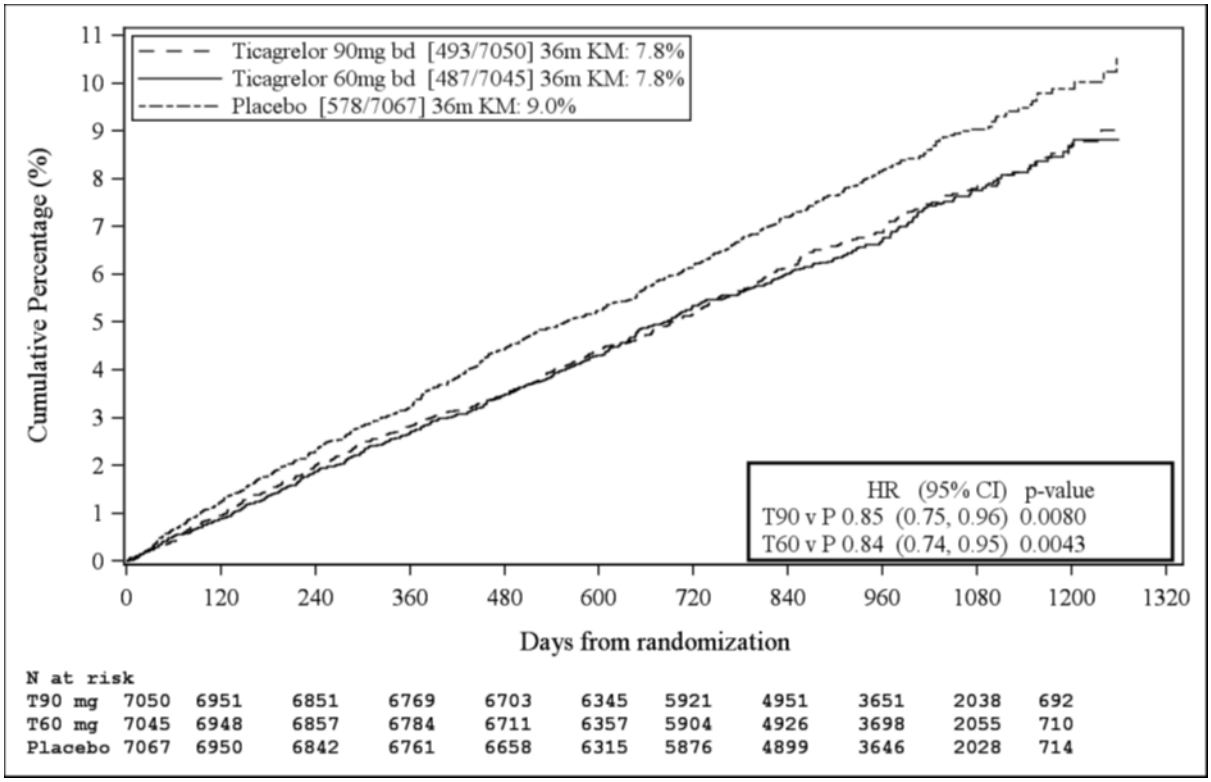
4.6 The company reported that long-term treatment with ticagrelor was superior to placebo in reducing the event rate of the primary composite endpoint (see Table 3). Ticagrelor 60 mg twice daily numerically decreased CV death (secondary endpoint) compared with placebo, although this was not statistically significant (relative risk 17%; HR 0.83; 95% CI 0.68 to 1.01) (see company submission Table 25). The company estimated that, for every 10,000 patients who began treatment (that is, in the ITT analysis), 42 primary endpoint events per year would be prevented with ticagrelor 60 mg compared with placebo.

Table 3 Endpoint PEGASUS –TIMI 54 composite primary outcomes for the whole ticagrelor 60 mg population at 36 months

Outcome	**Ticagrelor 60 mg (n=7,045)**	**Placebo (n=7,067)**	**HR (95% CI)**	**p value**
Composite of CV death, MI or stroke (%)	487 (6.9)	578 (8.2)	0.84 (0.74-0.95)	0.0043 (s)
CV death (%)	174 (2.5)	210 (3.0)	0.83 (0.68-1.01)	0.0676
MI (%)	285 (4.0)	338 (4.8)	0.84 (0.72-0.98)	0.0314
Stroke (%)	91 (1.3)	122 (1.7)	0.75 (0.57-0.98)	0.0337
Abbreviations: CI Confidence interval HR Hazard ratio Source: Company submission, Table 25				

4.7 The company provided a Kaplan Meier analysis on the primary composite endpoint (Figure 1).

Figure 1 Kaplan-Meier rates of CV death, MI and stroke over 3 years, according to study treatment groups (figure 8 in the company submission)



ERG comments

4.8 The ERG highlighted comments received from the UKCPA relating to restarting or initiating treatments post-event; as well as the UKCPA comments relating to selecting out high risk patients for treatment (see section 4.2 of the ERG report). The ERG commented that these practices are not representative of current UK practice.

4.9 The primary outcome in PEGASUS-TIMI 54 was time to first occurrence after randomisation of any event from the composite of cardiovascular (CV) death, MI or stroke. However, the company presented results for the individual components of the composite primary outcome. The ERG advised that in principle, the individual component end points may lack sufficient power to detect a statistically significant difference in treatment effect, although it

considered that this was unlikely to be the case in this study given the large number of patients enrolled.

4.10 The ERG noted that the results from PEGASUS-TIMI 54 were based on small numbers of events for each outcome compared with the total number of patients in each arm and should therefore be interpreted with a degree of caution.

4.11 The ERG stated that the annual number of continuation therapy ticagrelor 60 mg-eligible patients was likely to be higher than estimated by the company as the underlying figures only included England, that is ,it did not include Wales.

Health Related Quality of life

4.12 Health Related Quality of life (HRQoL) data for patients in the PEGASUS-TIMI 54 study were collected at baseline, at 8 months, 12 months, 18 months and subsequently every 6 months until the end of follow-up. These data were used to calculate the disutility associated with adverse events using the UK time trade off (TTO) tariff by applying a window of time to determine whether an event occurred within a window (see Table 98 in the company submission).

Subgroup analyses

4.13 A wide range of pre-specified subgroup analyses were reported by the company to examine the influence of patient characteristics on the primary endpoint (see Table 32 of the company's submission). The results of these subgroup analyses for patients receiving 60 mg ticagrelor twice daily and placebo are presented in Figures 17 and 18 of the company's submission.

4.14 Two pre-specified subgroup analyses related to time since qualifying MI and time from ADP receptor inhibitor withdrawal indicated that the benefit of ticagrelor may be greatest in patients <2 years from their last MI or in patients continuing on or re-starting after only a brief

interruption of ADP receptor inhibition (Table 34 and Figure 19 in the company submission). These analyses supported the final wording in the marketing authorisation for ticagrelor 60 mg twice daily which recommends use in eligible patients without interruption as continuation therapy after an initial one-year treatment with a previous ADP receptor inhibitor.

4.15 The company's undertook a post hoc subgroup analysis of patients in the PEGASUS-TIMI 54 trial who had received 60 mg ticagrelor and who had experienced a prior myocardial infarction <2 years previously. The company referred to this population as its 'label' population or 'base case' and this was the focus of its decision problem (see table 1). For details of the baseline patient characteristics for the company's 'label' population or 'base case', see Table 20 in the company's submission. For details of the composite and individual components of the primary efficacy endpoint for the company's 'label' population or 'base case', see Table 33 in the company's submission.

4.16 The company also presented further post hoc subgroup analyses for its 'label; population or 'base case' to address the subgroups listed in the final scope issued by NICE. For details of the baseline patient characteristics of the company's 'label' population or 'base case' with or without diabetes and those who have and who have not undergone a PCI, see Tables 21 and 22 of the company's submission. For details of the composite and individual components of the primary efficacy endpoint for the company's 'label' population or 'base case' with and without diabetes, see Table 35 in the company submission. For details of the composite and individual components of the primary efficacy endpoint for the company's 'label' population or 'base case' with and without a history of PCI, see Table 36 of the company submission.

4.17 The company also undertook a number of post hoc subgroup analyses to investigate further the relationship of age and multiple qualifying risk factors (for future thrombotic events) on outcomes. None of these variables was found to predict the treatment outcome.

4.18 The company stated that the population specified in the marketing authorisation, and its 'label' population or 'base case' were subgroups of PEGASUS-TIMI 54. Therefore any further subgroup analysis would therefore be subgroup data of a subgroup, and such analyses are not statistically sound as the trial was not powered to draw conclusions about (non-pre-specified) subgroups of subgroups. The company advised caution when interpreting these results.

Adverse effects of treatment

Adverse events related to bleeding

4.19 The expected adverse events of ticagrelor were associated with bleeding. The analysis focused on major bleeding events defined as fatal bleeding, intracranial haemorrhage and other major bleeding. The company reported that the PEGASUS-TIMI 54 study indicated that ticagrelor 60 mg was associated with an increase in major bleeding as shown in Table 41, of the company submission.

Adverse events not related to bleeding

4.20 The company indicated that non-bleeding adverse events reported in the PEGASUS-TIMI 54 trial were consistent with the existing evidence base for ticagrelor. Overall adverse events were reported more frequently in the ticagrelor group than in the placebo group with frequencies of 76.3% and 70% for ticagrelor 60 mg and placebo respectively. Rates of overall adverse events, serious adverse events and non-cardiovascular causes of death are reported in Tables 44 and 45 of the company submission.

4.21 There were significantly more patients treated with ticagrelor 60 mg who experienced events leading to study drug discontinuation compared with patients treated with placebo both in the whole population who received 60 mg of ticagrelor (HR: 5.95, 95% CI 4.42 to 8.01) and in the company's 'label' population or 'base case' (HR: 6.18, 95% CI 4.17 to 9.15).

4.22 The ERG noted that although there were differences between treatment groups and between populations the absolute number of patients who experienced major bleeds was small. There was a high degree of uncertainty surrounding the treatment effects as a result of the small number of events observed. The absolute number of patients who experienced serious adverse events was <0.5% of the number of patients treated.

4.23 There was an increase in the risk of gout in patients who received ticagrelor 60 mg compared with patients who received placebo. The difference was statistically significant in the whole population who received 60 mg ticagrelor (HR: 1.33, 95% CI 1. 01 to 1.76) however the difference was not statistically significant in the company's 'label population' or 'base case' (HR: 1.24, 95% CI 0.87 to 1.78).

5 Cost-effectiveness evidence

Model structure

5.1 The company developed a de novo Markov model to assess the cost effectiveness of ticagrelor plus aspirin, compared with aspirin alone, in reducing the rate of CV death/MI/stroke (primary endpoint in the PEGASUS-TIMI 54 trial). Health effects were reported in QALYs and the NHS and personal social services (PSS) perspective was adopted. The model time horizon was 40 years, with costs and benefits discounted at an annual rate of 3.5%.

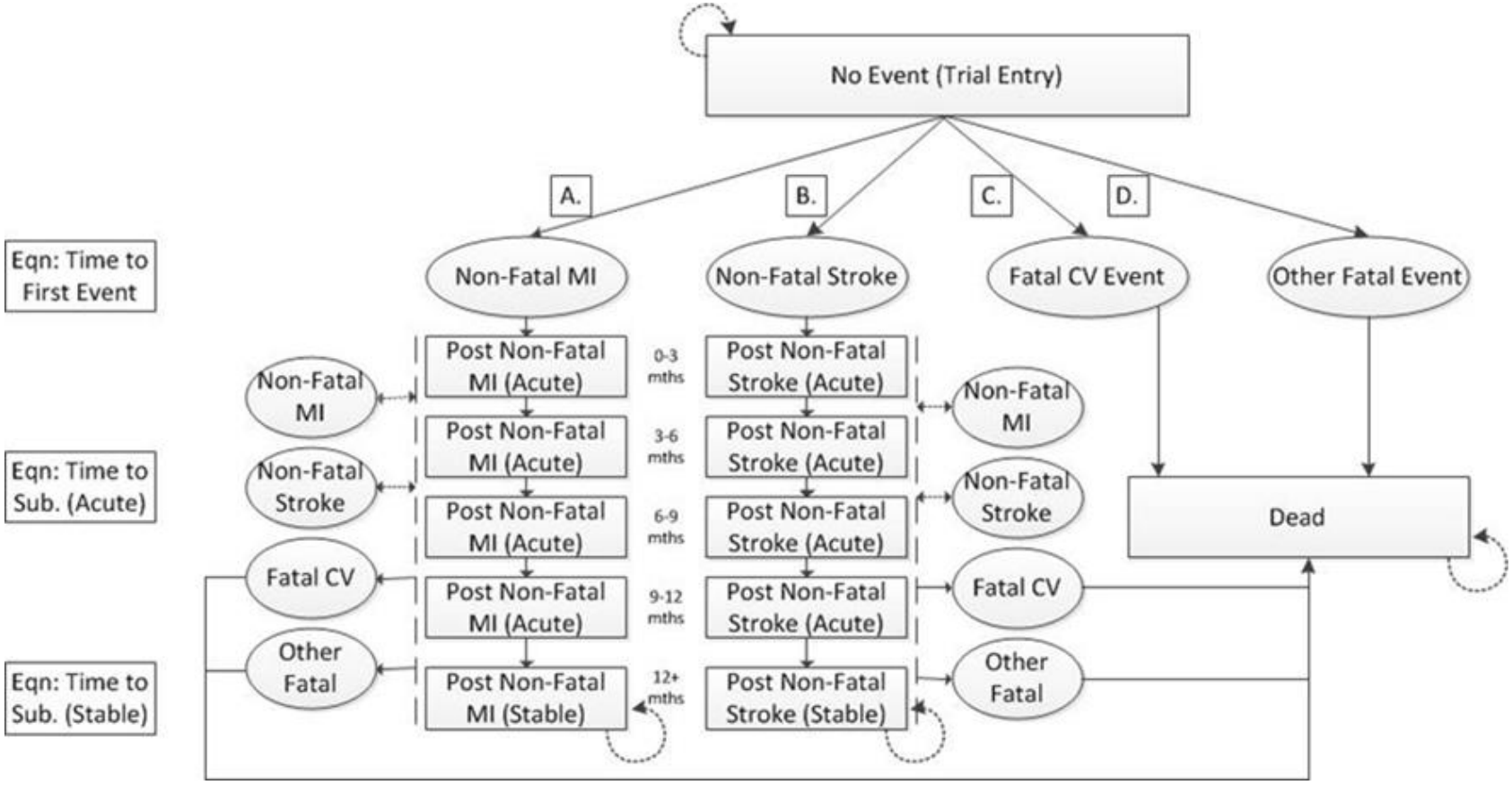
5.2 The company claimed that the modelled population reflected patients in the PEGASUS-TIMI 54 trial. Within the model, each of the components of the composite endpoint were re-modelled individually in a competing risks framework. The company stated that using a competing risks framework allowed for different impacts (coefficients) of characteristics for each separate endpoint that made up the composite primary outcome measure (that this cardiovascular (CV) death, MI or stroke). The risk equations were used to model individual events directly, rather than composite events which were then apportioned using the probability of that event being of a certain type. The company stated that for this reason, fewer assumptions were made in the modelling process.

5.3 A diagrammatic representation of the model is shown in Figure 2. Health states are represented in the diagram as rectangles, while events are represented as ovals. The model used a 3-month cycle length, with a maximum time horizon of 50 years (200 cycles) which can be varied between the observed trial time period (approximately 36 months) and the 50-year maximum (40 years in the base case). Half cycle corrections were applied to health state costs and QALYs.

5.4 Patients entered the model in the 'No Event (Trial Entry)' state and were modelled to have an individual risk for their first event (non-fatal MI, non-fatal Stroke, fatal CV event or other fatal event). This is represented in Figure 2 as 'Eqn: Time to First Event', A, B, C, and D. Patients who had a fatal event, entered an absorbing 'Dead' state, while those who had a non-fatal event, entered either a 'post non-fatal MI' or 'post non-fatal stroke' state depending on the first event experienced. Although patients can attain further events, those patients who entered a 'Post Non-Fatal MI' or 'Post Non-Fatal Stroke' state, remained in this health state until death. Subsequent events, non-fatal MI, non-fatal stroke, fatal CV and other fatal were estimated using a second set of risk equations. For further details on patient

progression in the model, see section 5.2 of the company's submission.

Figure 2 State transition diagram of company's cost-effectiveness model Figure 5.1 in the company submission



ERG comments

5.5 The ERG commented that the model structure included some simplifications that potentially influence health outcomes and costs: non-explicit modelling of subsequent events and adverse events, not distinguishing between non-fatal disabling and non-disabling stroke, and incorporating a difference in the occurrence of adverse events between treatments until ticagrelor 60 mg twice daily and aspirin treatment discontinuation only. The ERG further commented that as a result of not explicitly modelling non-fatal subsequent events and adverse events the occurrence of these events do not impact on survival and have only a temporary (3 months) impact on costs and quality of life. The ERG developed a graphical representation of the model structure to present the model structure more clearly (Figure 3).

5.6 The company was requested to adjust the model to incorporate the impact of non-fatal subsequent events and adverse events on survival, costs and quality of life beyond 3 months. In addition, the company was requested to undertake a scenario analysis explicitly incorporating subsequent events and the potential impact on survival to show that the model simplification did not have an impact on health outcomes and costs.

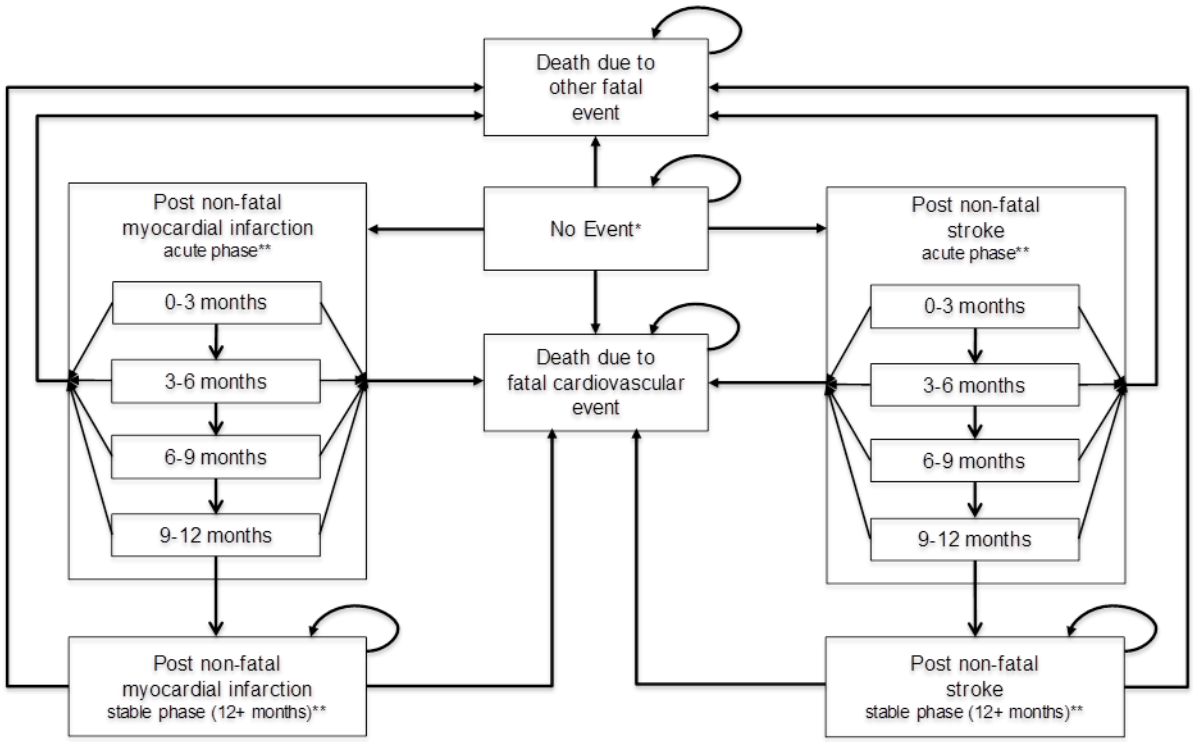
5.7 The company did not provide the model adaptation and scenario analysis and stated: *"A pragmatic decision was made to simplify the health states needed to model transition probabilities through the acute and sTable phase subsequent events, without losing important information. Therefore the risk equations were designed to capture the likelihood of multiple subsequent events (during the acute and sTable phase) in addition to the greater risk of a subsequent given the occurrence of a first event. Should the model slightly underpredict the occurrence of 3rd events (and beyond), this would represent a conservative modelling approach from the perspective of ticagrelor 60 mg BID + ASA, owing to the treatment effect observed for first*

events in PEGASUS-TIMI 54 and the influence of first events on subsequent events". The ERG agreed that the non-explicit modelling of subsequent events was likely to result in an underestimation of the impact of these events on costs and health outcomes, which was likely to be "conservative".

5.8 The ERG commented that the company's modelling of adverse events may result in an underestimation of the impact of major bleeding in particular, as the consequences of this adverse event are likely to exceed 3 months. Therefore, in the ERG's base-case a more conservative disutility for major bleeding was used.

5.9 The model structure did not distinguish between non-fatal disabling and non-disabling strokes, even though these have different clinical and economic impacts. The company and ERG agreed that not distinguishing between non-fatal disabling and non-disabling stroke based on data from PEGASUS-TIMI 54 trials was conservative.

Figure 3 Graphical representation of the ERG's model structure figure 5.1 in the company's submission



* Patients in the no event health state can experience adverse events (major and minor bleeding and major and minor dyspnoea). The risk is dependent on treatment and disutility and costs are incurred for the duration of one cycle (3 months).

** Patients in the post non-fatal myocardial infarction and the post non-fatal stroke states can experience adverse events (major and minor bleeding and major and minor dyspnoea) and subsequent non-fatal myocardial infarction and stroke. These risks are dependent on treatment and disutility and costs are incurred for the duration of one cycle (3 months).

Model details

Modelling of clinical effectiveness data

5.10 The company presented clinical outcomes data from PEGASUS-TIMI 54 which represented an analysis using a Cox proportional hazard regression that accounts for the treatment administered in Table 55 of the company submission. The economic model expanded on these analyses. For the purpose of this economic model the company disaggregated the composite outcome (of CV death, MI or stroke) into its components, to accord with the model structure outlined in Figure 3. Estimation of time-to-first-event analyses were completed using a competing risk approach, where 4 events (non-fatal MI, non-fatal stroke, fatal CV and fatal other) were competing to be the first event

experienced by each patient. A competing risk approach differs from standard survival analyses, as patients are censored from the 'at-risk' population when a competing event occurs. The approach generated 4 separate risk equations for each of the event types, where an individual treatment effect was incorporated into the equation. The risk equations therefore incorporated baseline characteristics as a tool to predict risk, accounting for overall patient heterogeneity.

5.11 The majority of the parametric time-to-event models used in the economic modelling were based on PEGASUS-TIMI 54. The company only (partly) adjusted 2 time-to-event models to reflect the 'label' population or 'base case' in the trial, since the label covariate was not statistically significant for the other time-to-event models.

Long-term extrapolation

5.12 For each of the time-to-event analyses (time to first event and time to subsequent events), the company extrapolated outcomes beyond the trial follow-up period.

Transition probabilities and outcomes

5.13 Individual patient data, collected from the 21,162 patients who entered the trial, were used to inform the risk equation for each endpoint considered in the model. However the base case population corresponded with the company's 'label' population or 'base case', that is the "MI <2 years" subgroup of the PEGASUS-TIMI 54 trial. To reflect the higher rate of subsequent events for the 12 months after the first event, five tunnel states were applied. The first 4 states tracked time since the first event with a diminishing risk for subsequent events: patients whose first event occurred 0–3 months prior, the second 3–6 months prior, the third 6–9 months prior and the fourth 9–12 months prior, for states 1 to 4, respectively. The fifth state applied a constant risk for subsequent events from 12 months or more

after the first event. United Kingdom, National Life Tables (2012-2014) were used to model non-cardiovascular mortality.

Health related quality of life

5.14 A systematic literature review was conducted to identify HRQoL and utility value studies relevant to the company's decision problem. However, the company did not use these in its model because the PEGASUS-TIMI 54 study collected data on health-related quality of life. Since HRQoL trial data were collected at set intervals during the course of the PEGASUS-TIMI 54 study, as opposed to following events, the company had to apply a window of time to determine whether an event occurred within a cycle. The utility decrements applied for events and health states in the model for each cycle are summarised in Table 99 of the company's submission.

5.15 After adjusting the baseline utility from PEGASUS-TIMI 54 for age, it was assumed that the patient population under consideration within the model was unlikely to have a higher baseline utility than that of the UK general population. Therefore in the base case, the baseline utility was assumed to be the same as that of the UK general population, which decreases over time with a linear reduction within each age banding. To determine patients' overall utility scores, a base utility score was combined with the utility decrements. Disutility for events and health states were taken from PEGASUS-TIMI 54 as described in sections 5.4.8 and 5.4.9 of the company's submission. A summary of utility values used in the cost-effectiveness analysis is provided in Table 4. Although there was a greater incidence of gout observed in PEGASUS-TIMI 54 for ticagrelor 60 mg compared with aspirin, this was not modelled as an adverse event in the company's original economic model.

Table 4 Summary of utility values for cost-effectiveness analysis

State	Utility
Baseline	UK population norm (age and gender specific)
Non-fatal MI	-0.0474
Non-fatal stroke	-0.0934
Post MI	-0.0342
Post stroke	-0.0665
Dyspnoea (Grade 3-4)	-0.0481
Dyspnoea (Grade 1-2)	-0.0154
TIMI minor bleed	-0.0129
TIMI major bleed	-0.0466
Abbreviations: MI: myocardial infraction, TIMI: thrombolysis in myocardial infarction Source: company submission Table 102	

Model resource use

5.16 The company estimated resource use on the basis of a literature review. Data from completed NICE technology appraisals were also extracted (see Table 104 in the company's submission). Resource use and associated costs are provided in Table 5. NHS reference costs were used to calculate the cost of an inpatient event for grade 3–4 dyspnoea (weighted average of DZ19 'Other Respiratory Diseases') owing to a lack of published values. The cost of ticagrelor 60 mg was £54.60 for 28 days supply, which equated to £1.95 a day. The generic medicine cost for aspirin of £0.03 per day was applied by the company.

Table 5 List of resource use and associated costs in the economic model

Resource use	Value
Inpatient	
Non-fatal MI	£4,476.18
Non-fatal stroke	£4,925.76
Fatal events (CAD and non-CAD)	£2,497.83
'No event'	£2,497.83
Outpatient and maintenance	
Post non-fatal MI (0-3 months)	£639.45

Post non-fatal MI (3-6 months)	£639.45
Post non-fatal MI (6-9 months)	£319.73
Post non-fatal MI (9-12 months)	£319.73
Post non-fatal MI (12+ months, every cycle)	£160.31
Post non-fatal stroke (0-3 months)	£1,343.39
Post non-fatal stroke (3-6 months)	£1,119.49
Post non-fatal stroke (6-9 months)	£877.57
Post non-fatal stroke (9-12 months)	£689.71
Post non-fatal stroke (12+ months, every cycle)	£689.71
'No event' (every cycle)	£160.31
Adverse events	
Grade 3-4 Dyspnoea	£732.98
Major TIMI bleed	£2,206.87
Minor TIMI bleed	£122.48
Abbreviations: MI: Myocardial Infraction; CAD: Coronary artery disease ;TIMI: Thrombolysis In Myocardial Infarction Source: company submission Table 113	

5.17 For a summary of the key variables included in the model, see Table 113 of the company's submission. For further details of the company's base case assumptions, see section 5.6 of the company submission.

ERG comments

5.18 The ERG commented that not all of the analyses of the PEGASUS-TIMI 54 trial used to inform the parameters in the model reflected the company's 'label' population or 'base case'; most analyses were based on the ITT population instead without adjustment to reflect the 'label' population or 'base case'. For further details, see Section 5.2.6 of the ERG report.

5.19 The ERG noted that the impact of gout on the quality of life of patients was not incorporated in the company base-case analysis in its original submission. In response to clarification, the company provided an up-dated model that incorporated the impact of gout on costs and quality of life in the economic analyses. The results of this analysis are

presented in Section 5.2.11 of the ERG submission, and used in the ERG's base-case and additional analyses.

5.20 The ERG highlighted that the company stated that the modelled population was a subpopulation of the population specified in the marketing authorisation and the population in the final scope issued by NICE. However, the European Public Assessment Report (EPAR), states that ticagrelor 60 mg may be initiated "up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment." The ERG commented that this implied that the modelled population was very similar to the population specified in the marketing authorisation. The only differences being that patients "within one year after stopping previous ADP receptor inhibitor treatment" are included in the marketing authorisation but not specifically mentioned in the description of the modelled population. The ERG considered that in practice, these populations may be similar. See table 5.9 of the ERG report for a comparison of the population in the final scope issued by NICE, the recommended population in the EPAR, and the company's 'label' or 'base case' population.

5.21 The treatment pathway was unclear to the ERG. Specifically, it was unclear how patients who experienced a subsequent non-fatal event were treated in the model. The company was requested to clarify whether these patients would receive ticagrelor 90 mg for 12 months, followed by ticagrelor 60 mg for 36 months. The company responded that the use of dual antiplatelet therapy after a subsequent event in the model could take place in clinical practice as patients are 'reset' as new ACS patients. In addition, the company clarified that this was not incorporated in the model, because of the complexity and time constraints. The company did provide a scenario analysis whereby the cost associated to the post non-fatal myocardial infarction (12+ months) health state was increased by £178.06 per cycle (the cost of

ticagrelor 60 mg twice daily per 3 months). This was similar to assuming ticagrelor 60 mg twice daily given for remaining lifetime from 12 months following a myocardial infarction. The ERG stated that as such, this scenario analysis overstated the impact on the ICER, but was illustrative of directional impact on the ICER. The company provided a scenario analysis assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI. The results of these analyses are provided in Section 5.2.10 of the ERG report.

5.22 The ERG considered that the company submission lacked transparency concerning the cost estimates used in the cost effectiveness model and therefore the company provided further detail. Further details are provided in table 5.25 of the ERG report following clarification from the company.

Company's base-case results and sensitivity analysis

5.23 The company provided deterministic results of the cost effectiveness model for the individual patient simulation (named 'complete' analysis by the company) and the cohort analysis (named 'simple' analysis by the company). In the individual patient simulation, all patients of the European Medicines Agency (EMA) 'label population' (n=10,779, post-hoc subgroup of patients within PEGASUS-TIMI 54 who conform to the population defined in the license from the EMA, that is experienced an MI <2 years previously or within 1 year of previous ADP inhibitor treatment) go through the model one at a time, hence risk equations are applied to each patient individually. Results are then averaged for each treatment arm. In the cohort analysis, a cohort with the average patient characteristics (based on PEGASUS-TIMI 54), goes through the model simultaneously, that is all patients in the cohort at a time. Table 6 below presents the company's base-case analysis.

Table 6 Company's Base-case results for population with MI <2 years ago

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) per inc QALY
Individual patient simulation							
Low-dose aspirin	£13,086	12.2453	9.1951	-	-	-	-
Ticagrelor 60 mg BID + low-dose aspirin	£14,518	12.3363	9.2645	£1,432	0.0909	0.0694	£20,098
Cohort analysis							
Low-dose aspirin	£14,264	13.4590	9.7949	-	-	-	-
Ticagrelor 60 mg BID + low-dose aspirin	£15,683	13.536	9,8541	£1,425	0.0771	0.0592	£24,070*

Source: Table 5.28 ERG report (based on the original cost effectiveness model and Table 114 of the company submission)

*The ICER reported in the CS for the cohort analysis was £24,378 (deterministic results)

BID: twice daily; ICER: incremental cost effectiveness ratio; Inc: incremental; LYG: life years gained; QALY: quality-adjusted life year

5.24 In response to clarification, the company provided a revised base-case cost effectiveness analysis where the following changes were included:

- Inpatient and adverse event costs based on NHS reference costs (see Section 5.2.9 of the ERG report)
- Parametric models for adverse events were selected based on the AIC (see Section 5.2.7 of the ERG report)
- Gout was included as an adverse event in the cost effectiveness model (both quality of life and economic impact) (see Section 5.2.8 and Section 5.2.9 of the ERG report)

In this revised base-case analysis, ticagrelor was associated with a deterministic ICER of £20,636 per QALY gained in the individual patient simulation, which was an increase of £538 compared with the company's original base-case analysis (see table 6).

Sensitivity and scenario analyses

5.25 The company stated that because of the computational requirements in undertaking an individual patient level sensitivity analysis a traditional deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were deemed infeasible. In this model, both the DSA and PSA were performed for a single individual patient profile. The company reported that the specific patient profile was chosen by selecting the patient with the ICER that most closely represented that of the 'complete' analysis (that is, the cohort as a whole). The ERG provided a comparison of the individual patient profile (used for the sensitivity analyses) with the average patient characteristics of the cohort (see Table 5.32 of the ERG report). The company emphasised that the PSA and DSA results should be compared to the results of this individual patient instead of being compared to the results based on the individual patient simulation of the entire population.

5.26 The company carried out a PSA. This resulted in a probabilistic ICER of £19,275 per QALY gained (see Table 118 of the company submission).

5.27 The company presented a range of scenario analyses based on the individual patient simulations (for further details, see section 5.8 in the company submission). The company stated that these analyses demonstrated that the ICER was most sensitive to the choice of distributions used to extrapolate the risk equations for first event beyond the length of the trial and the discount rate applied to health outcomes. The company reported that the substantial range of scenario analyses demonstrated that for patients aged 50 years and older the ICER remained below £30,000 per QALY gained, irrespective of the setting for initiation or source for utilities and costs information.

5.28 In response to clarification, the company provided an additional 8 scenario analyses based on the individual patient simulations. All of the scenario analyses provided an ICER below £30,000 per QALY gained. No probabilistic results of these analyses were provided. For further details, see Table 5.35 of the ERG report.

5.29 The company also performed subgroup analyses based on the individual patient simulations (for further details, see section 5.9 in the company submission). The deterministic results of the subgroup analyses are presented in table 7. For details of the probabilistic results for the subgroup analyses, see Tables 132, 134, 136, 138 and 140 of the company submission.

Table 7 Deterministic results across subgroups for population with MI <2 years ago (individual patient simulation)

Analysis	ICER per QALY gained
Base-case	£20,098
Continuation therapy	£20,890
Patients with diabetes	£14,246
Patients without diabetes	£24,845
Patients with history of PCI	£22,600
Patients without history of PCI	£12,856
Abbreviations: QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio Source: company submission table 142	

ERG comments

5.30 The ERG was of the opinion that the method used for the single individual patient selection on which the PSA and DSAs were conducted was inappropriate. The ERG agreed that performing a PSA on an individual patient simulation was computationally intensive. It was of the view that this did not justify the selection of an individual patient to perform PSA instead of all patients. The company was requested to perform PSA based on all patients of the individual patient simulation, since running the PSA based on a single patient

profile did not reflect the uncertainty in the output. In its response to this request, the company performed the PSA on 11 patient profiles instead of one patient profile. These 11 patients were also selected based on their ICER: the individual patient with the closest ICER to the ICER of the individual patient simulation and the 5 patients having the closest ICER below or above the ICER of the individual patient simulation (the '11 typical ICER patients'). The ICER for ticagrelor, based on the individual patient simulation of the 11 typical ICER patients was £20,604 per QALY gained. The ERG was of the opinion that the PSA was still not appropriate and should be based on the individual patient simulation including the entire patient population of 10,799 patients (that is the EMA 'label population'), or whatever number would produce stable results in order to reflect the uncertainty in the output. The company also used this methodology to provide probabilistic results for its subgroup analyses. The ERG did not consider these analyses provided reliable probabilistic estimates.

5.31 The ERG commented that costs were not incorporated within the company's PSA. According to the ERG this was incorrect. Prices are most often fixed and resource use may stochastically vary. Hence, prices should not be included in the PSA and resource use should be included in the PSA. In this case, costs were based on NHS reference costs, which are the product of prices and resource use estimates, and as a result may stochastically vary, and should be included in the PSA. The ERG incorporated the cost estimates (that is, those based on NHS reference costs) independently in the PSAs of its base-case and additional analyses (based on the cohort simulation).

ERG's exploratory analyses

5.32 The ERG estimated a new base case. It used the cohort simulation to obtain a probabilistic estimate of the ICER, as it considered the company's probabilistic sensitivity analysis of the patient level simulation was not implemented correctly. Therefore, all of the

following ERG adjustments were performed on the cohort analysis. The ERG's adjustments were subdivided into 3 categories:

- Fixing errors (correcting the model were the company's submitted model was unequivocally wrong). For further details, see section 5.3 of the ERG report.
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to). For further details, see section 5.3 of the ERG report
- Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred). For further details, see section 5.3 of the ERG report.

The combination of these corrections/amendments resulted in the ERG's probabilistic base-case ICER for ticagrelor of £24,711 per QALY gained (see table 8).

5.33 The ERG undertook additional exploratory sensitivity analyses to examine the potential impact of various alternative assumptions on the cost effectiveness estimates (see table 8). The ERG's explorative analysis which assumed treatment duration of 3 years unless a non-fatal event or death occurred resulted in an ICER for ticagrelor of £33,676 per QALY gained. The other explorative analyses did not substantially influence the ICER, which remained under £30,000 per QALY gained.

5.34 The ERG highlighted that its additional analyses were based on the cohort simulation, which may be an overestimation as this analysis does not take into account the nonlinearity in the model. The ERG also highlighted that all of the ERG's additional analyses were conditional on the time-to-event models that were unadjusted for the 'label population'. Although this may be conservative, the ERG was

unable to determine the magnitude and direction of the bias this may have caused.

Table 8 ERG's exploratory analyses

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Company's base case	£14,443	9.2742	£1,434	0.0708	£20,098
ERG's base case	£14,113	9.768	£1,439	0.058	£24,711
Hospitalisation probability for 'no event' state treatment dependent	£14,171	9.766	£1,499	0.058	£25,834
Time to fatal other (1st event) treatment dependent	£14,115	9.767	£1,437	0.058	£24,989
TTD because of non-fatal event or after 3 years	£14,609	9.760	£1,929	0.057	£33,676
Use of more conservative utilities	£14,116	9.790	£1,440	0.057	£25,091
Abbreviations: Inc: incremental; QALY: Quality adjusted life year; ICER: incremental cost effectiveness ratio; TTD: Time to treatment discontinuation Source ERG report Table 6.2					

Innovation

5.35 Justifications for considering ticagrelor to be innovative:

- Ticagrelor has a rapid onset of anti-platelet effect, low variability and reversibility that results in a faster onset of action compared with thienopyridines as well as a faster offset of action with more rapid recovery of platelet function.
- The company stated that the technology is not expected to produce substantial health-related benefits not already included in the QALY calculation.
- The UKCPA considered the application of the technology innovative and thought it offered health benefits.

5.36 The UKCPA commented that there are other studies currently on-going in which long-term treatment with ticagrelor is under investigation e.g. GLOBAL LEADERS. The UKCPA considered it

would be wise to wait for the outcomes of this study is warranted for further insights into the long-term safety of more potent P2Y12 inhibition.

6 Equality issues

6.1 The UKCPA commented that the trial excludes those patients with a previous stroke, GI bleed or need for anticoagulation - this is not representative of practice - should these patients present with a further ischaemic event they would still require treatment**.**

7 Authors

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Technical Lead(s)

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Appendix A: Clinical efficacy section of the European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001241/WC500203874.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ticagrelor within its marketing authorisation for the prevention of atherothrombotic events in adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events.

Background

Atherosclerosis is the build-up of fatty material in artery walls to form a plaque (also known as atheroma) causing narrowing of the artery and disrupted blood flow. If the atheroma ruptures, it can cause a blood clot (thrombus), a condition referred to as atherothrombosis, which may block blood flow to heart muscles causing a heart attack (myocardial infarction). Sometimes blood clots may dislodge and travel in the blood stream (embolism) and block blood flow to the brain causing a stroke.

Risk factors for coronary heart disease include smoking, a diet high in saturated fat, high blood pressure, diabetes, being overweight or obese, lack of exercise, age, gender and family history. In 2012/13 there were approximately 141,000 inpatient episodes recorded for myocardial infarction in England.[1]

After a first myocardial infarction people remain at an increased risk of further atherothrombotic events. Treatment of people who have had a myocardial infarction with oral anti-platelets manages the ongoing risk of having further atherothrombotic events against the increased risk of bleeding associated with treatment.

NICE clinical guideline 172 for the secondary prevention of atherothrombotic events for people following a myocardial infarction recommends exercise, dietary changes and help to stop smoking for people who smoke. It also recommends that everyone who has an acute myocardial infarction should be offered treatment with a combination of an angiotensin-converting enzyme inhibitor, dual antiplatelet therapy (aspirin plus a second antiplatelet agent), a beta-blocker and a statin. The guideline recommends that aspirin should be offered indefinitely after a myocardial infarction. NICE clinical guideline 172 also recommends clopidogrel monotherapy as an alternative for people with aspirin hypersensitivity.

Dual antiplatelet therapy following a myocardial infarction includes aspirin either with clopidogrel, prasugrel or ticagrelor. NICE clinical guidelines 172 (myocardial infarction - secondary prevention), 167 (acute management of myocardial infarction with ST-segment elevation) and 94 (early management of unstable angina and non-ST-segment-elevation myocardial infarction) as well as NICE technology appraisals 210 (Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events), 236 (Ticagrelor for the treatment of acute coronary syndromes) and 317 (Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes [review of TA182]) recommend dual antiplatelet therapy for up to 12 months following myocardial infarction, after which a single anti-platelet regimen with aspirin or clopidogrel (only in people with aspirin hypersensitivity) is continued in the long term.

The technology

Ticagrelor (Brilique, AstraZeneca) is an adenosine triphosphate analogue that binds reversibly to the P2Y12 class of adenosine diphosphate receptors on platelets and inhibits platelet activation and aggregation. It is administered orally.

Ticagrelor in combination with aspirin does not currently have a marketing authorisation in the UK. It has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction and a high risk of developing atherothrombotic events.

Ticagrelor co-administered with aspirin, has a marketing authorisation in the UK for “the prevention of atherothrombotic events in adult patients with acute coronary syndromes”.

Intervention(s)	Ticagrelor co-administered with aspirin
Population(s)	Adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events.
Comparators	• Aspirin • Clopidogrel in combination with aspirin

Outcomes	The outcome measures to be considered include: • non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary revascularisation • bleeding events • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows following subgroups will be considered separately: • People with or without diabetes • People who have or have not had prior revascularisation Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome (2015). NICE technology appraisal guidance 335. Review Proposal Date Feb 2018. Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of technology appraisal guidance 182)' (2014). NICE technology appraisal guidance 317. Review Proposal

	Date June 2017. Ticagrelor for the treatment of acute coronary syndromes (2011). NICE technology appraisal guidance 236. Guidance has been incorporated into Clinical Guideline 167 and Clinical Guideline 172. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90) (2010). NICE technology appraisal guidance 210. On static list. Related Clinical Guidelines: Secondary prevention in primary and secondary care for patients following a myocardial infarction (2013). NICE clinical guideline 172. Myocardial infarction with ST-segment elevation: The acute management of myocardial infarction with ST-segment elevation (2013). NICE clinical guideline 167. Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin (2010). NICE clinical guideline 95. Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction (2010). NICE clinical guideline 94. Related Public Health Guidelines: Prevention of cardiovascular disease (2010). NICE public health guideline 25. Next review date December 2015. Related NICE Pathways: NICE Pathway: Myocardial infarction secondary prevention, Pathway created Nov 2013: http://pathways.nice.org.uk/pathways/myocardial-infarction-secondary-prevention Related Quality standards Acute coronary syndromes including myocardial infarction. NICE quality standard 68. (2014)
Related National Policy	NHS England (2013/2014). Manual for prescribed specialised services, Chapter 7 Adult specialist cardiac service: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework

	2014-2015, Nov 2013. Domains 1, 2 and 3: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

References

1. British Heart Foundation. Cardiovascular disease statistics. Available from: https://www.bhf.org.uk/research/heart-statistics [Accessed 24 September 2015]

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ticagrelor for the secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • AstraZeneca (ticagrelor) Patient/carer groups • Blood Pressure UK • British Cardiac Patients Association • Cardiovascular Care Partnership • Coronary Prevention Group • Different Strokes • HEART UK • Thrombosis UK • Muslim Council of Britain • Network of Sikh Organisations • Pumping Marvellous • Somerville Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Stroke Association Professional groups • British Association for Nursing in Cardiovascular Care • British Association of Stroke Physicians • British Atherosclerosis Society • British Cardiovascular Intervention Society (BCIS) • British Cardiovascular Society • British Geriatrics Society • British Heart Foundation • British Heart Rhythm Society • British Hypertension Society • British Nuclear Cardiology Society • British Society for Haematology • British Society for Haemostasis and	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Allergan (aspirin, clopidogrel) • Aspire Pharma (clopidogrel) • Boehinringer Ingelheim (aspirin) • Beacon Pharmaceuticals (clopidogrel) • Consilient Health (clopidogrel) • GlaxoSmithKline (aspirin) • Intrapharm Laboratories (aspirin) • Pfizer (aspirin) • Reckitt Benckiser (aspirin) • Sandoz (aspirin, clopidogrel) • Sanofi (clopidogrel) • Teva UK (aspirin, clopidogrel) • The Boots Company (aspirin) • Thornton & Ross (aspirin) • Wockhardt UK (aspirin, clopidogrel)

Consultees	**Commentators (no right to submit or appeal)**
Thrombosis • British Society for Heart Failure • British Society of Cardiovascular Imaging • British Thoracic Society • Clinical Leaders of Thrombosis (CLOT) • ESPRIT • Nurses Hypertension Society • Royal College of Emergency Medicine • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Society for Cardiological Science & Technology • Society for Vascular Technology • Society of Vascular Nurses • UK Health Forum • UK Clinical Pharmacy Association • Vascular Society of Great Britain and Ireland <u>Others</u> • Department of Health • NHS England • NHS Greater Huddersfield CCG • NHS North East Lincolnshire CCG • Welsh Government	<u>Relevant research groups</u> • Antithrombotic Trialists Collaboration • British Society for Cardiovascular Research • Cardiac and Cardiology Research Dept. Barts • Central Cardiac Audit Database • Cochrane Heart Group • Cochrane Hypertension Group • Cochrane Peripheral Vascular Diseases Group • Cochrane Stroke Group • European Council for Cardiovascular Research • MRC Clinical Trials Unit • National Centre for Cardiovascular Prevention and Outcomes • National Heart Research Fund • National Institute for Health Research • Society for Research in Rehabilitation • Wellcome Trust <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

AstraZeneca evidence submission

April 2016

File name	Version	Contains confidential information	Date
		Yes/no	

Contents

Tables and figures

1 Executive summary

Cardiovascular (CV) disease is the leading cause of death in the Western world with an increase over the last few decades. Atherosclerosis with its different manifestations in the coronary artery tree, the cerebral, as well as peripheral arteries is the basis for cardiovascular events, such as myocardial infarction, stroke, and cardiovascular death. Atherosclerosis is a diffuse, progressive, and chronic inflammatory disease that has been demonstrated to result in persistent cardiovascular risk.

Myocardial infarction (MI), or heart attack, is an interruption of blood supply to part or all of the heart, causing the muscle cells to die. The most common cause is an occlusion of a coronary artery due to rupture of an atherosclerotic plaque. The ruptured plaque causes platelet aggregation and thrombus formation, and can lead to total occlusion of the coronary artery. This results in ischemia and hypoxia that can cause damage or necrosis of the heart muscle tissue.

Even though there has been significant improvement in treating patients in the acute phase of an MI, mainly due to greater use of reperfusion therapy, primary percutaneous intervention (PCI) and modern antithrombotic therapy, considerable long-term morbidity and mortality remains in these patients and the risk of CV death and recurrent ischaemic events is sustained beyond 1 year after the index event and may be the result of coronary and systemic atherosclerosis progression.

This residual long term risk of CV events from subsequent atherosclerotic lesions is likely to originate either from the initial culprit lesion at the original site or from a new plaque at a different site or in a completely different vessel. Consequently, patients with a history of MI have a much higher risk of subsequent CV mortality and recurrent events compared with controls and numerous risk factors can contribute to the recurrence of CV events such as older age, >1 prior MI, multi-vessel coronary artery disease (CAD), diabetes mellitus or chronic kidney disease (CKD).

According to registry data, approximately 20% of English patients who remain event-free 1 year after an MI (described as “history of MI” in this submission) with a high CV risk (age ≥ 65 years, >1 prior MI, multi-vessel CAD, diabetes or chronic non-end stage renal dysfunction), will experience another MI, a stroke, or suffer CV death in

the subsequent 3 years. This suggests that there is a significant unmet need to reduce the long-term CV risk and that this population may benefit from more intensive secondary prevention.

Activated platelets play a key role in all stages of atherothrombosis through a number of mechanisms and antiplatelet therapies have been a cornerstone of the management of atherothrombotic conditions for a number of years. After an MI, aspirin is recommended for use indefinitely to prevent further atherothrombotic events and dual antiplatelet therapy with aspirin and an adenosine diphosphate (ADP) receptor inhibitor (ticagrelor, clopidogrel, prasugrel) was recommended for up to 12 months after an index MI based on studies in acute coronary syndrome (ACS) demonstrating the superiority of dual antiplatelet therapy over aspirin alone for up to a year. Both ticagrelor and prasugrel also demonstrated better efficacy in reducing major CV events compared to clopidogrel in ACS.

The continued risk of further CV events in the years following an initial MI represents an unmet medical need that may be addressed by an intensive antiplatelet therapy over a longer period of time. Although post hoc data suggest that extended dual antiplatelet therapy (DAPT) may reduce cardiovascular events in patients with a history of MI (CHARISMA, DAPT trial), before PEGASUS-TIMI 54, this had yet to be prospectively tested. The rationale for investigating ticagrelor in this setting was supported by its established mechanism of action, by the results of the PLATO trial and by the hypothesis based on the post hoc analysis of CHARISMA, that extended DAPT therapy in high risk patients with prior MI may provide clinical benefit.

Ticagrelor 60 mg BID is the first antiplatelet agent available to be prescribed in the UK for long-term use with aspirin in this population (i.e. patients with a history of MI at high risk of further atherothrombotic events). Clopidogrel is only licensed for use as a monotherapy in this setting and is usually only used in patients intolerant of ASA; it is not licensed to be used in combination with ASA in patients with a history of MI and high risk of atherothrombotic events.

Current NICE guidance recommends that all eligible patients who have had an MI should be treated with DAPT for up to 12 months from their index event, followed by aspirin monotherapy beyond the first 12 months, continued indefinitely. Similarly, in

MI patients with ST-segment elevation (STEMI), the recommendation from the updated NICE guidelines in 2012 is for DAPT with an ADP receptor inhibitor to be continued for up to 12 months with aspirin monotherapy continued indefinitely.

The most recent international guidelines related to ACS have considered the extension of DAPT beyond 12 months. The updated (2015) European guidelines for ACS patients without ST-segment elevation (NSTEACS) recommend a ADP receptor inhibitor should be added to aspirin as soon as possible and maintained for 12 months unless there are contraindications such as excessive risk of bleeding (Level I A) with, also now included, a recommendation to consider continuation of DAPT beyond 1 year following careful assessment of the ischaemic and bleeding risks (Level IIb A).

The 2016 ACC/AHA Focused Update on the Duration of DAPT guidelines recommend that in ACS patients (NSTE-ACS or STEMI), who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable (Class IIb) and this, irrespective of the initial management (patients treated with PCI, with fibrinolytic therapy or treated with medical therapy alone).

In terms of current real world prescribing practice in England and Wales, a recent survey (Feb/Mar 2016) of 135 cardiologists, revealed that the discharge letters for patients who had been hospitalised with MI and were at high risk of subsequent atherothrombotic events (as defined in the PEGASUS-TIMI 54 study) routinely prescribe DAPT for up to 12 months from their index event. Patients recruited to the PEGASUS-TIMI 54 study had suffered an MI 1-3 years prior to study enrolment, had been CV event-free for at least 1 year prior to study enrolment and all had at least one additional risk factor (age ≥ 65 years, >1 prior MI, multi-vessel CAD, diabetes or chronic non-end stage renal dysfunction). In the prescribing survey, approximately 90% of 631 “PEGASUS-like” patients (i.e. having at least one of the risk factors required for enrolment in the PEGASUS-TIMI 54 study and also listed and not meeting the trial exclusion criteria) were discharged from secondary care with instructions to receive dual antiplatelet therapy (ticagrelor (44%)/prasugrel (8%)/clopidogrel (39%) + ASA) for up to 12 months. Following completion of this

initial course of dual antiplatelet therapy, almost all patients are recommended to continue taking low-dose ASA indefinitely from 12 months (89% of “PEGASUS-TIMI 54-like” patients). A very small minority of patients (approximately 5%) are recommended to continue on dual antiplatelet therapy beyond 12 months (clopidogrel + ASA is recommended in approximately 4% of all cases) and even fewer (approximately 1%) are recommended clopidogrel monotherapy. These findings align with those from an earlier similar survey conducted with cardiologist in England & Wales in Jun/July 2015.

The conclusion is that cardiologists practicing in the NHS today follow established clinical guidelines from NICE and others when considering appropriate antiplatelet therapy for high risk patients (PEGASUS-TIMI 54-like) and prescribing behaviour has not been affected by the results of recent studies of long-term treatment with dual antiplatelet therapies or following the granting of the licence extension for ticagrelor 60mg BID. Thus, ASA monotherapy represents established NHS practice for cardiologists recommending treatment regimens for patients beyond 12 months from an MI and is the only relevant comparator for this appraisal.

1.1 Statement of decision problem

The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of ticagrelor within its marketing authorisation for the prevention of atherothrombotic events in adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults who have had a myocardial infarction and are at increased risk of atherothrombotic events	Adults who have had a myocardial infarction between 1 and 2 years ago and are at increased risk of atherothrombotic events	This is a pre-specified subgroup within the limits of the marketing authorisation in this indication.
Intervention	Ticagrelor co-administered with aspirin	Ticagrelor 60mg BID co-administered with aspirin for up to 3 years.	This is the dose specified in the marketing authorisation and there is limited data beyond 3 years.
Comparator (s)	• Aspirin • Clopidogrel in combination with aspirin	• Aspirin	Comparison with clopidogrel + aspirin is not presented • There is no head-to-head trial data and robust indirect comparison of pivotal trial outcomes is not feasible owing to important differences between studies • Clopidogrel + aspirin is not established NHS clinical practice in the population of interest • Clopidogrel + aspirin does not have a licence in this indication
Outcomes	The outcome measures to be considered include: • non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary	The outcome measures considered include: • non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary	N/A

	revascularisation • bleeding events • mortality • adverse effects of treatment • health-related quality of life.	revascularisation • bleeding events • mortality • adverse effects of treatment • health-related quality of life.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life-year The time horizon in the model is 40 years. At this point 98.8% of patients have died and all important differences in costs and CV outcomes are captured Costs are considered from an NHS and Personal Social Services perspective	N/A
Subgroups to be considered	If the evidence allows following subgroups will be considered separately: • People with or without diabetes • People who have or have not had prior revascularisation	Consideration has been given to the following subgroups: • People with or without diabetes • People with or without a history of PCI	"History of PCI" was a pre-specified subgroup in the pivotal trial and is used as a proxy. Results for the primary efficacy and safety endpoints are presented for both subgroups requested in the ITT analysis and in a subset of patients who had an MI <2 years ago. Data for other key endpoints are presented for the subset who had an MI <2 years ago only.

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Ticagrelor 60mg (brand name: Brilique™)
Marketing authorisation/CE mark status	An application for marketing authorisation (centralised process) was made by AstraZeneca to the EMA on 26 March 2015 CHMP positive opinion was received on 18 December 2015 EU approval was received on 19 February 2016
Indications and any restriction(s) as described in the summary of product characteristics	From the summary of product characteristics: 4.1 Therapeutic indications Brilique™, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event (see sections 4.2 and 5.1). 4.2 Posology and method of administration Posology Patients taking Brilique™ should also take a daily low maintenance dose of ASA 75-150 mg, unless specifically contraindicated. History of myocardial infarction Brilique™ 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event (see section 5.1). Treatment may be started without interruption as continuation therapy after the initial one-year treatment with Brilique™ 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of Brilique™ beyond 3 years of extended treatment. If a switch is needed, the first dose of Brilique should be administered 24 hours following the last dose of the other antiplatelet medication.
Method of administration and dosage	Ticagrelor is an oral treatment and the licensed dose for this indication is 60mg twice daily.

1.3 Summary of the clinical effectiveness analysis

Ticagrelor is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents ADP-mediated $P2Y_{12}$-dependent platelet activation and aggregation. Ticagrelor also inhibits adenosine reuptake via the Equilibrative Nucleoside Transporter 1 (ENT1). It has a rapid onset of anti-platelet effect, low variability and reversibility that results in a faster onset of action compared with thienopyridines as well as a faster offset of action with more rapid recovery of platelet function. Ticagrelor 90 mg BID is licensed for use with low-dose ASA (following a loading dose of 180 mg) for the prevention of atherothrombotic events in patients with ACS for 12 months from the index event unless discontinuation is clinically indicated.

Between 2010 and 2014, the PEGASUS-TIMI 54 study (The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin), a randomised, double-blind , placebo-controlled, 3 arm parallel group study, investigated whether long-term therapy with ticagrelor on a background of low-dose aspirin, reduced the risk of major CV events compared to placebo plus low-dose aspirin in patients who have had a history of myocardial infarction and are at a high risk of developing atherothrombotic events. Over 21,000 eligible patients in 31 countries (including 647 from the UK) were randomised to receive either ticagrelor 90 mg BID, ticagrelor 60 mg BID or placebo on a background of low-dose aspirin. Patients had experienced a spontaneous MI 1 to 3 years before enrolment, were aged ≥50 years, and all had at least one additional risk factor (age ≥ 65 years, >1 prior MI, multi-vessel CAD, diabetes or chronic non-end stage renal dysfunction). The primary efficacy endpoint was the composite of CV death, MI, or stroke, while the primary safety endpoint was TIMI major bleeding.

Following completion of the study an application was made to EMA to extend the existing marketing authorisation for a new strength of ticagrelor (60 mg dose) with a new indication for the prevention of atherothrombotic events in adult patients with a history of MI (MI occurred at least 1 year ago) and a high risk of developing an atherothrombotic event. As a result, the observations for the ticagrelor 90 mg BID arm of PEGASUS-TIMI 54 are not presented as part of this submission.

Results

PEGASUS-TIMI 54 demonstrated that ticagrelor 60 mg BID significantly reduced the incidence of the composite primary efficacy endpoint of CV death, MI or stroke compared with placebo in high risk patients with a history of MI. The ITT analysis of the primary composite endpoint events in the full study population (1.27% ARR at 36 months; HR 0.84; 95% CI 0.74 to 0.95; p=0.0043) are shown in Table 3. Each individual component contributed to the reduction in the primary composite endpoint. The clinical relevance of the results is further supported by the consistent findings over time, across other clinical endpoints, and across patient subgroups.

As expected, ticagrelor 60 mg BID increased the risk of TIMI Major bleeding compared with placebo, although there was no impact on the rates of fatal bleeding or intracranial haemorrhage (ICH). This observed increased risk was driven by a higher frequency of other TIMI major bleeding events (e.g. gastrointestinal bleeds). The on-treatment (OT) analysis of the primary safety endpoint is shown in Table 3 (1.20% ARI at 36 months; HR 2.32; 95% CI 1.68 to 3.21; p<0.001). There was no apparent heterogeneity among major subgroups.

When comparing the efficacy and safety of a drug, it is often useful to use comparable analyses, i.e. use the OT analyses for both outcomes. The OT analysis of the primary composite efficacy endpoint demonstrated a greater reduction in the number of events that occurred in the ticagrelor 60 mg BID group compared with the placebo group (1.62% ARR at 36 months; HR 0.78; 95% CI 0.68 to 0.90; p=0.0006).

The primary efficacy and safety endpoints present an initial perspective on the benefit-risk profile (net clinical benefit (defined as time from randomisation to first occurrence of any event from the composite of: CV death, MI, stroke or TIMI major bleeding) of HR = 0.95, 95% CI; 0.85 – 1.06). Further assessment of the benefit-risk profile focused on events with the most severe consequences, i.e. endpoints that measure the risk of death or “irreversible harm” to the patient. In the context of this study, the ‘benefit’ events of the greatest clinical importance were CV mortality, MI, and stroke, which are considered against the risks of fatal bleeding and intracranial haemorrhage. This analysis demonstrated a reduction in the event rate for ticagrelor 60 mg BID compared with placebo: HR 0.87 (95% CI 0.78, 0.97).

In summary, for the full population of the PEGASUS-TIMI 54 study, when the benefits of reducing the risk of further ischaemic events are weighed against the risk of an increase in fatal bleeding/intracranial haemorrhage, a favourable benefit:harm profile is demonstrated for ticagrelor 60 mg BID.

Key pre-specified subgroups of interest

Two pre-specified subgroup analyses related to time since qualifying MI and time from ADP receptor inhibitor withdrawal indicate that the benefit of ticagrelor may be greatest in patients <2 years from their last MI or in patients continuing on or re-starting after only a brief interruption of ADP receptor inhibition (Table 3). These analyses supported the final wording in the EMA licence for ticagrelor 60 mg BID which recommends use in eligible patients without interruption as continuation therapy after an initial one-year treatment with a previous ADP receptor inhibitor.

The focus of this submission is on patients who had an MI <2 years ago. The licence (as described in Section 1.2) focusses eligibility on those patients for whom the benefit:harm profile was most favourable in the PEGASUS-TIMI 54 study and allows it to be used in MI ≤2 years or ≤12 months since last ADP inhibitor treatment. As such, the licence allows ticagrelor 60 mg BID to be initiated in patients who were beyond 2 years from MI but within 1 year of treatment with a previous ADP receptor inhibitor. Based on clinical practice in England, we believe there to be very few such patients, so it is most relevant to focus solely on patients who experienced an MI <2 years ago. Feedback from UK cardiologists indicates that when considering a strategy of prolonged DAPT in high-risk patients, ticagrelor 60mg BID will be used as “continuation therapy” following an initial one-year treatment with an ADP receptor inhibitor as described in the licence (see Section 1.2).

Analysis of the net clinical benefit in patients with MI <2 years ago showed that the risks associated with ticagrelor 60mg BID are outweighed by the benefits (HR = 0.86, 95% CI; 0.75, 0.99). However this analysis gives equal weighting to the primary safety and efficacy endpoints; TIMI major bleeds and CV death, MI or stroke. Assessment of the most severe consequences (i.e. CV death, MI, stroke, fatal bleeding and intracranial haemorrhage) demonstrated a reduction in the irreversible harm event rate for ticagrelor 60mg BID compared with placebo: HR 0.81 (95% CI 0.71, 0.94).

In summary, for the subgroup of licensed patients who experienced a MI <2 years ago (base case population), when the benefits of reducing the risk of further ischaemic events are weighed against the risk of an increase in bleeding, a favourable benefit:harm profile is demonstrated for ticagrelor 60 mg BID when compared with placebo, irrespective of whether harm is defined as fatal bleeding/intracranial haemorrhage or as TIMI major bleeding.

These results support the use of ticagrelor 60 mg BID, when initiated for up to 3 years treatment duration in conjunction with aspirin, in patients with a history of MI (<2 years ago) and a high risk of developing an atherothrombotic event, including use as continuation therapy after the initial one year of dual antiplatelet treatment with an ADP receptor inhibitor therapy.

Table 3: Primary efficacy and safety endpoints for the PEGASUS-TIMI 54 population and key pre-specified subgroups within the licensed population (ticagrelor 60 mg BID compared to placebo on a background of low-dose ASA)

	Composite primary efficacy endpoint: CV death, MI or stroke (ITT analysis)			**Primary safety endpoint: TIMI major bleeding (on treatment (OT) analysis)**		
	HR (95% CI)	**Absolute Risk Reduction (%)**	**P value**	**HR (95% CI)**	**Absolute Risk Increase (%)**	**P value**
PEGASUS-TIMI 54 full analysis set (Randomised patients)	**0.84 (0.74-0.95)**	**1.27**	**0.0043**	**2.32 (1.68-3.21)**	**1.20**	**<0.001**
Licensed subgroups						
Subgroup: MI <2 years ago (base case)	**0.77 (0.66-0.90)**	**1.90**	**0.001**	**2.05 (1.38-3.03)**	**1.20**	**0.0004**
Subgroup: <30 days since ADP inhibitor withdrawal	0.76 (0.62-0.93)	1.90	0.0075	3.37 (1.85-6.16)	2.0	<0.0001
Subgroup: 30 days – 1 year since ADP inhibitor withdrawal	0.81 (0.65-1.01)	1.60	0.0584	2.92 (1.65-5.19)	1.50	0.0003
Subgroups containing un-licensed patients						
Subgroup: MI ≥2 years ago	0.96 (0.79, 1.17)	0.1	0.6945	3.17 (1.76, 5.70)	1.50	0.0001
Subgroup: >1 year since ADP inhibitor withdrawal	1.08 (0.82, 1.42)	-0.2	0.5726	2.12 (1.05, 4.25)	1.00	0.0355

Note that values for subgroups based on time since ADP inhibitor withdrawal differ from those in peer-reviewed article due to calculation differences.

Indirect comparison against clopidogrel + ASA

The scope provided by NICE asked for comparison against clopidogrel + ASA as well as against ASA alone. However, there are no head-to-head data for ticagrelor 60mg BID + low dose ASA vs clopidogrel + low dose ASA. After thorough assessment via both an independent agency specialising in systematic literature reviews & network meta-analysis, it was concluded that it is not feasible to formulate a robust indirect comparison of ticagrelor 60mg BID + low dose ASA vs clopidogrel + ASA, owing to key differences between the 3 main studies in this setting; PEGASUS-TIMI 54 trial, post-hoc analysis of the prior-MI patients in the DAPT trial and post-hoc analysis of the prior-MI patient sub-population in the CHARISMA trial. If an indirect comparison were conducted it would be necessary to assume that relative treatment effect is not impacted by (among other things):

- Duration of prior antiplatelet therapy
- Time since cessation of prior antiplatelet therapy
- Time since prior MI and type of MI experienced
- Experience of multiple different prior events (MI, stroke or PAD)
- Differences in age, smoking, diabetes status, incidence of hypertension (all known risk factors for cardiovascular events)
- Previous PCI (and type of stent)

These are only the main reasons - the complete list can be found in the main body of the submission. It is not considered clinically appropriate to make such assumptions and therefore indirect comparison would be highly unsafe and has not been conducted. This decision has been validated by an advisory board of clinical and statistical experts and the same conclusion was also reached by the authors of the review supporting the recent update to ACC/AHA guidelines on long term DAPT following an MI.

1.4 Summary of the cost-effectiveness analysis

Approach to cost-effectiveness analysis

An Excel-based cost-utility analysis model has been developed in line with the NICE reference case (1). The objective of the model is to reflect the PEGASUS-TIMI 54 trial, which used a composite endpoint of CV death/MI/stroke as the primary efficacy

outcome. Within the model, each of the components of the composite endpoint are modelled individually in a competing risks framework, such as that used in the Scottish Cardiovascular Disease (CVD) Policy model (2). The principal advantage of using a competing risks framework is that it allows for different impacts (coefficients) of characteristics for each separate endpoint. For example, systolic blood pressure may be expected to be more important for cerebrovascular disease than for coronary heart disease outcomes, as was evident in the Scottish CVD Policy model. For this reason, this approach is considered most appropriate to reflect the risks of each event in the PEGASUS-TIMI 54 trial. Furthermore, the risk equations are used to model individual events directly, rather than composite events which are then apportioned using the probability of that event being of a certain type. For this reason, fewer assumptions are made in the modelling process.

Individual patient data, collected from the 21,162 patients who entered the trial, has been used to inform the risk equation for each endpoint considered by the model. The log–logistic function has been chosen to model first CV-related events for the base case, owing to goodness of fit with the observed data and the expectation that CV risk will be highest initially following the qualifying MI and diminish over time. Adverse events, consisting of TIMI bleeding events (major and minor) and dyspnoea (grades 3-4 and grades 1-2) are captured in the model.

In the base case, utility valuations for health states, events and adverse events are informed by more than 118,000 EQ-5D questionnaire responses collected directly from patients within the PEGASUS-TIMI 54 trial and valued using UK public preferences. Costs for health states, events and adverse events are sourced from Evidence Review Group developed models associated to previous NICE technology appraisals for oral antiplatelets, inflated to 2015 prices.

The base case considers patients with a MI <2 years ago and a ticagrelor 60mg BID treatment duration of up to 3 years, aligned with median follow-up in the trial of 33 months. A discount rate of 3.5% is applied for both costs and quality-adjusted life years (QALYs) and the model uses a lifetime (40 years) time horizon, in line with the reference case. Uncertainty is explored via deterministic and probabilistic sensitivity analyses.

Cost-effectiveness analysis is presented vs. ASA monotherapy only, owing to key differences between trials rendering robust indirect comparison to clopidogrel + ASA infeasible.

Cost-effectiveness results

The results of the cost-effectiveness analysis are shown in Table 4 below. For the base case population, the deterministic incremental cost-effectiveness ratio (ICER) for ticagrelor 60mg BID + low dose ASA vs. low dose ASA monotherapy is £20,098 per QALY.

Table 4: Deterministic incremental cost-effectiveness results – Base case (MI <2 years)

Technology (and comparators)	Low dose ASA monotherapy	Ticagrelor 60mg BID + low dose ASA
Total costs	£13,019	£14,443
Total life years	12.2453	12.3363
Total QALYs	9.2034	9.2742
Incremental costs	-	£1,434
Incremental life years	-	0.0909
Incremental QALYs	-	0.0708
ICER versus baseline	-	£20,098
Incremental analysis	-	£20,098

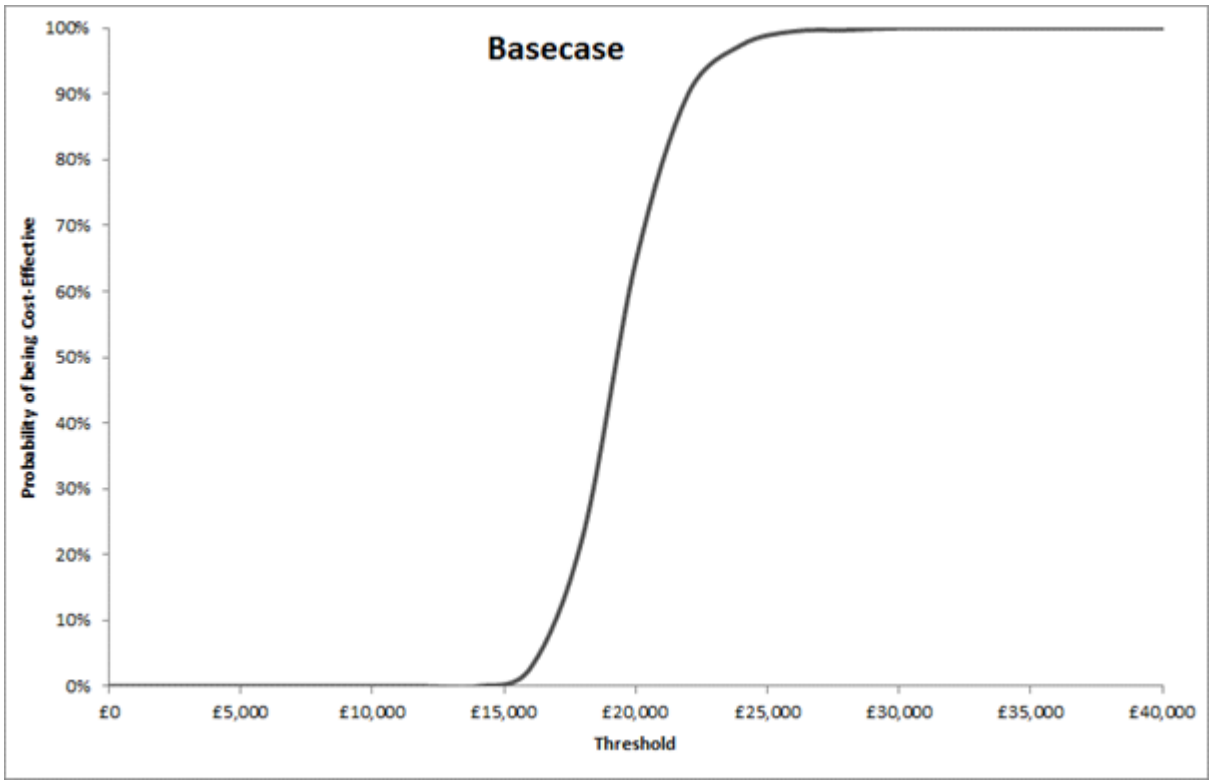
Probabilistic sensitivity analysis, which considers a representative patient profile and considers all of the risk equations within the model to be probabilistic, yields a mean ICER of £19,275 and illustrates that at a willingness-to-pay (WTP) of £20,000 per QALY, ticagrelor 60mg BID + low dose ASA has a 64.6% probability of being cost-effective vs. low dose ASA monotherapy, increasing to 100% at a WTP of £30,000 per QALY, based on the individual patient profile that yields the ICER closest to that of the base case cohort as a whole. The cost-effectiveness acceptability curve can be seen in Figure 1.

The deterministic sensitivity analysis showed that the ICER was most sensitive to the distributions chosen to extrapolate the risk equations for CV events beyond the length of the trial, especially the use of the Weibull and Gompertz functions, which render the ICER for ticagrelor 60mg BID + low dose ASA to be >£30,000. However

for these functions risk continues to increase over time, which is counter to clinical rationale that risk will be highest initially following the qualifying MI and diminish over time.

The ICER remains below £30,000 across all scenario analyses conducted for the population of interest, including the exploration of alternative starting ages, input values for utilities, costs and non-CV related mortality and alternative scenarios regarding the setting for the initiation of ticagrelor 60mg BID.

Figure 1: Base-case PSA CEACs (MI <2 years ago)



2 The technology

2.1 Description of the technology

Generic name: Ticagrelor

Brand name: Brilique™

Approved name: Brilique 60 mg film-coated tablets.

Therapeutic class: Platelet aggregation inhibitors excluding heparin.

ATC code: B01AC24 ticagrelor.

Mechanism of action

Ticagrelor was discovered and developed in the UK and is a direct-acting $P2Y_{12}$ receptor antagonist that has a different mechanism of action than the thienopyridines. Ticagrelor, one of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines (CPTP), is the first reversibly binding oral adenosine diphosphate (ADP) receptor antagonist. It is a selective ADP-receptor antagonist acting on the $P2Y_{12}$ ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor does not interact with the ADP binding site itself, but interacts with platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction. Ticagrelor also inhibits adenosine reuptake via the Equilibrative Nucleoside Transporter 1 (ENT1).

2.2 Marketing authorisation/CE marking and health technology assessment

Marketing Authorisation

The European Medicines Agency (EMA) Committee for Medicinal Products for Human use (CHMP) adopted a positive opinion on 18th December 2015 and Marketing Authorisation was granted on 19th February 2016. Ticagrelor 60mg has been available in the UK since March 2016. The SmPC is provided in a PDF format.

Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

Brilique 60 mg twice daily (with a daily low maintenance dose of ASA 75-150 mg, unless specifically contraindicated) is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event (age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multi-vessel CAD, or chronic non-end-stage renal dysfunction). Treatment may be started without interruption as continuation therapy after the initial one-year treatment with Brilique 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of Brilique beyond 3 years of extended treatment.

Main issues discussed by EMA

According to the EPAR, the PEGASUS-TIMI 54 study design (i.e. a randomised, double-blind, placebo-controlled, 3-arm parallel group study) was considered appropriate to evaluate the primary objective to compare the effect of long-term treatment with ticagrelor 90 mg BID and 60mg BID vs. placebo on a background of ASA (75 to 150 mg daily) on the event rate of the composite of CV death, non-fatal MI, or non-fatal stroke in patients with history of MI and high risk of developing atherothrombotic events. The use of two different doses of ticagrelor was also considered acceptable, allowing comparison of the optimal dose in terms of efficacy and bleeding risk and the background therapy of only ASA was considered common practice.

There was one global amendment to the clinical study protocol which occurred after the start of the study to stop patients with history of prior ischaemic stroke from receiving study drug. The primary reason for this amendment was emerging data from studies of other antiplatelet drugs (none of them ticagrelor) suggesting that more intensive antiplatelet therapy might pose high risk of intracranial haemorrhage (ICH) in patients with a history of ischaemic stroke (3, 4). This amendment to the

study (approximately 4 months following first patient randomised) directed that 102 (0.5%) patients with history of stroke be discontinued from study drug.

Based on the efficacy and safety data from PEGASUS-TIMI 54, 60 mg BID for use in patients with a history of the MI at high risk of atherothrombotic events was the proposed recommended dose and new indication in the application by AstraZeneca. In the course of the CHMP review of the application, a concern was raised regarding the net clinical benefit of ticagrelor 60 mg BID in patients with old MI (greater than 2 years after the onset of the qualifying MI) compared to those with more recent MI (< 2 years) and according to time since previous ADP receptor inhibitor withdrawal. As a result, the eligible patient population (as defined in Section 4.2) was restricted to patients within 2 years since their most recent MI or within 1 year since stopping their previous ADP inhibitor treatment.

A number of post hoc subgroup analyses were conducted to investigate further the relationship of age and multiple qualifying risk factors (for future thrombotic events) on outcomes. Firstly, the observation of a possibly diminished effect of age above 65 years was judged to be likely due to random variation. Secondly, across all subgroups of patients with single or multiple qualifying risk factors the relative treatment effect was approximately similar, without any obvious outliers. However, this potential increase in benefit appeared to be aligned with an increased risk of TIMI major bleedings, and the low number of bleeding events prohibited strong conclusions being drawn. In conclusion, age and number of risk factors did not clearly identify subgroups of patients in which the benefit:harm balance might be better or worse, therefore restrictions of the intended patient group were not considered necessary.

Health Technology Assessments

A submission to the Scottish Medicines Consortium for reimbursement in Scotland will be made in September 2016, with a final recommendation expected in January 2017.

2.3 Administration and costs of the technology

Table 5: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Film-coated tablet	(5)
Acquisition cost (excluding VAT) *	List price: £54.60 for a 28 day pack. Patients taking ticagrelor should also take a daily low maintenance dose of ASA 75-150 mg, unless specifically contraindicated.	(5)
Method of administration	Oral	(5)
Doses	60mg	(5)
Dosing frequency	Twice daily	(5)
Average length of a course of treatment	Median length of follow-up in the pivotal study was 33 months. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.	(6) (5)
Average cost of a course of treatment	£54.60/28 x 365.25 x 3 = £2,136.71	Calculation based on maximum treatment duration of 3 years.
Anticipated average interval between courses of treatments	Repeated courses are not anticipated.	(5)
Anticipated number of repeat courses of treatments	Not applicable - see above	
Dose adjustments	No dose adjustments are required. This includes the elderly population and those with renal impairment or mild hepatic impairment.	(5)
Anticipated care setting	It is expected that initiation of DAPT and continuation of treatment beyond 12 months at 60 mg BID will be led by a cardiologist at the time of the qualifying MI event, while monitoring and follow-up will be led by primary care physicians.	

2.4 Changes in service provision and management

No additional tests or investigations are needed and there are no particular administration requirements for the technology. Patients taking ticagrelor should also take a daily low maintenance dose of ASA 75-150 mg, unless specifically contraindicated.

2.5 Innovation

The technology is not expected to produce substantial health-related benefits not already included in the QALY calculation.

3 Health condition and position of the technology in the treatment pathway

Myocardial infarction (MI) is a component of cardiovascular disease (CVD) which comprises cardiac disease, vascular diseases of the brain and peripheral arterial disease (PAD). MI is also grouped with unstable angina (UA) under the collective term acute coronary syndromes (ACS) (7). ACS is an acute form of coronary artery disease (CAD) that arises when ruptures in atherosclerotic plaques and thrombus development physically limit the blood supply to the heart muscle, often leading to chest pain and other symptoms of inadequate blood flow.(7, 8)

Pathologically, MI is defined as myocardial cell death due to prolonged ischaemia.(9) MI occurs when there is sudden impairment or interruption of blood flow to the myocardium, resulting in heart muscle injury. This is usually caused by a blockage due to a rupture of an atherosclerotic plaque and subsequent thrombus formation in the coronary arteries that supply blood to the myocardium (9).

Myocardial infarctions

There are two main types of MI:(9)

- ST-elevation myocardial infarction (STEMI)
- Non-ST-elevation myocardial infarction (NSTEMI)

ST elevation refers to a section on the electrocardiogram (ECG). Therefore, the diagnosis of these conditions is based on the results of an ECG and the analysis of specific blood marker levels.(9)

Although both STEMI and NSTEMI arise from the rupture of an atherosclerotic plaque, as described above, there are some differences. In a STEMI, a major coronary artery is completely occluded leading to elevated troponin levels,(10) whereas in NSTEMI, a major coronary artery is usually narrowed by a non-occlusive thrombus.(7) Initially, the prognosis is worse after STEMI than after NSTEMI.(11) However, at around 200 days the proportional mortality crosses so that longer-term mortality is worse for NSTEMI. Thus, NSTEMI becomes a risk factor for long-term mortality.

Stable coronary artery disease (SCAD) is generally characterised by episodes of reversible ischaemia/hypoxia which are commonly associated with transient chest discomfort (angina pectoris). SCAD also includes the stabilised, often asymptomatic, phases that follow ACS (12).

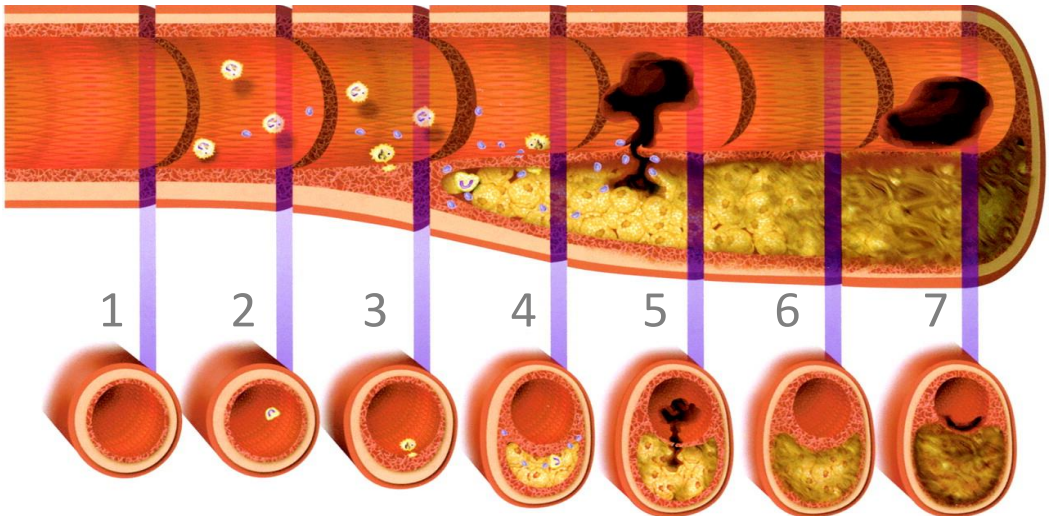
Atherosclerosis

MI generally develops from coronary atherosclerosis, a progressive disease which can affect multiple arterial beds (10). Figure 2 shows the events underlying the development of ACS starting from a normal artery to resorption of a thrombus.(7, 13) This process is known as atherothrombosis.(10)

An atherosclerotic lesion initiation typically occurs when endothelial cells, activated by risk factors such as hyperlipoproteinemia (abnormally elevated levels of lipids and/or lipoproteins in the blood) attract inflammatory leukocytes, namely macrophages and T lymphocytes.(13) During this process extracellular lipid begins to accumulate in the intima, the innermost layer of the artery. The lesion then evolves to the ‘fibrofatty stage’ (3), in which macrophages engulf lipoproteins and become lipid-laden foam cells. As the lesion progresses (4), the inflammatory events lead to a weakening and sometimes rupture of the fibrous cap (the outer layer of the plaque).(13)

If the fibrous cap ruptures (5), coagulation factors in the blood may gain access to the thrombogenic lipid core of the plaque, causing thrombosis or non-occlusive atherosclerotic plaque. When the thrombus resorbs (6), the healing response can lead to increased collagen accumulation and smooth muscle cell growth. In this manner, the fibrofatty lesion can evolve into advanced fibrous and often calcified plaque that may cause significant stenosis (7) (abnormal narrowing of a blood vessel, Figure 2).(13)

Figure 2: Initiation, progression and complication of human coronary atherosclerotic plaque (13)



Normal artery (1) and lesion initiation (2), lesion progression (3–4) to development (5) and finally resorption (6–7) of a thrombus.(7, 13)

Platelets play a key role in thrombosis and plaque formation, and platelet adhesion, activation and aggregation are established steps in thrombus formation.(14) It has also been shown that platelets contribute to all stages of atherothrombosis by producing inflammatory molecules(15) and interacting with many cells involved in the formation atherosclerotic plaques.(16)

Risk factors for recurrent atherothrombotic events

The main risk factors for recurrent atherothrombotic events include:

- Diabetes mellitus
- Recurrent MI
- Multi-vessel coronary artery disease
- Chronic non-end stage renal disease (creatinine clearance <60 ml/min)
- Older age (≥ 65 years)

The presence of these risk factors is common in post MI patients. Real-world data from studies across four countries (England, France, Sweden and the US) show that a considerable number of post MI patients have diabetes (23.2% to 48.9%), history of >1 prior MI (9.7% to 14.4%) and history of renal disease (5.4% to 11.2%); see

Table 6.(17-19) Older age (≥65 years) was also common in these patients (54.5% to 70.3%, excluding the Medicare population).(17).

Although each of these risk factors are associated with increased risk of further atherothrombotic events, patients commonly experience several of them; one study assessing 7,238 patients with MI who remained event-free 12 months found that 76.2% of patients (n=5,512) had ≥1 of the risk factors outlined above.(20)

Patients with CAD often have evidence of atherosclerotic lesions in other parts of the coronary vasculature and in other vascular beds (21, 22). Furthermore, according to the PROSPECT study, a prospective study of the natural history of atherosclerosis over 3 years in patients with ACS who underwent PCI, at least half of recurrent atherothrombotic events are likely to originate from a lesion outside of the initial culprit lesion(23).

Rate of subsequent events

Atherosclerosis and ischemic CV diseases like coronary artery disease (CAD) are progressive systemic disorders and patients with an established history of atherothrombotic disease are at particular risk of future cardiac or cerebral events, and vascular death.

Following an MI, although the highest risk of subsequent CV events occurs in the initial months, patients remain at significant long-term risk of recurrent events and mortality. Several studies have determined the long-term risk of further atherothrombotic events including death in history of MI patients; (11) The risk is shown to be continuous and linear for up to 5 years (24, 25); and ~1 in 5 patients with ACS will die within 5 years of their index event (26).

Analysis of data taken from the Swedish Acute Myocardial Infarction Statistics from 1969 to 2001 report that the mean time interval to recurrent MI was 30.3 months for women (median, 13.7; interquartile range [IQR], 3.4 to 41.6) and 39.5 months for men (median, 19.9; IQR, 4.8 to 57.9).(27)

Table 6: Prevalence of baseline risk factors in history of MI patients

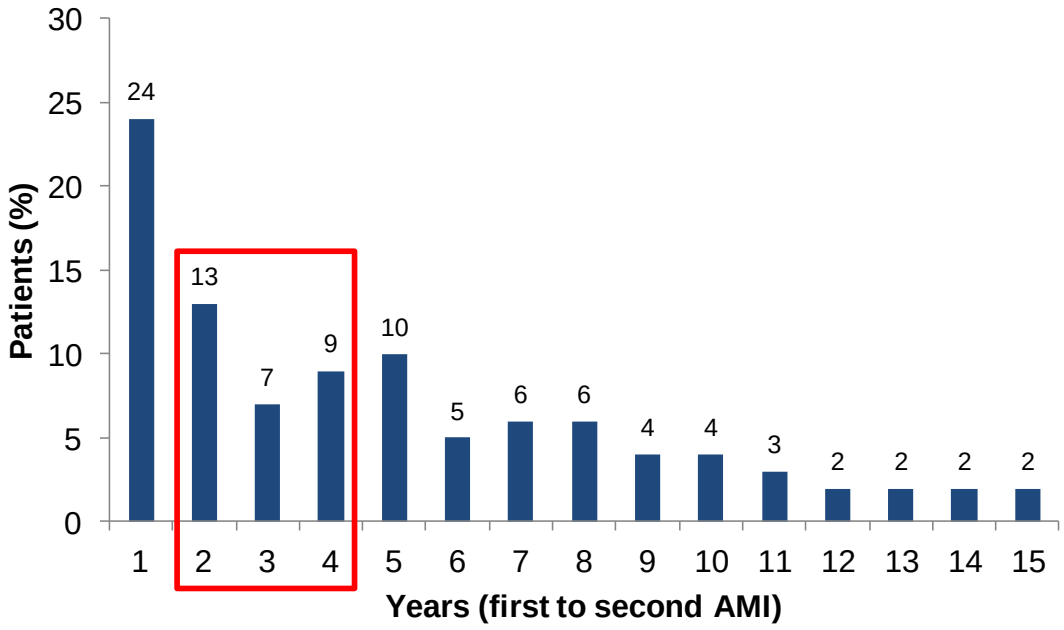
Risk factor	Country and reference					
	France (n=1,764) (17)	England (n=7,238) (17)	US (n=53,909) (17)	US† (n=13,492) (18)	US‡ (n=53,909) (19)	Sweden (n=77,976) (17)
Diabetes (%)	28.0	23.2	38.5	30.2	48.9	25.4
History of >1 MI (%)	13.5	12.2	11.7	9.7	12.0	14.4
Renal disease (%)	7.8	7.8	11.2	10.9	8.3	5.4
PAD (%)	0.4	7.2	10.5	5.2*	28.6	4.2

MI: myocardial infarction; PAD: peripheral arterial disease

† Patients were aged 65 years or under, ‡ Patients were aged 65 years or over, *Defined as peripheral vascular disease

Another study reported that 24% of recurrent MIs occurred within the first year after the initial event and approximately 29% of recurrent MIs occurred during years 2 to 4 (Figure 3).(28)

Figure 3: Proportion of patients who experience a recurrent MI 1 to 15 years from initial MI[28]



AMI: acute myocardial infarction

The APOLLO study programme used observational data from national registers and insurance claims databases to review the long-term incidence of CV events or death among patients surviving more than one year after a MI in 4 countries.(17)

The 3-year risk of atherothrombotic events has been assessed by the analysis of linked electronic health records and disease registries (England, Sweden) and administrative data (US, France) according definitions based on admission ICD-10 codes and common analysis protocol.(17) Patients were included in the study if they had experienced a prior MI, were at high risk of further atherothrombotic events and were alive with no further MI for 12 months following hospitalisation from 2002 to 2011. The total number of patients included in the analysis was 140,880.(17) Event rates remained high throughout follow-up with fairly constant risks per year. Large differences in the observed 3- year cumulative risk for MI, stroke or death across the countries were found (between 17.9% in France and 36.2% in US, Table 7). After

adjustments however, the differences in risk of MI/stroke/death across all four countries was reduced (between 16.7% in France and 21.3% in England, Table 7). There was a consistency across all four countries in the high level of risk of further MI, stroke, or death.

In conclusion, analysing hospital record data in the US and 3 European countries, including England, reveals a consistently high adjusted risk of death, further MI, and stroke in the chronic phase after MI. These data demonstrate that the morbidity burden for post MI patients continues beyond 12 months following the index event with approximately 1 in 5 patients who are event-free in the first year after an MI go on to suffer an MI, stroke or CV death within the subsequent 3 years.

Table 7: Observed and adjusted 3 year cumulative risk of MI, stroke and all-cause mortality in high-risk patients post MI[(17)]

Cumulative 3 year risk of MI, stroke, or death	Sweden n=77,976 % (95% CI)	England n=7,238 % (95% CI)	France n=1,757 % (95% CI)	US n=53,909 % (95% CI)
Observed	26.9 (26.5–27.2)	24.1 (22.7–25.5)	17.9 (16.01–19.8)	36.2 (35.7–36.6)
Adjusted	19.8 (19.4–20.2)	21.3 (18.2–24.2)	16.7 (14.3–19.2)	18.2 (17.6–18.9)

CI = confidence interval; MI = myocardial infarction

Oral antiplatelet treatment options used in the first year from MI

Treatment of atherothrombotic patients must include the management of cardiovascular risk factors and antiplatelet treatment for the prevention of thrombotic complications. The main aim of antiplatelet therapy is to prevent the occurrence of acute ischaemic events through inhibition of platelet thrombus formation.

Pharmacological platelet inhibition has long been a key strategy in the management of thrombotic conditions, including acute coronary syndromes (ACS). Aspirin (acetylsalicylic acid) is able to inhibit platelet aggregation by irreversibly inhibiting cyclooxygenase-1 (COX-1), leading to suppression of the release of thromboxane A2 (TxA2), a prothrombotic eicosanoid, from platelets. The efficacy of aspirin in the treatment and secondary prevention of ischaemic heart disease was established in the latter decades of the last century and has remained a central component of treatment ever since (29).

A second group of antiplatelet agents, the platelet $P2Y_{12}$ receptor antagonists ('$P2Y_{12}$ inhibitors'), have subsequently been used alongside aspirin in ACS management. The thienopyridines, ticlopidine, clopidogrel and prasugrel, act via active metabolites that bind selectively and irreversibly to $P2Y_{12}$, an ADP G-protein-coupled receptor (GPCR), found on the surface of platelets. This receptor plays a prominent role in amplifying platelet activation and sustaining platelet aggregation, leading to thrombus stabilisation and extension.

Ticlodipine is not in common use, but clopidogrel is still widely prescribed. However, several features can limit its effectiveness. Once administered, it has a relatively slow onset time (30) and must be converted to the active metabolite by a two-step hepatic CYP-dependent process which is subject to genetic variability. Pharmacogenomic analyses have identified loss of function alleles of CYP 2C19 to be the predominant genetic determinants of the variability in the antiplatelet activity of clopidogrel. Carriers of this variant have been shown to have a lower active metabolite levels, higher platelet reactivity and a higher rate of CV events (31-33).

Prasugrel, a third-generation thienopyridine, has advantages over clopidogrel of less variable levels of platelet inhibition and shorter time to optimum effect. Like clopidogrel, it is a prodrug but its metabolism does not significantly limit the speed of onset and there is no evidence of a resistant phenotype in the population (34), although dose-related inter-individual response variability occurs during maintenance therapy.

Reversibly binding ADP receptor inhibitors have also been developed, such as ticagrelor, which belongs to a novel chemical class, the cyclopentyl-triazolopyrimidines. Ticagrelor is an oral agent with an onset time of around 30 min in stable patients and offset of action over 2–5 days (35). Ticagrelor 90 mg BID is licensed for use to 12 months following an MI or unstable angina. Unlike the thienopyridines, ticagrelor also inhibits the clearance of adenosine through inhibition of Equilibrate Nucleoside Transporter-1 (ENT-1) and this may provide an additional mechanism for inhibition of platelet aggregation by increasing activation of the platelet adenosine 2A (A2A) receptor (36). Another class of reversibly binding ADP receptor inhibitors are analogues of ATP that include cangrelor, an intravenous drug

that allows very rapid onset and offset of platelet inhibition. These reversibly-binding inhibitors are active drugs that do not require metabolism to exert their effect.

Table 8: ADP receptor inhibitors (adapted from(37))

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine		cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral			Intravenous
Dose	300-600 mg, then 75mg qd	60 mg, then 10mg qd	180mg, then 90mg BID	30mcg/kg bolus and 4mcg/kg/min infusion
Binding reversibility	Irreversible		Reversible	
Activation	Prodrug with variable liver metabolism	Prodrug with predictable liver metabolism	Active drug, with additional active metabolite	Active drug
Onset of loading dose effect	2-6 hrs	30 mins		2 mins
Duration of effect	3-10 days	7-10 days	3-5 days	1-2 hours
Withdrawal before surgery	5 days	7 days	5 days	1 hour
Plasma half-life of active ADP receptor inhibitor	30-60 mins		6-12 hours	5-10 mins
Inhibition of adenosine reuptake	No		Yes	Yes (inactive metabolite only)

Antithrombotic treatment options with a licence for use beyond 12 months from an MI

Although a number of antiplatelet agents are approved for the reduction of atherothrombotic events in patients with ACS there are few agents that can be used beyond 12 months for patients with a history of MI.

Vorapaxar (Zontivity®), although it is not available in the UK, is licensed by the EMA in combination with aspirin, and where appropriate clopidogrel, as part of a triple therapy in patients with a history of MI.(38, 39) The EMA label states that vorapaxar

should be initiated at least 2 weeks after a MI and preferably within the first 12 months from the acute event.(38) Continued therapy beyond 24 months must be based on a re-evaluation of the individual benefits and risks.

Clopidogrel monotherapy is licensed for post MI patients for therapy initiated up to 35 days following the MI event with no restriction on the duration of treatment.(40)

The oral factor Xa inhibitor rivaroxaban(Xarelto®) is indicated, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers . Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited.(41)

Existing NICE guidance

Current NICE guidelines for the secondary prevention of MI, updated in November 2013, recommend that dual antiplatelet therapy for up to 12 months is offered to all individuals who have experienced an MI followed by ASA monotherapy indefinitely thereafter (Table 9).(42) Unless there is a high risk of bleeding, patients receiving anticoagulation therapy should continue to do so at the same time as receiving antiplatelet therapy (recommended therapies are aspirin or clopidogrel).

Table 9: Recommendations from NICE guidelines: secondary prevention of MI(42)

Therapy	Dose	Recommendation
Antiplatelet therapy		
Aspirin*	Not stated	Should be offered to all patients after an MI, with treatment continuing indefinitely, unless they are intolerant or contraindicated Aspirin should also be offered to those who had their MI >12 months previously, with therapy continuing indefinitely
Clopidogrel	Not stated	Should be offered for up to 12 months to those with NSTEMI (regardless of treatment) and STEMI (if they have received a bare-metal or drug-eluting stent) Should be used instead of aspirin in patients who also have other clinical vascular disease and who have: Had an MI and stopped dual antiplatelet therapy or Had an MI more than 12 months ago
Prasugrel	Not stated	Not yet incorporated
Ticagrelor	Not stated	90 mg BID (following a loading dose of 180 mg) is recommended in combination with low dose aspirin for <12 months in patients with ACS, but no recommendation

Therapy	Dose	Recommendation
		exists for MI Treatment should be continued for ≥1 month to <12 months for patients with STEMI

CV =: cardiovascular; MI =: myocardial infarction; NE =: no examples given

*Recommended for use >12 months

ESC guidelines for the management of ACS

In 2011, the European Society of Cardiology (ESC) published its recommendations on the management of NSTE-ACS and these have been subsequently reinforced in the 2015 NSTE-ACS guidelines (37).

- A loading dose of aspirin (150–300 mg) followed by 75–100 mg once daily (OD) and no higher (class I recommendation, level A evidence) is advised.
- In addition, an oral ADP receptor inhibitor is recommended for 12 months unless contraindications such as excessive risk of bleeding are present (ticagrelor and prasugrel are preferred over clopidogrel).
- Ticagrelor given as a 180 mg loading dose followed by 90 mg two times per day is recommended for those patients at high risk of further ischaemic events, for example, those with elevated cardiac biomarkers, regardless of whether or not a revascularisation strategy is planned (I,B).
- Prasugrel (60 mg loading dose followed by 10 mg OD) is recommended as an alternative only in patients in whom PCI is planned, that is, following coronary angiography (I,B).
- Clopidogrel (300–600 mg loading dose followed by 75 mg OD) should be reserved for those patients with contraindications to the newer agents (I,B) or who also require oral anticoagulation (I,B).
- If CABG is planned, withholding the ADP receptor inhibitor is recommended for 5 days (ticagrelor/clopidogrel) or 7 days (prasugrel), although shorter durations may be guided by platelet function testing in those at lower bleeding risk.

With regard to patients with ST elevation myocardial infarction (STEMI), the ESC published specific guidelines in 2012 (43). Once again, clinicians are given the option of using aspirin (I,B) in combination with

- ticagrelor (I,B) or
- prasugrel (I,B), although only an option in patients with no history of cerebrovascular accident (CVA)/transient ischaemic attack and age <75 years.
- Clopidogrel is only advised if the other agents are contraindicated (I,C).

Aspirin monotherapy is recommended after this 1-year period.

Eligible patients for treatment with 60mg ticagrelor BID

The expectation is that ticagrelor 60mg BID + ASA will be used as continuation therapy, following the initial one-year treatment with dual antiplatelet therapy following myocardial infarction, in patients with a high risk of an atherothrombotic event.

The number of hospital admissions for 'actual myocardial infarction' (ICD10 code; I21) in England in the year 2014/15 was 78,397 (44). Each is assumed to represent one patient. Of these patients, 90% are assumed to receive aspirin-based DAPT in the first year following MI (45). Of the resultant cohort, 67% are expected to remain CV event-free over the next year (17). For the purposes of the budget impact analysis, it is assumed that all of these patients remain on DAPT for the year following MI. Of these patients, 59% are expected to meet the PEGASUS-TIMI 54 inclusion criteria and not meet the exclusion criteria (17).

This yields the estimate for the annual number of incident continuation therapy ticagrelor 60mg-eligible patients to be 27,887.

Current clinical practice

The prescribing intention of the cardiologist, as described in the discharge letter, is the most appropriate record of current NHS management of oral antiplatelet (OAP) therapy in the post-MI setting and has been explored in 2 waves of market research conducted on behalf of AstraZeneca in June 2015 (Wave 1, soon after presentation

of the PEGASUS-TIMI 54 and DAPT results) and March 2016 (Wave 2, soon after approval of the extension to the licence for ticagrelor for use in the post-MI indication) (46).

A total of n=85 cardiologists in Wave 1 and n=115 in Wave 2 were invited to complete 10-15 retrospective patient records regarding adult patients who the cardiologist was treating for MI via a 30-minute online survey. Both clinical cardiologists and interventional cardiologists were recruited (Table 10) at random and screened upon entering the survey. Qualifying cardiologists had to have specialised in cardiology for 3-30 years, spend ≥60% of their time in direct patient care (vs. teaching, research etc.) and be responsible for writing discharge prescribing instructions to GPs for OAP therapies. The characteristics of the cardiologists surveyed were consistent in the two waves.

Table 10: Characteristics of cardiologists completing the survey in England & Wales

Cardiologist characteristics	**England and Wales (n=85)**	**England, Wales (n=135)**
	June 2015	**March 2016**
Region		
North of England, n (%)	29 (34)	44 (33)
Midlands and East of England, n (%)	23 (27)	34 (25)
London, n (%)	15 (18)	30 (22)
South of England, n (%)	14 (16)	25 (19)
Abertawe Bro Morgannwg University Health Board, n (%)	2 (2)	- (-)
BetsiCadwaladr University Health Board, n (%)	1 (1)	1 (0.5)
Cardiff & Vale University Health Board, n (%)	1 (1)	- (-)
Cwm Taf Health Board, n (%)	- (-)	1 (0.5)
Specialty		
Clinical cardiologist, n (%)	30 (35)	63 (47)
Interventional cardiologist, n (%)	55 (65)	72 (53)
Years specialised as Interventional/ Clinical cardiologist		
Mean, years, n	13.6	13.5
Median, years, (range)	12 (5-25)	13 (3-30)
Percentage of professional time spent in direct patient care*		
Mean, %	8570.00%	85.6
Median, % (range)**	85 (70-100)	90 (60-100)
Number of discharge instructions written for MI patients in a typical month		

Cardiologist characteristics	England and Wales (n=85)	England, Wales (n=135)
Mean, n	35.8	42.4

* Rather than teaching, research etc. Number documented is an approximate figure based on cardiologists' judgement

**Cardiologists had to spend at least 60% of their time in direct patient care to qualify for the study

*** The allowed range within the survey was 0-99

Cardiologists were asked to complete anonymised patient record forms for the last 10-15 adult patients that had been treated for MI and had been discharged to primary care with instructions to the patients' GP relating to OAP treatment; this patient selection criteria was included to avoid bias in the data collected. Cardiologists entered information on patient age, type of heart attack, revascularisation, presence of co-morbidities and patient medical history, as well as OAP treatment initiated and the intended duration of treatment as described in the patient's discharge letter.

Patient records were collected for all patients that had been treated for an MI, at analysis stage the patient population was sub-divided into PEGASUS-like and non-PEGASUS-like patient records according to the selection criteria for the PEGASUS-TIMI 54 trial (Table 11). It is recognised that there is a difference in time since MI between those patients considered in this study (recent MI) and those in the PEGASUS trial (MI 1-3 years ago), however the term "PEGASUS-like" is used for purposes of simplification. This study elicits cardiologists' OAP prescribing intentions beyond the first year since MI and thus captures the period considered by the PEGASUS-TIMI 54 trial.4

Table 11: PEGASUS-like patient criteria

Exclusion criteria (any one of the below)	Inclusion criteria (must be at least one of the below)
• ≤ 50 years old • History of ischaemic stroke • History of intracranial bleed or GI bleed(<6 months) • Treatment with antithrombotics (at time of MI currently described) • Planned coronary, cerebrovascular, or peripheral arterial revascularisation • Aspirin intolerance	• ≥ 65 years old • Diabetes requiring medication • Previous spontaneous MI (prior to the MI currently described) • Multivessel coronary artery disease • Chronic non-end-stage renal disease

A total of 2661 patient records were collected across England and Wales in 2 separate surveys; of these, n=946 (36%) patient records fit the PEGASUS-like criteria and form the basis of the analysis. Of the patient records collected, the proportions excluded in line with the PEGASUS exclusion criteria and considered "low risk" i.e. not meeting the PEGASUS inclusion criteria, were consistent across to the 2 surveys (Table 12).

Table 12: Patients included in the study and proportion of the sample fitting the PEGASUS-like criteria

Survey date	Jun 2015	March 2016
Patient records collected	850	1811
Patients excluded due to not meeting the PEGASUS inclusion criteria	433 (51%)	1016 (56%)
Patients excluded due to being 'low risk'	102 (12%)	164 (9%)
PEGAUS-like patient records	315 (37%)	631 (35%)

The baseline characteristics of the patients described as PEGASUS-like in this market research were found to be consistent in the 2 waves of research, but differ from the patients recruited for the PEGASUS-TIMI 54 study in terms of age (UK patients are older) and type of qualifying MI (NSTEMI more prevalent than STEMI) and proportion with diabetes (Table 13).

Table 13: Characteristics of PEGASUS-like Patients in England, Wales compared with baseline characteristics in the PEGASUS-TIMI 54study

Patient Characteristics	England and Wales June 2015 (N=315)	England and Wales March 2016 (N=631)	PEGASUS-TIMI 54 study (N=21,162)
Age, y, median (IQR)	71 (65-78)	71.1 (65-77)	65 (59-71)
Qualifying –NSTEMI, n (%)	180 (57)	361 (57)	(41)
Qualifying –STEMI, n (%)	135 (43)	270 (43)	(54)
Qualifying –MI, type unknown (%)	-	-	(5)
Age ≥ 65 years, n (%)	256 (81)	504 (80)	(55)
Diabetes requiring medication, n (%)	139 (44)	273 (43)	(28)
Previous spontaneous MI	51 (16)	87 (14)	(17)

(prior to current), n (%)			
Multi-vessel CAD, n (%)	104 (33)	230 (36)	(59)
Chronic non-end stage renal disease, n (%)	34 (11)	86 (14)	(6)
Peripheral arterial disease, n (%)	24 (8)	68 (11)	(5)

Of 946 PEGASUS-like patients, 855 (90%) were prescribed DAPT at discharge (Table 14). Ticagrelor + ASA was the most frequently prescribed regimen at discharge and was prescribed to 421 (45%) patients, followed by clopidogrel + ASA which was prescribed in 366 (39%) cases. Only 88 (9%) patients were prescribed a monotherapy OAP regimen, where in two-thirds of cases the agent was ASA. These prescribing behaviours were consistently observed in both waves of the market research.

For the great majority of patients in both waves of the research, the second OAP or ADP receptor inhibitor was to be stopped at 12 months after discharge, meaning that beyond 12 months, 843 (89%) patients were prescribed ASA monotherapy, 15 (2%) clopidogrel monotherapy and 43 (5%) were prescribed no oral antiplatelet treatment. A small number of patients were recommended to remain on DAPT: 32 (3%) on clopidogrel + ASA, 9 (1%) on ticagrelor + ASA and 4 (>1%) on prasugrel + ASA (Table 14).

Table 14: Cardiologist prescribing intentions for PEGASUS-like Patients in England and Wales

	England and Wales (N=315)	**England, Wales (n=631)**	**Combined (n=946)**
Therapy at discharge	**Jun 2015**	**March 2016**	**-**
ASA monotherapy, n (%)	17 (5)	44 (7)	61 (6)
clopidogrel monotherapy, n (%)	11 (3)	12 (2)	23 (2)
clopidogrel + ASA, n (%)	123 (39)	243 (39)	366 (39)
prasugrel + ASA, n (%)	18 (6)	50 (8)	68 (7)
ticagrelor + ASA, n (%)	145 (46)	276 (44)	421 (45)
clopidogrel + ticagrelor, n (%)	1 (0)	1 (0)	2 (0)
prasugrel monotherapy	-(-)	2 (0)	2 (0)
ticagrelor monotherapy	-(-)	3 (0)	3 (0)
Treatments patients receive post 12 months			

ASA monotherapy, n (%)	281 (89)	562 (89)	843 (89)
clopidogrel monotherapy, n (%)	6 (2)	9 (1)	15 (2)
clopidogrel + ASA, n (%)	8 (3)	24 (4)	32 (3)
prasugrel + ASA, n (%)	2 (1)	2 (0.3)	4 (0)
ticagrelor + ASA, n (%)	3 (1)	6 (1)	9 (1)
No oral antiplatelet prescribed, n (%)	15 (5)	28 (4)	43 (5)

NICE guidelines state that patients should remain on aspirin “indefinitely” (47) and SIGN guidelines state patients should remain on aspirin “long term” (48). In concordance with this, 89% of PEGASUS-like patients were set to receive aspirin monotherapy in the post 12 month setting, with 5% of patients receiving no therapy at all post 12 months: only 2% of PEGASUS-like patients were recommended to receive clopidogrel + ASA beyond the initial 12 month acute phase of treatment.

A key strength of the study design for this research is that the cardiologists taking part were not required to apply any selection criteria to their pool of patients before reporting their prescribing intentions. Rather, they were asked to record the background characteristics for all patients who had experienced a qualifying MI. This approach is expected to have reduced the potential for selection bias by the cardiologists.

The key limitation of this study is that it is based on the treatment intention of the cardiologist as described in the discharge letter, rather than what the patient actually received in practice. It is unclear how closely those instructions were followed in the primary care setting following discharge and there are many reasons why patients may be switched from one drug to another, treatment prolonged or stopped sooner than recommended by the cardiologist.

Conclusion

The prescribing intention data collected in this survey confirms that prescribing to PEGASUS-like patients is 12 months DAPT followed by (lifelong/indefinite) use of aspirin; this is in accordance with both marketing authorisations for the antiplatelet treatment options considered, as well as recommendations from both NICE guidance and international professional guidelines. 90% of PEGASUS-like patients in England and Wales received ASA monotherapy in the 12 months post-MI setting and it can

therefore be concluded that ASA monotherapy represents established clinical practice in the NHS for these patients.

Equality issues

We are not aware of any equality issues concerning the use of ticagrelor in patients with a history of MI.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy, tolerability and safety of prolonged DAPT (ticagrelor, clopidogrel, prasugrel, vorapaxar in combination with aspirin) including rivaroxaban in adult patients with a history of MI in September 2014. This review was updated in January 2015 and again in December 2015. The list of potential treatments/comparators in the search strategy was deliberately broad to facilitate the generation of a network of studies which could provide a comparison of ticagrelor against the treatment regimens in the final scope (i.e. clopidogrel + ASA).

Search strategy

To identify relevant RCTs for inclusion a literature search was performed on the 8th of September 2014. No date restrictions were imposed on the searches. An updated search was conducted on the 6th of January 2015 to identify potentially eligible studies which may have been published subsequent to the date of the original search. The following databases were searched via OVID and the Cochrane library:

- MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present (via OVID)
- Embase, 1980 to present (via OVID)
- The Cochrane Library, via the OVID platform, incorporating;
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- The Health Technology Assessment Database (HTA)
- Cochrane Database of Systematic Reviews (Cochrane Reviews)
- Database of Abstracts of Reviews of Effects(DARE)

A detailed search strategy was developed to identify all relevant published and unpublished RCTs. The full search strategies used, text words (free text), subject index headings (for example, MeSH) and the relationship between search terms (for example, Boolean), are provided in Appendices 2.1-2.3 for the original and updated searches.

Searching other resources

Clinical trial registers and conference proceedings were examined to identify ongoing and as yet unpublished RCTs

Clinical trial registry

The following clinical trial registers were searched:

- EU clinical trials register
- ClinicalTrials.gov
- The Australian New Zealand Clinical Trials Registry (ANZCTR)
- World Health Organisation (WHO) international clinical trials registry platform (ICTRP)

Conference proceedings

The following conference proceedings were searched over the last 3 years:

- European Society of Cardiology: http://www.escardio.org/Pages/index.aspx
- American Heart Association [AHA]: http://www.heart.org/HEARTORG/
- American College of Cardiology: http://content.onlinejacc.org/

Additional hand searching

References of all identified studies, review articles, and poster presentations were also examined.

Study selection

Studies (published or unpublished) that randomized adult patients with previous MI (STEMI or NSTEMI) with at least 18 months duration of dual anti-platelet therapy were considered for inclusion in this review. Studies were excluded if they were not truly randomized, patients had no previous history of MI and did not receive prolonged (at least 18 months) dual anti-platelet therapy (Table 15).

Table 15: Eligibility criteria for study inclusion

	Inclusion criteria	Exclusion criteria
Population	Adult patients with previous MI (STEMI or NSTEMI) occurring prior to study randomisation with ≥18 months of DAPT received between randomisation and study completion/results reporting	Patients without a previous MI or receiving DAPT for <18 months
Interventions	DAPT (comprising ticagrelor, clopidogrel, prasugrel, vorapaxar, or rivaroxaban in combination with aspirin)	-
Comparators	Placebo Monotherapy Triple therapy	-
Outcomes	Efficacy: • Composite of CV death, MI or stroke (total, fatal, non-fatal) • CV death • MI (total, fatal, non-fatal) • Stroke (total, fatal, non-fatal) • All-cause mortality • Composite of CV death or coronary or cerebrovascular arterial thrombosis hospitalisation • Composite of coronary heart disease death, MI or stroke • Coronary stent thrombosis • QoL Safety, including but not limited to: • Dyspnoea • TIMI-defined major/minor bleeding • PLATO-defined major bleeding • GUSTO-defined major/minor bleeding	-
Study design	RCTs: blinded, open-label, open-label extensions of parallel group trials, phase 2 and above	-
Language restrictions	No restriction	-

Abbreviations: CV,: cardiovascular; DAPT,: dual anti-platelet therapy; GUSTO,: Global Use of Strategies to Open Occluded Coronary Arteries; MI,: myocardial infarction; NSTEMI,: non-ST segment elevation myocardial infarction; PLATO,: Platelet Inhibition and Patient Outcomes; QoL,: quality of life; RCT,: randomised controlled trial; STEMI,: ST segment elevation myocardial infarction; TIMI,: Thrombolysis in Myocardial Infarction.

Titles and abstracts identified were assessed using the inclusion criteria outlined in Table 15. Non-relevant studies were excluded on 1st pass, and studies for potential

inclusion were retrieved for full review on 2nd pass. A log of excluded studies at 2nd pass, along with reason(s) for exclusion are provided in Appendix 2.5 (Table 4).

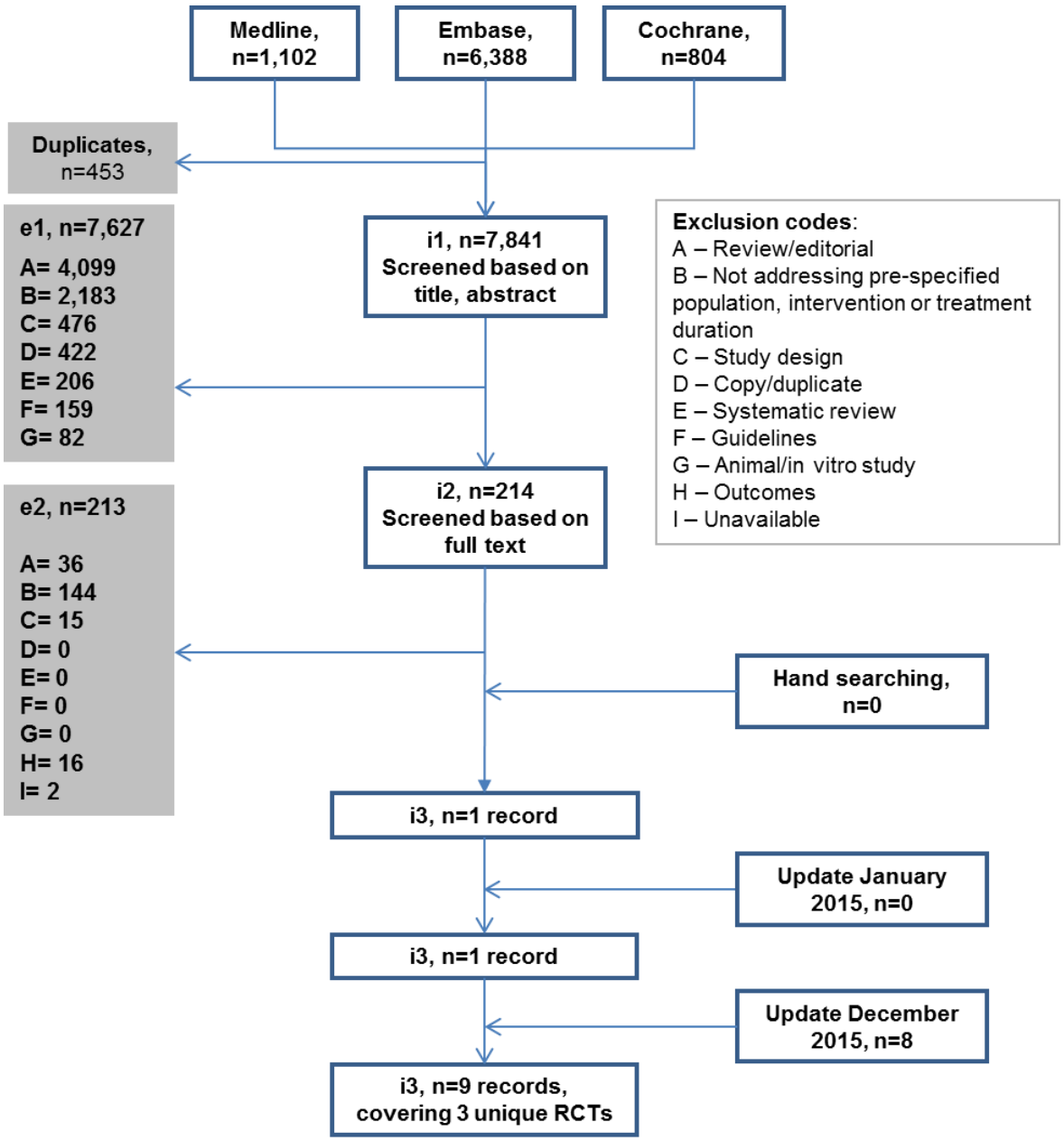
Identified studies on 2nd pass were independently assessed by a reviewer in order to ascertain whether they met the pre-specified inclusion and exclusion criteria. Any uncertainties around inclusion were resolved by discussion with a second reviewer. Data extraction table (DET) in Microsoft Excel file was developed and pilot tested for possible data extraction of eligible RCTs on prolonged (at least 18 months) dual anti-platelet therapy involving aspirin, ticagrelor, clopidogrel, vorapaxar, prasugrel or rivaroxaban.

The original electronic database search (conducted in September 2014) identified 8294 citations of which 7841 were screened at 1st pass after removal of duplicates. In total, 214 citations reporting on dual anti-platelet therapy (aspirin, ticagrelor, clopidogrel, vorapaxar, prasugrel) or rivaroxaban were judged to be potentially relevant on review of title and abstract. After reviewing the publications in full with further inclusion and exclusion criteria applied (described in Table 15), one study was identified for inclusion. An updated electronic database search carried out in January 2015 did not identify any additional relevant publications for inclusion. A list of publications excluded on full publication review from the January 2015 update (n=14) is provided in Appendix 2.5 (Table 5).

The electronic database searches carried out in December 2015 identified a total of 556 citations. Following removal of duplicates, 449 titles and abstracts were screened at first pass. Forty-eight papers were deemed to be potentially relevant and were screened on the basis of full publication. Of these, 45 were excluded. Hand searching yielded an additional three relevant papers, resulting in a total of eight publications covering two unique RCTs for inclusion in the update.

Overall, the original systematic review and subsequent updates identified a total of 9 records covering three unique relevant RCTs for inclusion. The flow of studies through the original review and the two updates is presented in the PRISMA flow diagram in (Figure 4). A list of studies excluded from the December 2015 update on the basis of full publication is provided in Appendix 2.5 (Table 6).

Figure 4: PRISMA flow diagram for clinical review



Overall, the original systematic review and subsequent updates of the available clinical evidence identified nine records covering three unique RCTs examining prolonged DAPT in the population of interest;

1. the PEGASUS-TIMI 54 trial (49)
2. a post-hoc sub-group analysis of the CHARISMA trial examining patients enrolled with documented prior MI, ischaemic stroke, or symptomatic PAD (50)

3. a post-hoc sub-group analysis of the DAPT trial examining the efficacy of DAPT in patients with and without MI (51)

In addition, six publications linked to the PEGASUS-TIMI 54 trial were identified (two full publication, and four abstracts) (52-54):

1. comparison of results for men versus women with a prior MI (54)
2. an investigation of the efficacy of ticagrelor regarding the reduction in sub-types and sizes of MI (52)
3. an investigation of the efficacy of ticagrelor in relation to time from ADP receptor inhibitor withdrawal in patients with prior MI (53)
4. an investigation into the reduction in CV events associated with the long-term use of ticagrelor (55)
5. an investigation of the efficacy of ticagrelor in patients with coronary stents from PEGASUS-TIMI 54 (56)
6. an investigation into the safety and efficacy of ticagrelor in relation to renal function (57).

The three identified unique RCTs were assessed for feasibility in a network meta-analysis and indirect treatment comparison and are summarised in Table 16.

Table 16. List of relevant studies identified by the clinical review

Trial no. (acronym)	Study design	Population (sample size)	Intervention	Comparator	Treatment duration	Outcomes reported	Primary study ref(s)	Additional refs identified
NCT01225562 (PEGASUS) (49)	Double blind, placebo-controlled RCT	Patients with a spontaneous MI 1-3 years prior to study enrolment, aged ≥50 years, and with at least one of the following additional high-risk factors: (i) age ≥65 years; (ii) DM requiring medication; (iii) a second prior spontaneous MI; (iv) multi-vessel coronary artery disease; or (v) chronic renal dysfunction defined as an estimated creatinine clearance of <60 ml/minute. Sample size: 21,162 patients randomised	Ticagrelor 90 mg BID + aspirin 75-150 mg/day Ticagrelor 60 mg BID + aspirin 75-150 mg/day	Placebo + aspirin 75-150 mg/day	NR – median duration of follow up was 33 months	Primary end points: Composite of CV death, MI or stroke TIMI-defined major bleeding Secondary end points: CV death All-cause mortality ICH Fatal bleeding	Bonaca et al, 2015 (49)	Sub-analyses: Men vs women (54) MI sub-types and sizes (52) Length of time since withdrawal from previous ADP receptor inhibitor (53) Reduction in total CV events with ticagrelor (55) Stented patients (56) Safety and efficacy in relation to renal function (57).
NCT00050817	Double-blind,	Full study cohort: patients with	Clopidogrel + aspirin	Placebo + aspirin	Median duration of	Primary end points:	Original CHARISMA	None

Trial no. (acronym)	Study design	Population (sample size)	Intervention	Comparator	Treatment duration	Outcomes reported	Primary study ref(s)	Additional refs identified
(CHARISMA [post- hoc analysis]) (50)	placebo-controlled RCT	documented CAD, cerebrovascular disease, or PAD, or with multiple risk factors for atherothrombosis Post hoc analysis: patients with a documented prior MI, documented prior IS, or symptomatic PAD from full study cohort Sample size: post-hoc analysis included 9,478 patients			28 months	Composite of CV death, MI or stroke GUSTO-defined severe bleeding Secondary end points: CV death, MI, stroke or rehospitalisation for UA, TIA, or a revascularisation procedure GUSTO-defined moderate bleeding	study: Bhatt et al, 2004 (58)	
NCT00977938 (DAPT [sub-analysis]) (51)	Double blind, placebo-controlled RCT	Patients with CAD, candidates for DAPT and who received treatment with FDA-approved DES and BMS devices Post-hoc analysis: patients with MI compared with those without	Thienopyridine (clopidogrel or prasugrel) + aspirin	Placebo + aspirin	12 versus 30 months of DAPT	Co-primary end points: Incidence of definite or probable stent thrombosis and incidence of MACCE GUSTO-defined moderate or	Original DAPT study: Mauri et al, 2014 (59)	None

Trial no. (acronym)	Study design	Population (sample size)	Intervention	Comparator	Treatment duration	Outcomes reported	Primary study ref(s)	Additional refs identified
		Sample size: 11,648 patients randomised (3,576 patients with MI)				severe bleeding Secondary end points: MI		

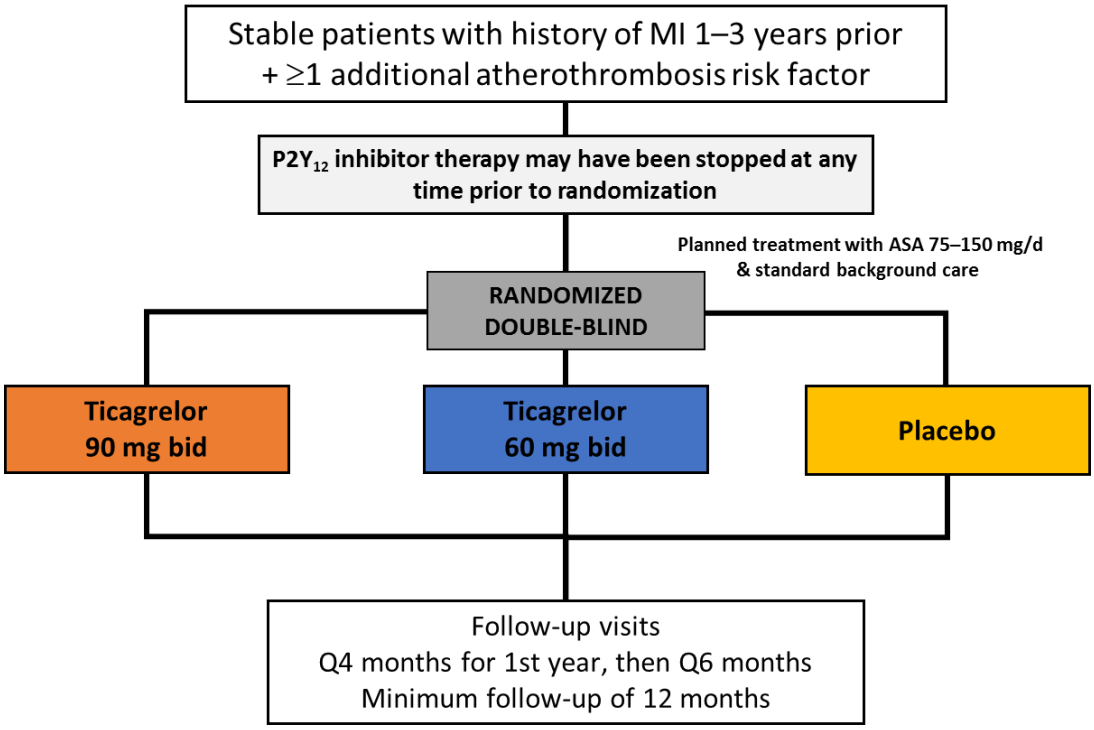
Abbreviations: BMS,: bare metal stent; CV,: cardiovascular; DAPT,: dual anti-platelet therapy; DES,: drug-eluting stent; DM,: diabetes mellitus; FDA,: US Food and Drug Administration; GUSTO,: Global Use of Strategies to Open Occluded Coronary Arteries; ICH,: intracranial haemorrhage; MACCE,: major adverse cardiac and cerebrovascular event; MI,: myocardial infarction; NR,: not reported; PAD,: peripheral artery disease; RCT,: randomised controlled trial; TIA,: transient ischaemic attack; TIMI,: Thrombolysis in Myocardial Infarction; UA,: unstable angina.

4.2 List of relevant randomised controlled trials

The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54; NCT01225562) was a randomised, double-blind, placebo-controlled multinational clinical trial which commenced in October 2010 and concluded in December 2014. The trial investigated whether long-term therapy with ticagrelor plus low dose aspirin reduced the risk of atherothrombotic events compared with placebo plus low dose aspirin in patients who had experienced an MI 1 to 3 years before enrolment, were aged ≥50 years and had at least one of the following additional high-risk features: age ≥65 years, diabetes mellitus requiring medication, a second prior MI, multi-vessel CAD, chronic non-end stage renal dysfunction defined as an estimated creatinine clearance of <60 ml/min.(60)

The trial investigated two different doses of ticagrelor (90 mg BID and 60 mg BID) on a background of low dose aspirin in comparison with placebo plus low dose aspirin. A schematic of the study design of the PEGASUS-TIMI 54 trial is presented in Figure 5. In total, 21,162 eligible patients were randomised in a 1:1:1 ratio to receive either ticagrelor 90 mg BID, ticagrelor 60 mg BID, or placebo in combination with low-dose (75-150mg daily) ASA.(61) The trial was conducted in 31 countries over 1,161 sites.(60)

Figure 5: Schematic for the PEGASUS-TIMI 54 trial(61)



BID =: twice daily; MI =: myocardial infarction

*Age ≥65 years, diabetes, second prior MI, multi-vessel CAD or chronic non-end stage renal dysfunction

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
NCT01225562 (PEGASUS-TIMI 54)	Eligible patients had experienced a spontaneous MI 1 to 3 years before enrolment, were aged ≥50 years and had at least one of the following additional high-risk features: • Age ≥65 years • Diabetes Mellitus requiring medication • Second prior MI • Multi-vessel CAD • Chronic non-end stage renal dysfunction defined	• 90mg ticagrelor BID + low dose ASA • 60mg ticagrelor BID + low dose ASA	Placebo + low dose ASA	(61)

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
	as an estimated creatinine clearance of <60 ml/min			

4.3 Summary of methodology of the relevant randomised controlled trials

Inclusion and Exclusion Criteria

Patients included in the study must have been at least 50 years old, with a documented history of spontaneous MI occurring 12 to 36 months prior to randomisation as well as at least one additional atherothrombotic high-risk factor (Table 17).(61) Patients also had to be prescribed and tolerating ASA and must have been able to be prescribed ASA 75 to 150 mg once daily for the duration of the study.

Table 17: PEGASUS-TIMI 54 inclusion and exclusion criteria(61)

Inclusion criteria	Exclusion criteria
Aged ≥50 years Spontaneous MI 12–36 months prior At least one of the following risk factors: • Aged ≥65 years • Diabetes mellitus on medication • A second prior MI • Multi-vessel CAD (≥50% in more than two coronary territories) • Chronic renal dysfunction (non-end stage, creatinine	Planned use of ADP receptor blockers, dipyridamole or cilostazol Planned revascularisation (coronary, peripheral, cerebrovascular) Potent inducer/inhibitor/substrate of CYP3A use Chronic anticoagulation Known bleeding diathesis or coagulation disorder Increased risk of bleeding defined as: A history of intracranial bleed at any time A central nervous system tumour or intracranial vascular abnormality (e.g. aneurysm, arteriovenous malformation) at any time Intracranial or spinal cord surgery within 5 years A GI bleed within the past 6 months Major surgery within 30 days History of ischaemic stroke Patients considered to be at risk of bradycardic events (e.g. known sick sinus syndrome or second or third degree atrioventricular block) unless already treated with a permanent pacemaker

clearance <60 mL/min) Taking aspirin 75–150 mg daily Contraception in women of child-bearing potential Provided written informed consent	CABG in the last 5 years Known severe liver disease Renal failure requiring dialysis Pregnancy or lactation Life expectancy <1 year Any condition judged by the investigator to make participation unsafe for the patient Concern for inability to comply with the protocol Prior participation in a trial with Ticagrelor (if treated with active Ticagrelor) Involvement in planning or conduct of the study Participation in another clinical study with an investigational product during the prior 30 days

ADP =: adenosine diphosphate; CABG =: coronary artery bypass grafting; CAD =: coronary artery disease; CYP3A =: cytochrome P450; GI =: gastrointestinal; MI =: myocardial infarction

Treatment dose selection

Ticagrelor 90 mg BID was selected as a dose to be tested in the PEGASUS study based on available data.(62) This dose was well tolerated and showed high and consistent levels of IPA in phase II studies. In PLATO, ticagrelor 90 mg BID reduced major CV events by 16%, CV mortality by 21% and all-cause mortality by 22% compared with clopidogrel. There was no significant difference between ticagrelor 90 mg BID and clopidogrel in the rates of total major bleeding (the primary safety endpoint), fatal and fatal/life-threatening bleeding. Minor bleeding and non-CABG and non-procedure-related major bleeding were higher with ticagrelor. Overall, the benefit:harm balance for ticagrelor 90 mg BID was favourable in patients with ACS and was considered appropriate for study in stable patients with a history of MI.(62)

Ticagrelor 60 mg BID had not been directly tested prior to the PEGASUS- TIMI 54 study. However, since in the chronic setting the optimal intensity of platelet inhibition for long-term therapy is unknown, it was postulated that having outcomes data for two doses of ticagrelor may allow tailoring of dosing to optimise the risk benefit ratio and may provide further guidance on the optimal use of ticagrelor in this setting. Although the risk of recurrent thrombotic events following an MI persists over time, it is higher in the first year history of MI; consequently, a lower intensity of platelet inhibition than utilised in the ACS setting may be sufficient to prevent major CV events during chronic therapy.(62)

Ticagrelor 60 mg was chosen as it was expected, based on pharmacokinetic (PK) and pharmacodynamic (PD) modelling of IPA response and clinical findings in the phase II DISPERSE study (D5130C00008), to provide less platelet inhibition than ticagrelor 90 mg BID but greater mean platelet inhibition and less variability than clopidogrel 75 mg daily, with a favourable benefit-risk balance.(62)

Treatment duration of a minimum of 12 months was selected with the goal of demonstrating long-term efficacy and safety. A placebo control arm was included as guidelines did not recommend continuing DAPT beyond 12 months after an MI. Moreover, patients who had an approved clinical indication for DAPT at time of the enrolment were not randomised.(62)

Study objectives

Primary objective:(62)

- To compare the effect of long-term treatment with ticagrelor versus placebo on a background of low dose aspirin (75 to 150 mg daily) on the event rate of the **composite endpoint of cardiovascular death (CV death), MI, or stroke** in patients with history of MI and high risk of developing atherothrombotic events. The primary efficacy variable was time to first occurrence of any event after randomisation from the composite of CV death, MI, or stroke.

Secondary objectives:(62)

- To compare the effect of long-term treatment with ticagrelor versus placebo on a background of low dose aspirin on the event rate of **CV death** in patients with history of MI and high risk of developing atherothrombotic events. The efficacy variable was time to occurrence of CV death after randomisation.
- To compare the effect of long-term treatment with ticagrelor versus placebo on a background of low dose aspirin on the event rate of **all-cause mortality** in patients with history of MI and high risk of developing atherothrombotic events. The efficacy variable was time to occurrence of all-cause mortality after randomisation.

Other efficacy objectives:(62)

The other secondary efficacy objectives, which were not under type I error control and are referred to as 'other efficacy objectives', were as follows:

- To compare the effect of long-term treatment with ticagrelor versus placebo on a background of low dose aspirin on the event rate of **the composite of CV death, non-fatal MI, non-fatal stroke, or urgent coronary revascularisation**. The efficacy variable was time to first occurrence of any event after randomisation from the composite of CV death, non-fatal MI, non-fatal stroke, or urgent coronary revascularisation.
- To compare the effect of long-term treatment with ticagrelor versus placebo on a background of low dose aspirin on the event rate of **the composite of CV death or coronary or cerebrovascular arterial thrombosis hospitalisation (including non-fatal MI, non-fatal stroke, urgent coronary revascularisation, unstable angina, or transient ischaemia attack [TIA])**. The efficacy variable was time to first occurrence of any event after randomisation from the composite of CV death or coronary or cerebrovascular arterial thrombosis hospitalisation. The individual components were also to be examined in an analogous manner.
- To compare the effect of long-term treatment with ticagrelor versus placebo on a background of low dose aspirin on the event rate of **the composite of CHD death, non-fatal MI, or non-fatal stroke.** The efficacy variable was time to first occurrence of any event after randomisation from the composite of CHD death, non-fatal MI, or non-fatal stroke. The individual component of CHD death was also to be examined in an analogous manner.
- To evaluate the **net clinical benefit** of long-term treatment with ticagrelor versus placebo on a background of low dose aspirin. The efficacy variable was the time to first occurrence of any event after randomisation from **the composite of CV death, non-fatal MI, non-fatal stroke, or TIMI Major bleeding**.

- To compare the effect of the long-term treatment with ticagrelor versus placebo on a background of low dose aspirin on the **incidence of coronary stent thrombosis**. The efficacy variable was the time to first occurrence of coronary stent thrombosis after randomisation.
- To collect health care utilisation associated with hospitalisations and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) to support health technology assessment and health economic modelling.

Safety objectives:

The safety objective of this study was to assess the safety and tolerability of long-term therapy with ticagrelor compared with placebo on a background of low dose aspirin in patients with history of MI and high risk of developing atherothrombotic events. Bleeding events were analysed using the TIMI, PLATO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial (GUSTO), and International Society on Thrombosis and Haemostasis (ISTH) definitions. Specific focus was on:

- Time to first **thrombolysis in myocardial infarction (TIMI) Major bleeding event** following the first dose of study drug, as well as the time to first **TIMI Major or Minor bleeding**
- Time to **discontinuation of study drug due to any bleeding event**
- **Evaluation of AEs**

The primary safety endpoint is major bleeding as defined by the TIMI classification system (an overview of this classification system is presented in Table 18).(61) All efficacy endpoints and bleeding episodes were assessed by a central clinical events committee, who were unaware of treatment assignment.(60)

Table 18: TIMI bleeding classification system(63)

Category	Definition
Major	Any intracranial bleeding, or Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL (or when haemoglobin is not available, a fall in

	haematocrit of ≥15%), or Fatal bleeding (a bleeding event that directly led to death within 7 days).
Minor	Any clinically overt sign of haemorrhage (including imaging) that is associated with a fall in haemoglobin of 3 to <5 g/dL (or, when haemoglobin is not available, a fall in haematocrit of 9 to <15%).
Medical attention	Any overt sign of haemorrhage that meets one of the following criteria and that does not meet criteria for a major or minor bleeding event, as defined above: Requiring intervention: defined as medical practitioner-guided medical or surgical treatment to stop or treat bleeding including temporarily or permanently discontinuing or changing the dose of a medication or study drug. Leading to hospitalisation: defined as leading to or prolonging hospitalisation. Prompting evaluation: defined as leading to unscheduled contact with a healthcare professional and diagnostic testing (laboratory or imaging).
Minimal	Any overt bleeding event that does not meet the criteria above.

TIMI: thrombolysis in myocardial infarction

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

For the primary efficacy analysis each treatment dose was tested independently against placebo. To control the overall type I error at 5%, alpha was apportioned equally to each ticagrelor dose vs placebo comparison.(61) The primary efficacy analysis was conducted on an intention-to-treat basis, with each of the two doses individually compared with placebo, as a time to event analysis from randomisation to the first occurrence of any element of the primary composite endpoint. All efficacy analyses were performed according to an intention-to-treatment (ITT) principle for all patients randomised irrespective of protocol adherence or the duration of exposure to study treatment. Event probabilities are expressed as Kaplan-Meier (KM) estimates of cumulative incidence at 36 months. The median duration of follow up was 33 months (IQR 28–37).

Hazard ratios (HR) and 95% confidence intervals (CI) were generated using a Cox proportional hazards model and all reported p values are two-sided.(62)

Secondary endpoints were tested in a hierarchical manner for each dose if the primary endpoint was confirmed for that dose. The hierarchical analysis started with

CV death and then all-cause mortality; additional endpoints were then evaluated on an exploratory basis.(62)

The significance level, adjusted for one interim analysis at 46% of final events, for each dose-placebo comparison of the primary endpoint in the final analysis was 0.02598.(62) If tests of both doses were significant for the primary variable then CV death for a given dose would be tested at 0.02478.(62) If the primary variable was significant for only 1 of the doses, then CV death was tested for that dose at 0.02106.(62) Similarly, only if CV death was confirmed as significant for a given dose would all-cause mortality be tested for that dose in a confirmatory sense. If tests of both doses were significant for CV death, then all-cause mortality would be tested at 0.02478. If CV death was significant for only one of the doses, then all-cause mortality would be tested for that dose at a 0.02106 significance level.(62)

Safety analyses included all randomised patients who received at least one dose of study drug and for whom post-dose data were available. The pre-specified primary safety analysis approach was an on-treatment analysis where patients were censored 7 days after their last dose of study drug and grouped by actual treatment received.(61, 62) Safety endpoints were evaluated on an exploratory basis; the p-values for these endpoints were considered descriptive and not indicative of statistical significance.

Trial sample size determination was made with the assumptions of a 3.5% per year event rate for the primary endpoint in the placebo group based on prior studies in similar populations and a target RRR for the 90 mg dose of 20% and approximately 19% for the 60 mg dose compared with placebo.(50, 61, 64) The estimates for the RRRs were based on observations in studies comparing DAPT to monotherapy in similar stable populations.(50) The risk reduction of the lower dose of ticagrelor was modelled using inhibition of platelet aggregation data from the Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in Non–ST-Segment Elevation Myocardial Infarction (DISPERSE) trial(65) and assuming that the log hazard ratio for clinical outcomes is proportional to the ratio of mean inhibition of platelet aggregation for the 60 mg dose relative to the 90 mg dose. Based on these assumptions it was estimated that a total of 1,360 primary endpoint events

would provide approximately 90% power for the 90 mg dose and approximately 83% power for the 60 mg dose when compared independently with placebo.(61)

4.5 Participant flow in the relevant randomised controlled trials

The baseline characteristics of the 21,162 patients enrolled into the PEGASUS-TIMI 54 trial are presented in Table 19. The median time from the qualifying MI to randomisation was 1.7 years (interquartile range, 1.2 to 2.3) and 53.6% of the qualifying events were ST-segment elevation myocardial infarctions.(60) The majority of patients (83.0%) had a history of percutaneous coronary intervention, ~59% had multi-vessel CAD, ~32% had diabetes mellitus, ~16% had experienced more than one prior MI and 5% had PAD. Nearly all the patients (99.9%) had received either 75 mg or 100 mg of aspirin (Table 19).(60)

A total of 20,942 patients received at least one dose study drug, including ticagrelor 90 mg BID (n=6,988), ticagrelor 60 mg BID (n=6,958) or placebo (n=6,996). Of these, 33.8% of patients in the ticagrelor 90 mg group, 28.7% of patients in the ticagrelor 60 mg group and 21.4% of patients in the placebo group discontinued treatment prematurely ($p<0.001$).(60) The majority of the discontinuations in the ticagrelor groups were due to AEs (see Figure -6). The median duration of follow-up was 33 months (IQR 28 to 37) representing 56,004 patient-years of follow-up.(60) Ascertainment of the primary endpoint was complete for 99.2% of these patient-years. Only 10 patients were lost to follow-up during the study (Figure -6).(63)

Figure -6: PEGASUS-TIMI 54 trial CONSORT diagram(63)

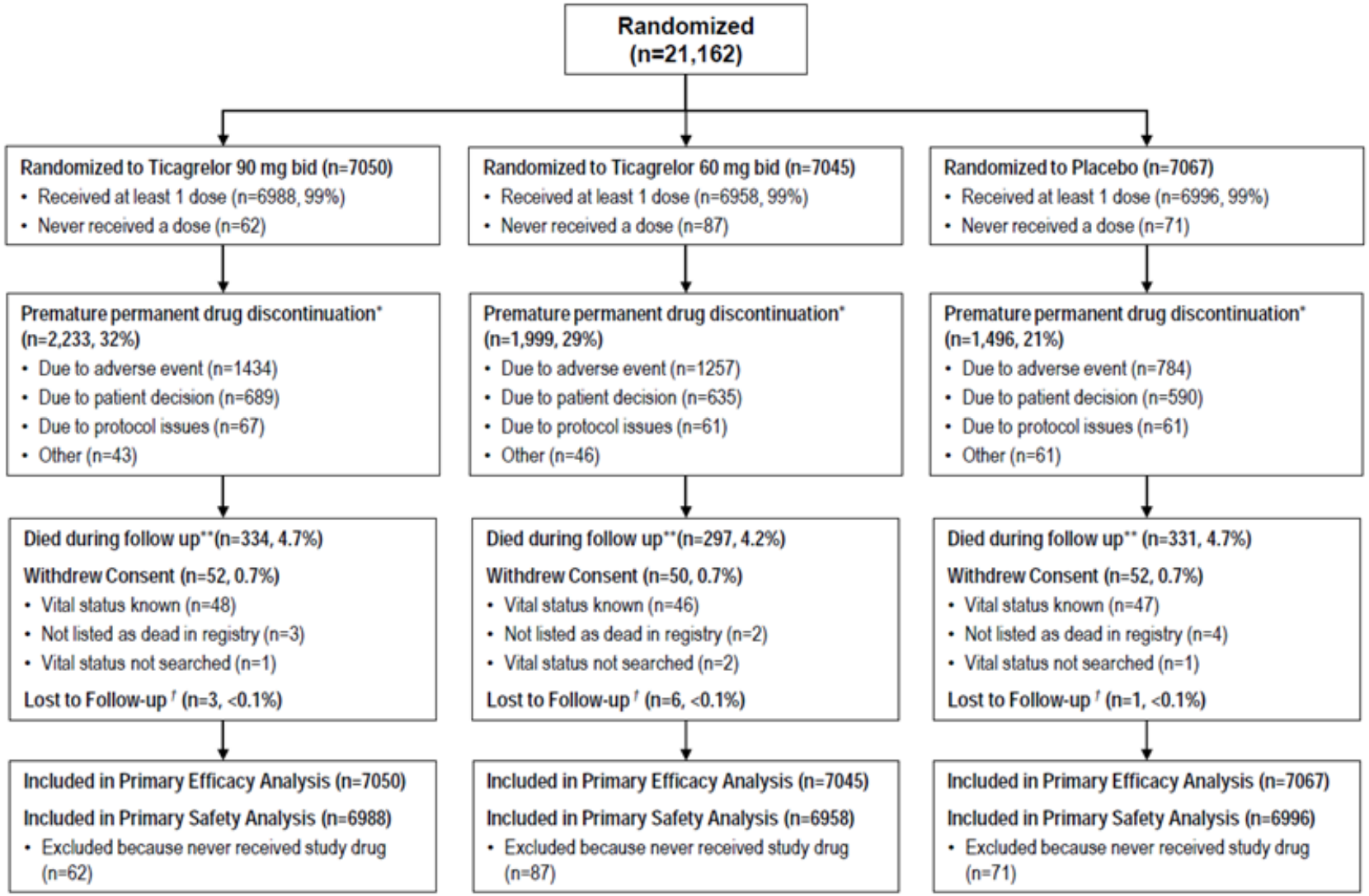


Table 19: Baseline characteristics in the PEGASUS-TIMI 54 trial(60)

Baseline characteristic	Ticagrelor 90 mg BID (n=7,050)	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)
Age – years (±SD)	65.4 ± 8.4	65.2 ± 6.4	65.4 ± 8.3
Female sex – n (%)	1,682 (23.9)	1,661 (23.6)	1,717 (24.3)
White race – n (%)[†]	6,126 (86.9)	6,077 (86.3)	6,124 (86.7)
Weight – kg (±SD)	82.0 ± 16.7	82.0 ± 17.0	81.8 ± 16.6
Hypertension – n (%)	5,462 (77.5)	5,461 (77.5)	5,484 (77.6)
Hypercholesterolemia – n (%)	5,410 (76.7)	5,380 (76.4)	5,451 (77.1)
Current smoker – n (%)	1,187 (16.8)	1,206 (17.1)	1,143 (16.2)
DM – n (%)	2,241 (31.8)	2,308 (32.8)	2,257 (31.9)
Multi-vessel CAD – n/total n (%)	4,155/7,049 (58.9)	4,190/7,042 (59.5)	4,213/7,067 (59.6)
History of PCI – n/total n (%)[‡]	5,852/7,049 (83.0)	5,879/7,044 (83.5)	5,837/7,066 (82.6)
>1 prior MI – n (%)	1,143 (16.2)	1,168 (16.6)	1,188 (16.8)
eGFR <60 ml/min/1.73m^2 – n/total n (%)[§]	1,653/6,958 (23.8)	1,547/6,955 (22.2)	1,649/6,985 (23.6)
Qualifying event[¥]			
Median years since MI	1.7	1.7	1.7
Interquartile range	1.2–2.3	1.2–2.3	1.2–2.3
Type of MI – n/total n (%)			
STEMI	3,763/7,043 (53.4)	3,757/7,035 (53.4)	3,809/7,057 (54.0)
NSTEMI	2,898/7,043 (41.1)	2,842/7,035 (40.4)	2,843/7,057 (40.3)
Unknown type	382/7,043 (5.4)	436/7,035 (6.2)	405/7,057 (5.7)
Medication at enrolment – n (%)			
Aspirin at any dose	7,039 (99.8)	7,036 (99.9)	7,057 (99.9)
Statin	6,526 (92.6)	6,495 (92.2)	6,583 (93.2)
Beta-blocker	5,812 (82.4)	5,796 (82.3)	5,878 (83.2)
ACE inhibitor or ARB	5,702 (80.9)	5,631 (79.9)	5,697 (80.6)
Previous treatment with an ADP receptor inhibitor – n (%)			
Any	6271 (89.0)	6289 (89.3)	6285 (88.9)
Clopidogrel	5922 (84.0)	5915 (84.0)	5878 (83.7)
Prasugrel	287 (4.1)	317 (4.5)	325 (4.6)
Ticlopidine	34 (0.5)	35 (0.5)	38 (0.5)
Ticagrelor	31 (0.4)	26 (0.4)	38 (0.5)
Missing	4 (0.1)	1 (0.0)	5 (0.1)

ARB: Angiotensin II receptor blockers; BID: twice daily; CAD: coronary artery disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction

† Race was self-reported. ‡ A total of 96.5% of PCIs involved stenting. § The eGFR was calculated with the use of the Modification of Diet in Renal Disease equation. ¥ Patients for whom it could not be verified that they had had an MI were excluded from the denominator (7 patients in the 90 mg group, 10 in the 60 mg group and 10 in the placebo group) as well as from the calculation for the median years since the MI.

The baseline characteristics and medical history of patients demonstrate that the population enrolled is representative of a global population with history of MI and at high risk of developing an atherothrombotic event. The demographic characteristics of the patients were balanced across the treatment groups.

Baseline characteristics of the MI <2 years ago subgroup of the full trial population (used as the base case for the submission) are presented in Table 20 below.

In addition, the baseline characteristics of the 4 patient subgroups requested by NICE in the scope (i.e. patients with or without diabetes and those who have or have not undergone a PCI) are presented in Table 21 and Table 22. Note that these subgroups are based on the MI <2 years ago subgroup since this was a pre-specified subgroup that is within the limits of the marketing authorisation and the remit of the NICE scope.

Table 20: Baseline characteristics of the MI <2 years ago subgroup (base case)

Baseline characteristic	**Ticagrelor 60 mg BID (n=4331)**	**Placebo (n=4333)**
Age – years (±SD)	65.2 ± 8.5	65.4 ± 8.3
Female sex – n (%)	1021 (23.6%)	1070 (24.7%)
White race – n (%)[†]	3734 (86.2%)	3740 (86.3%)
Weight – kg (±SD)	82 ± 16.9	81.4 ± 16.5
Hypertension – n (%)	3354 (77.4%)	3346 (77.2%)
Hypercholesterolemia – n (%)	3265 (75.4%)	3332 (76.9%)
DM – n (%)	1419 (32.8%)	1322 (30.5%)
Multi-vessel CAD – n/total n (%)	2601 (60.1%)	2586 (59.7%)
History of PCI – n/total n (%)[‡]	3638 (84.0%)	3623 (83.6%)
>1 prior MI – n (%)	709 (16.4%)	699 (16.1%)
eGFR <60 ml/min/1.73m^2 – n/total n (%)[§]	806 (18.9%)	853 (20.0%)
Qualifying event[¥]		
Median months since MI	16	16
Range	3 - 24	2 - 24

Baseline characteristic	Ticagrelor 60 mg BID (n=4331)	Placebo (n=4333)
Type of MI – n/total n (%)		
STEMI	2309 (53.3%)	2370 (54.7%)
NSTEMI	1770 (40.9%)	1759 (40.6%)
Unknown type	252 (5.8%)	204 (4.7%)
Medication at enrolment – n (%)		
Aspirin at any dose	4324 (99.8)	4322 (99.7)
Statin	3958 (91.4%)	4021 (92.8%)
Beta-blocker	3616 (83.5%)	3661 (84.5%)
ACE inhibitor or ARB	3500 (80.8%)	3513 (81.1%)

ARB: Angiotensin II receptor blockers; BID: twice daily; CAD: coronary artery disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction

† Race was self-reported. § The eGFR was calculated with the use of the Modification of Diet in Renal Disease equation. ¥ Patients for whom it could not be verified that they had had an MI were excluded from the denominator as well as from the calculation for the median years since the MI

Table 21: Baseline characteristics of patients who had an MI <2 years ago, diabetic vs non-diabetic subgroup

Baseline characteristic	Diabetes		No Diabetes	
	Ticagrelor 60 mg BID (n=1419)	Placebo (n=1322)	Ticagrelor 60 mg BID (n=2912)	Placebo (n=3011)
Age – years (±SD)	63.9 ± 8.3	64.1 ± 8.3	65.7 ± 8.6	66 ± 8.2
Female sex – n (%)	379 (26.7%)	380 (28.7%)	642 (22.0%)	690 (22.9%)
White race – n (%)†	1153 (81.3%)	1096 (82.9%)	2581 (88.6%)	2644 (87.8%)
Weight – kg (±SD)	85.5 ± 18.1	85.4 ± 18.6	80.3 ± 16.1	79.7 ± 15.2
Hypertension – n (%)	1225 (86.3%)	1128 (85.3%)	2129 (73.1%)	2218 (73.7%)
Hypercholesterolemia – n (%)	1120 (78.9%)	1053 (79.7%)	2145 (73.7%)	2279 (75.7%)
Multi-vessel CAD – n/total n (%)	705 (49.7%)	690 (52.2%)	1896 (65.1%)	1896 (63.0%)
History of PCI – n/total n (%)‡	1152 (81.2%)	1065 (80.6%)	2486 (85.4%)	2558 (85.0%)
>1 prior MI – n (%)	228 (16.1%)	222 (16.8%)	481 (16.5%)	477 (15.8%)
eGFR <60 ml/min/1.73m^2 – n/total n (%)§	237 (17.0%)	245 (18.8%)	569 (19.8%)	608 (20.5%)
Qualifying event¥				
Median months since MI	16.1	16	16	15.9
Range	3 - 24	4.7 - 24	3 - 24	2 - 24
Type of MI – n/total n (%)				
STEMI	738 (52.0%)	695 (52.6%)	1571 (53.9%)	1675 (55.6%)
NSTEMI	604 (42.6%)	564 (42.7%)	1166 (40.0%)	1195 (39.7%)
Unknown type	77 (5.4%)	63 (4.8%)	175 (6.0%)	141 (4.7%)
Medication at enrolment – n (%)				
Aspirin at any dose	1417 (99.9)	1320 (99.8)	2907 (99.8)	3002 (99.7)
Statin	1292 (91.1%)	1212 (91.7%)	2666 (91.6%)	2809 (93.3%)
Beta-blocker	1196 (84.3%)	1131 (85.6%)	2420 (83.1%)	2530 (84.0%)
ACE inhibitor or ARB	1186 (83.6%)	1102 (83.4%)	2314 (79.5%)	2411 (80.1%)

ARB: Angiotensin II receptor blockers; BID: twice daily; CAD: coronary artery disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction

† Race was self-reported. § The eGFR was calculated with the use of the Modification of Diet in Renal Disease equation. ¥ Patients for whom it could not be verified that they had had an MI were excluded from the denominator as well as from the calculation for the median years since the MI

Table 22: Baseline characteristics of patients who had an MI <2 years ago, history of PCI vs non-history of PCI subgroup

Baseline characteristic	History of PCI		No history of PCI	
	Ticagrelor 60 mg BID (n=3638)	Placebo (n=3623)	Ticagrelor 60 mg BID (n=692)	Placebo (n=709)
Age – years (±SD)	64.8 ± 8.4	65.1 ± 8.1	67 ± 8.9	67.1 ± 8.8
Female sex – n (%)	776 (21.3%)	821 (22.7%)	245 (35.4%)	249 (35.1%)
White race – n (%)†	3148 (86.5%)	3142 (86.7%)	585 (84.5%)	598 (84.3%)
Weight – kg (±SD)	82.5 ± 16.9	81.8 ± 16.7	78.9 ± 16.7	79.3 ± 15.5
Hypertension – n (%)	2751 (75.6%)	2761 (76.2%)	603 (87.1%)	585 (82.5%)
Hypercholesterolemia – n (%)	2801 (77.0%)	2833 (78.2%)	464 (67.1%)	498 (70.2%)
DM – n (%)	1152 (31.7%)	1065 (29.4%)	267 (38.6%)	256 (36.1%)
Multi-vessel CAD – n/total n (%)	2434 (66.9%)	2398 (66.2%)	166 (24.0%)	187 (26.4%)
>1 prior MI – n (%)	576 (15.8%)	553 (15.3%)	133 (19.2%)	145 (20.5%)
eGFR <60 ml/min/1.73m2 – n/total n (%)§	616 (17.2%)	670 (18.8%)	190 (27.8%)	183 (26.2%)
Qualifying event¥				
Median months since MI	15.9	15.9	16.5	16.2
Range	3 - 24	2 - 24	3 - 24	5.7 - 24
Type of MI – n/total n (%)				
STEMI	2042 (56.1%)	2077 (57.3%)	267 (38.6%)	293 (41.3%)
NSTEMI	1449 (39.8%)	1407 (38.8%)	320 (46.2%)	352 (49.6%)
Unknown type	147 (4.0%)	139 (3.8%)	105 (15.2%)	64 (9.0%)
Medication at enrolment – n (%)				

Baseline characteristic	History of PCI		No history of PCI	
	Ticagrelor 60 mg BID (n=3638)	Placebo (n=3623)	Ticagrelor 60 mg BID (n=692)	Placebo (n=709)
Aspirin at any dose	3631 (99.8)	3614 (99.8)	692 (100.0)	707 (99.7)
Statin	3373 (92.7%)	3390 (93.6%)	585 (84.5%)	630 (88.9%)
Beta-blocker	3064 (84.2%)	3077 (84.9%)	551 (79.6%)	583 (82.2%)
ACE inhibitor or ARB	2931 (80.6%)	2949 (81.4%)	568 (82.1%)	563 (79.4%)

ARB: Angiotensin II receptor blockers; BID: twice daily; CAD: coronary artery disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction

† Race was self-reported. § The eGFR was calculated with the use of the Modification of Diet in Renal Disease equation. ¥ Patients for whom it could not be verified that they had had an MI were excluded from the denominator as well as from the calculation for the median years since the MI

Compliance

The compliance (the number of pills taken divided by the expected number of pills taken) of patients receiving either ticagrelor (60 mg BID or 90 mg BID) or placebo was assessed. A summary of compliance rates for each treatment cohort is presented in Table 23.(62, 66) These data show that for the total patient population receiving ticagrelor 60 mg BID the compliance rate of >80% was high at 83.5% of patients.(66) Compliance was similar across the treatment groups with slightly lower proportion of patients (82.8%) achieving >80% compliance in the 90 mg BID treatment group.(66)

Table 23: Study drug compliance (full analysis set)(66)

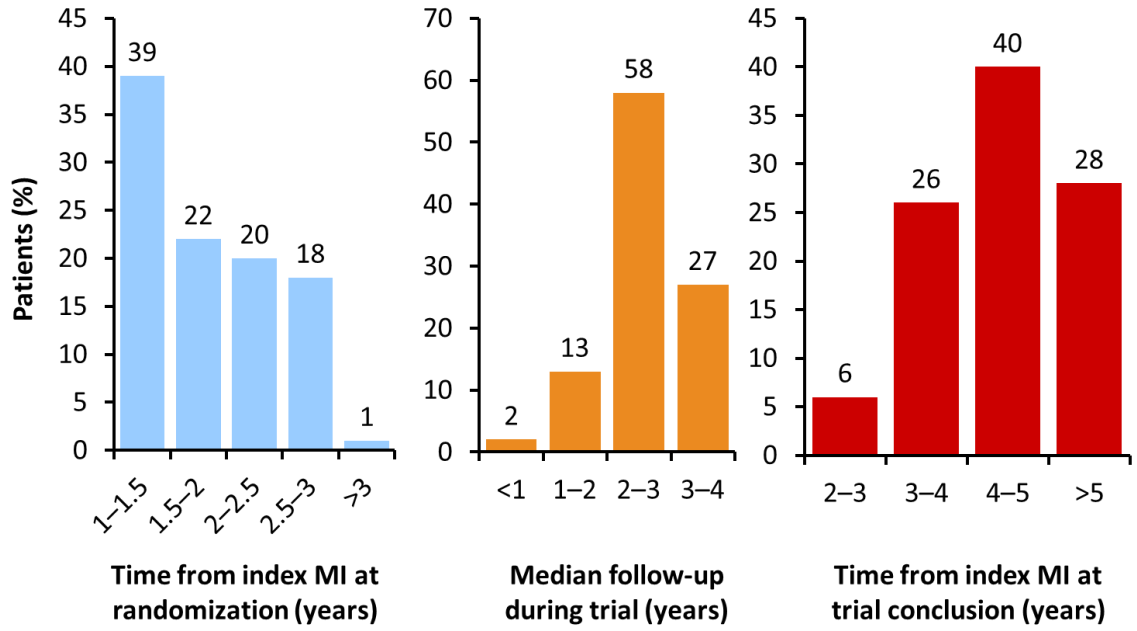
Patient category	Compliance (%) with study drug	Number (%) of patients			
		Ticagrelor 90 mg BID (n=7,050)	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Total (n=21,162)
All patients	n	6,829	6,832	6,857	20,518
	1st quartile	87.2	87.7	90.0	88.3
	Median	96.20	96.54	96.94	96.57
	3rd quartile	99.1	99.2	99.3	99.2
	Compliance >80% n, (%)	5,652 (82.8)	5,703 (83.5)	5,926 (86.4)	17,281 (84.2)
Patients who were on treatment with study drug at least until first follow-up[a]	n	5,889	6,119	6,484	18,492
	1st quartile	89.0	89.1	90.6	89.5
	Median	96.55	96.81	97.06	96.84
	3rd quartile	99.2	99.2	99.3	99.2
	Compliance >80% n (%)	5,031 (85.4)	5,225 (85.4)	5,672 (87.5)	15,928 (86.1)

Estimated compliance is derived from pill counts as the number of pills taken divided by the expected number of pills taken, from first dose date to last dose date, accounting for prescribed dose interruptions.

n is the number of patients with derived compliance, and is used as denominator for percentages. a Patients with last dose date on or after day 110 following randomisation (4 months target date - 10 day window).

By the end of the follow-up period, 28% of patients were more than 5 years out from their index MI (Figure 7).(67)

Figure 7: Time from index MI at randomization(67)



MI = myocardial infarction; yrs = years

4.6 Quality assessment of the relevant randomised controlled trials

Table 24. Results of quality assessment using the Cochrane Collaboration's tool for assessing risk of bias

Domain	Bonaca 2015 (49)	
	Support for judgement	**Review authors' judgement**
Selection bias.		
Random sequence generation.	Randomisation was performed using a central computerised telephone or web-based system	Low risk
Allocation concealment.	Randomisation was performed using a central computerised telephone or web-based system	Low risk
Performance bias.		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes).	Assignment was double-blinded; a modified study drug option (blinded, double-dummy ticagrelor or clopidogrel) was provided to investigators for patients with an indication for ADP receptor blockade	Low risk
Detection bias.		
Blinding of outcome	A central clinical-events committee,	Low risk

Domain	Bonaca 2015 (49)	
	Support for judgement	**Review authors' judgement**
assessment Assessments should be made for each main outcome (or class of outcomes).	whose members were unaware of treatment assignments, adjudicated all efficacy end points and bleeding episodes	
Attrition bias.		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes).	Missing outcome data balanced across groups and similar reasons for missing data across groups (trial CONSORT diagram provided in Supplementary appendix)	Low risk
Reporting bias.		
Selective reporting.	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk
Other bias.		
Other sources of bias.	The study appears to be free of other sources of bias	Low risk

BMS: bare metal stent; DES: drug-eluting stent.

Cochrane Collaboration tool for assessing risk of bias (68).

4.7 Clinical effectiveness results of the relevant randomised controlled trials

The approved dose for this indication is 60 mg BID, and so for clarity and to aid understanding, the results for patients receiving the 90mg dose of ticagrelor in PEGASUS-TIMI 54 are presented only in figures taken from the clinical study report (CSR). These results will not be discussed further in this report.

Efficacy results for the full PEGASUS-TIMI 54 population are presented initially. Results for the base case of patients who had an MI <2 years ago are found in Section 4.8.

Overview of efficacy results

Long-term treatment with Ticagrelor 60 mg BID in combination with low dose aspirin versus low dose aspirin alone in patients with a history of MI (1 to 3 years prior to randomisation) and at high risk of an atherothrombotic events met the primary efficacy objective and found a clinically relevant and statistically significant benefit for the composite primary endpoint (CV death, MI or stroke).(62) A directionally consistent effect was observed on all components of the primary endpoint, including

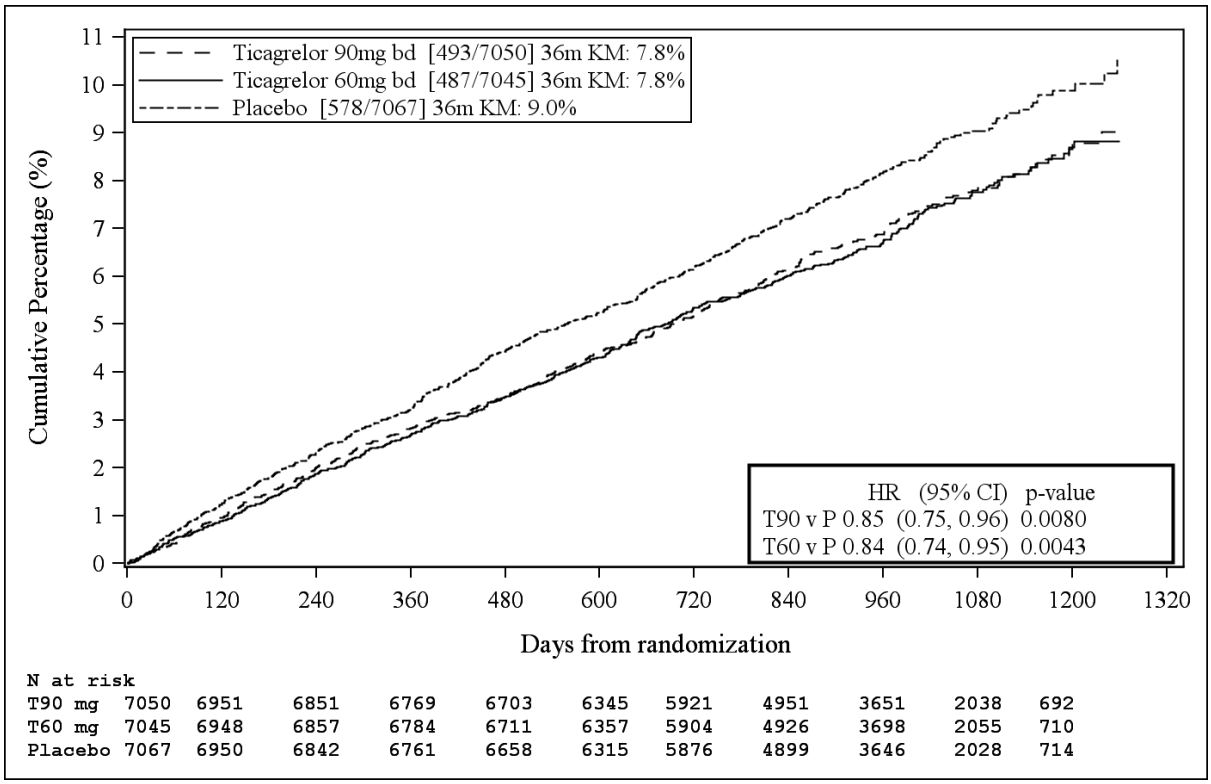
CV death. This benefit was consistent throughout the duration of the study and was supported by consistent findings across patient subgroups and across the secondary and other efficacy endpoints.(62)

Primary efficacy endpoint and its three components

Long-term treatment with ticagrelor and low dose aspirin is superior to placebo (low dose aspirin alone) in reducing the event rate of the primary composite endpoint (CV death, MI or stroke).(62) Primary composite endpoint events prior to Common Study End Date (CSED) were reported for 487 and 578 patients on ticagrelor 60 mg BID and placebo, respectively, corresponding to Kaplan-Meier percentages at 36 months of 7.8%, and 9.0% (ticagrelor 60 mg BID 16% RRR; HR 0.84; 95% CI 0.74 to 0.95; p=0.0043; Figure 8).(62) The Kaplan Meier curves started to separate soon after randomisation and continued to separate throughout the study.(62) The superior treatment effect of ticagrelor 60 mg BID compared to placebo was consistent throughout the study.

It is estimated that, for every 10,000 patients who began treatment (i.e. in an intention-to-treat (ITT) analysis), 42 primary endpoint events per year would be prevented with ticagrelor 60 mg BID compared to placebo.(33)

Figure 8: Kaplan-Meier rates of CV death, MI and stroke over three years, according to study group (full analysis set)(60)



CI confidence interval; HR: hazard ratio; KM: Kaplan Meier; m: month; P: placebo; T: ticagrelor

A directionally consistent effect of ticagrelor 60 mg BID treatment was observed across all components of the composite primary efficacy endpoint (Table 25).(62) Each of the primary endpoint components – CV death (Figure 9), MI (Figure 10) and stroke (Figure 11) – contributed to the reduction in the primary composite endpoint.(62)

Table 25: Analysis of the composite and individual components of the primary efficacy endpoint (full analysis set)(62)

Characteristic	Ticagrelor 60 mg BID (n=7,045)		Placebo (n=7,067)		Ticagrelor 60 mg BID versus Placebo	
	Patients with events	KM%	Patients with events	KM%	HR (95% CI)	p value
Composite of CV death, MI or stroke (%)	**487 (6.9)**	**7.8**	**578 (8.2)**	**9.0**	**0.84 (0.74–0.95)**	**0.0043 (s)**
CV death (%)	174 (2.5)	2.9	210 (3.0)	3.4	0.83 (0.68–1.01)	0.0676
MI (%)	285 (4.0)	4.5	338 (4.8)	5.2	0.84 (0.72–0.98)	0.0314
Stroke (%)	91 (1.3)	1.5	122 (1.7)	1.9	0.75 (0.57-0.98)	0.0337

S, statistically significant

Figure 9: Kaplan-Meier plot of CV death (full analysis set)(62)

CI = confidence interval; HR = hazard ratio; KM = Kaplan Meier; m = month; P = placebo; T = ticagrelor

Figure 10: Kaplan-Meier plot of MI (full analysis set)(62)

CI: confidence interval; HR: hazard ratio; KM: Kaplan Meier; m: month; P: placebo; T: ticagrelor

Figure 11: Kaplan-Meier plot of stroke (full analysis set)(62)

CI: confidence interval; HR: hazard ratio; KM: Kaplan Meier; m: month; P: placebo; T: ticagrelor

Other efficacy endpoints

The benefit of ticagrelor 60 mg BID was directionally consistent for the secondary endpoint of CV death, with a numerical decrease versus placebo, although this did not reach statistical significance (RRR 17%; HR 0.83; 95% CI 0.68 to 1.01).(62) Since no statistically significant difference versus placebo for CV death was observed in the pre-specified hierarchical testing procedure, the testing procedure was stopped. As such, the assessment of all other efficacy endpoints is considered to be exploratory (nominal p values).(62)

For all-cause mortality, there was also a numerical decrease in favour of ticagrelor 60 mg BID (RRR 11%; ARR 0.5%; HR 0.89; 95% CI 0.76 to 1.04).(62) In the exploratory analyses (nominal p values), there was a reduction in the rates of both MI and stroke with ticagrelor 60 mg BID compared with placebo (Table 26).(60) In addition, ticagrelor 60 mg BID reduced the rate of the composite end point of death from coronary heart disease, MI or stroke.

Figure 12: Kaplan-Meier plot of all-cause mortality (full analysis set)(37)

Table 26: Efficacy endpoints as 3-year Kaplan-Meier estimates (ITT analysis)(60)

Endpoint	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID vs placebo		
	n (%)	n (%)	HR (95% CI)	ARR	p value
CV death, MI or stroke	487 (7.77)	578 (9.04)	0.84 (0.74–0.95)	1.27	0.004 (s)
Death from CHD, MI or stroke	445 (7.09)	535 (8.33)	0.83 (0.73–0.94)	1.24	0.003*
CV death or MI	422 (6.77)	497 (7.81)	0.85 (0.74–0.96)	1.04	0.01*
Death from CHD or MI	360 (5.75)	429 (6.68)	0.84 (0.73–0.96)	0.93	0.01*
CV death	174 (2.86)	210 (3.39)	0.83 (0.68–1.01)	0.53	0.07*
Death from CHD	106 (1.72)	132 (2.08)	0.80 (0.62–1.04)	0.36	0.09*
MI	285 (4.53)	338 (5.25)	0.84 (0.72–0.98)	0.72	0.03*
Any stroke	91 (1.47)	122 (1.94)	0.75 (0.57–0.98)	0.47	0.03*
Ischaemic stroke	78 (1.28)	103 (1.65)	0.76 (0.56–1.02)	0.37	0.06*
Death from any cause	289 (4.69)	326 (5.16)	0.89 (0.76–1.04)	0.47	0.14*

ARR: absolute risk reduction; BID: twice daily; CHD: coronary heart disease; CI confidence interval; CV: cardiovascular; HR: hazard ratio; ITT: intention-to-treat; MI: myocardial infarction; (s): statistical significance

*Nominal p-value

No significant differences in the rates of urgent coronary revascularization for unstable angina, hospitalization for unstable angina, or TIA were reported between patients receiving ticagrelor compared with placebo; these events each occurred in less than 1.2% of the patients overall (Table 27).(63)

There was a numerical reduction in the rate of coronary stent thrombosis for ticagrelor 60 mg BID compared with placebo: 18% RRR, HR 0.82 (95% CI 0.54, 1.23), p=0.3328.

Table 27: Other efficacy endpoints in the PEGASUS-TIMI 54 trial(63)

Endpoint	**Ticagrelor 60 mg BID (n=7,045)**	**Placebo (n=7,067)**	**Ticagrelor 60 mg BID vs placebo**	
	n (%)	**n (%)**	**HR (95% CI)**	**p value***
Hospitalisation for UA	[redacted]	[redacted]	[redacted]	[redacted]
Urgent coronary revascularisation for UA	[redacted]	[redacted]	[redacted]	[redacted]
TIA	[redacted]	[redacted]	[redacted]	[redacted]
Patients with a history of coronary stent implantation or receiving a stent during the study	N = 5695	N = 5661		
Stent thrombosis	41 (0.70)	50 (0.90)	0.82 (0.54, 1.23)	0.3328

BID: twice daily; CI =: confidence interval; HR: hazard ratio; TIA: transient ischaemic attack; UA: unstable angina

*Nominal p value

Table 28: Primary efficacy endpoint for patients with and without a history of coronary stent implantation

		Ticagrelor 60 mg BID(N=7045)	**Placebo (N=7067)**
History of coronary stent implantation	n	5658	5621
	Patients with events	347 (6.1%)	409 (7.3%)
	KM %	6.8%	8.0%
	Hazard Ratio (95% CI)	0.84 (0.73, 0.97)	
	p-value	0.0161	
No history of	n	1362	1423

	Patients with events	140 (10.3%)	169 (11.9%)
	KM %	11.7%	13.2%
	Hazard Ratio (95% CI)	0.85 (0.68, 1.06)	
	p-value	0.1412	
	p-value for interaction	0.9464	

Long term treatment with ticagrelor 60 mg BID consistently reduced the incidence of CV death/MI/stroke regardless of stenting history.

Types and sizes of MI

In PEGASUS TIMI 54 trial, a large proportion of the events prevented were recurrent MI. A post-hoc analysis explored the effect of ticagrelor based on MI classification (according to MI Universal Definition) and magnitude of troponin (Tn) elevation

In terms of MI, a total of 1,042 MIs occurred in 898 patients in all 3 treatment arms of the PEGASUS-TIMI 54 study at a median of 440 days after randomization (IQR 198 to 705). The majority (76%) of the MIs were spontaneous, Type 1 MIs and those associated with a large troponin elevation: events which have the potential to have significant negative prognostic implications.(69)

Table 29: Type of MIs observed in PEGASUS-TIMI 54 study (patients randomised to 90 mg ticagrelor, 60 mg ticagrelor or placebo + ASA)

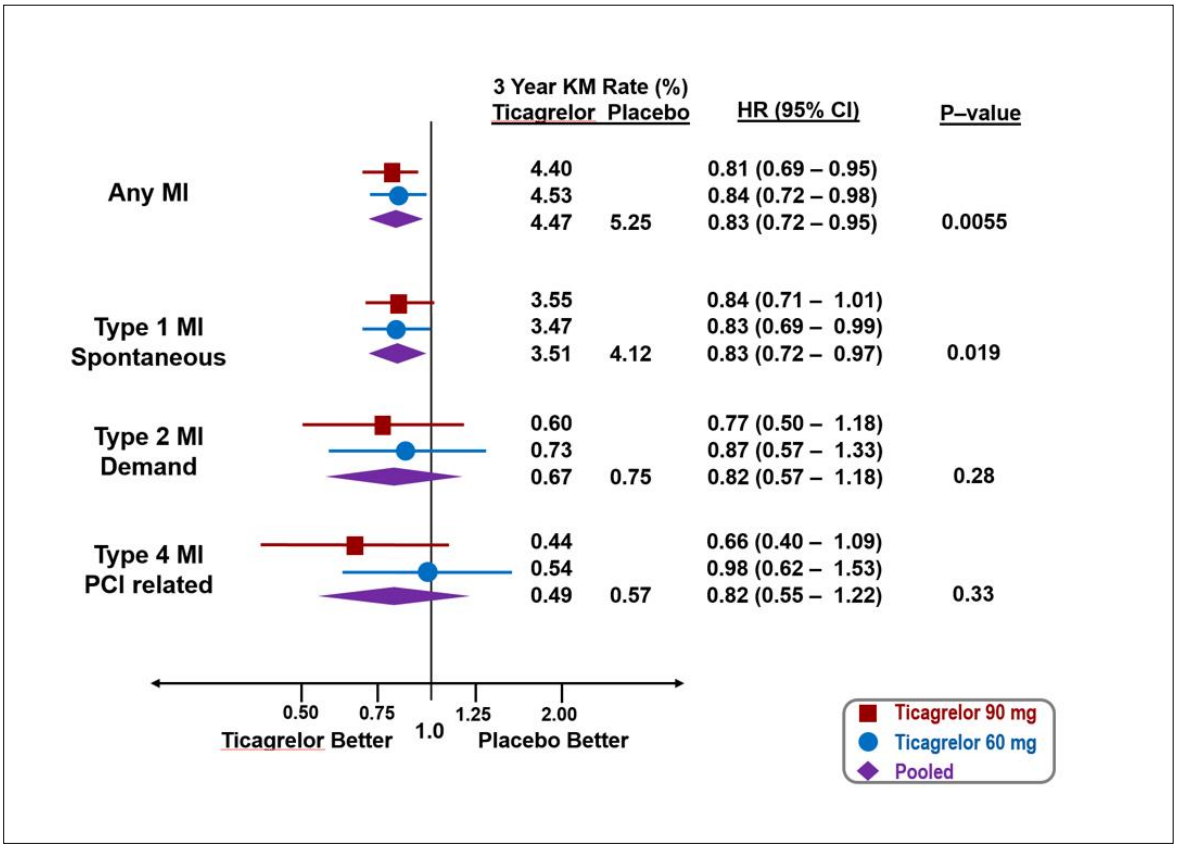
Type of MI	Number of events	% of all MIs
Type 1: Spontaneous	792	76%
Type 2: Demand	138	13%
Type 3: Fatal prior to Tn testing	7	1%
Type 4: PCI- related	104	10%
Type 5: CABG- related	1	0%
Total MIs	1042	100%

Using elevation in Tn, MI were classified as:

- Large MIs (Tn ≥10x ULN): 57%
- Very large MIs (Tn ≥100x ULN): 24%

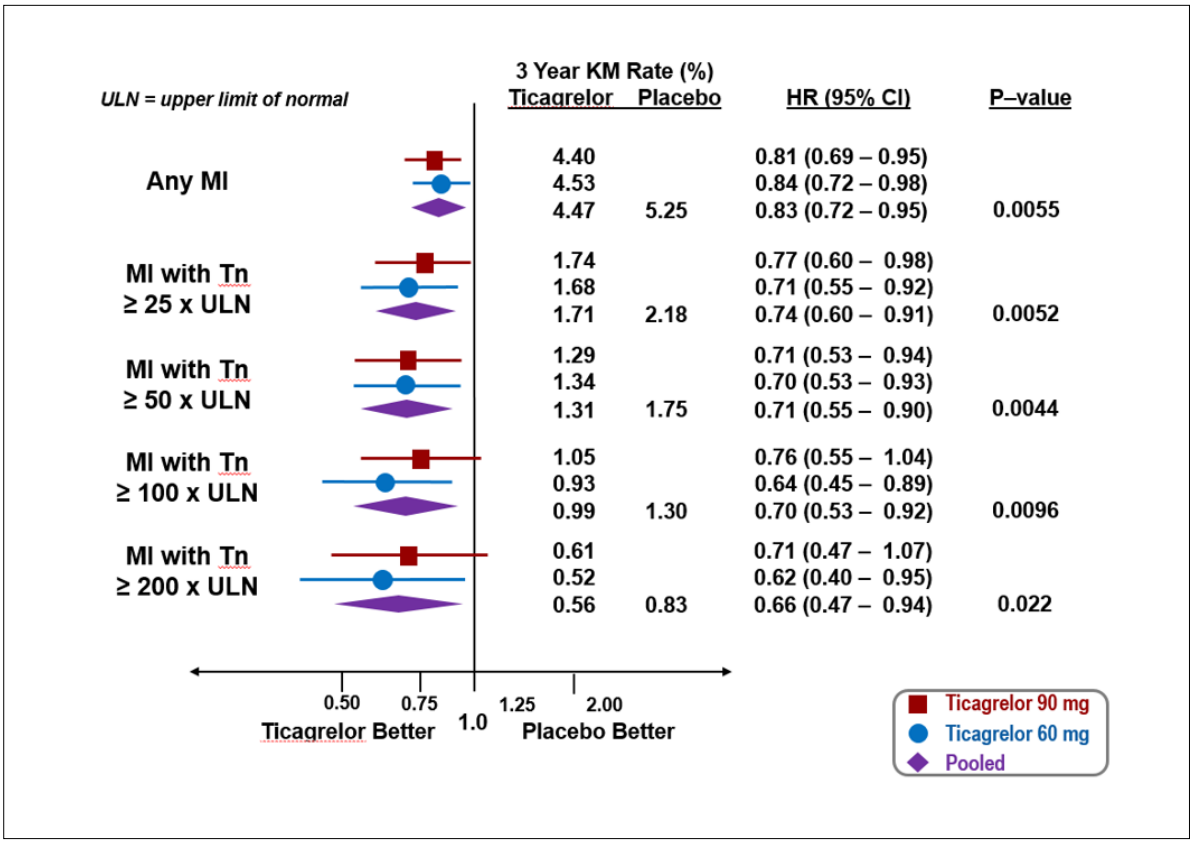
Overall, ticagrelor 60mg BID reduced MI at 3 years (4.53% v 5.25%, HR 0.84, 95% CI 0.72 – 0.98, p=0.031). The benefit was highly consistent among the different subtypes of MI (Figure 13) and with increasing size of MI by elevation of Tn (Figure 14), The benefit was also observed for STEMI (Figure 15).

Figure 13: Benefit of Ticagrelor by MI type(69)



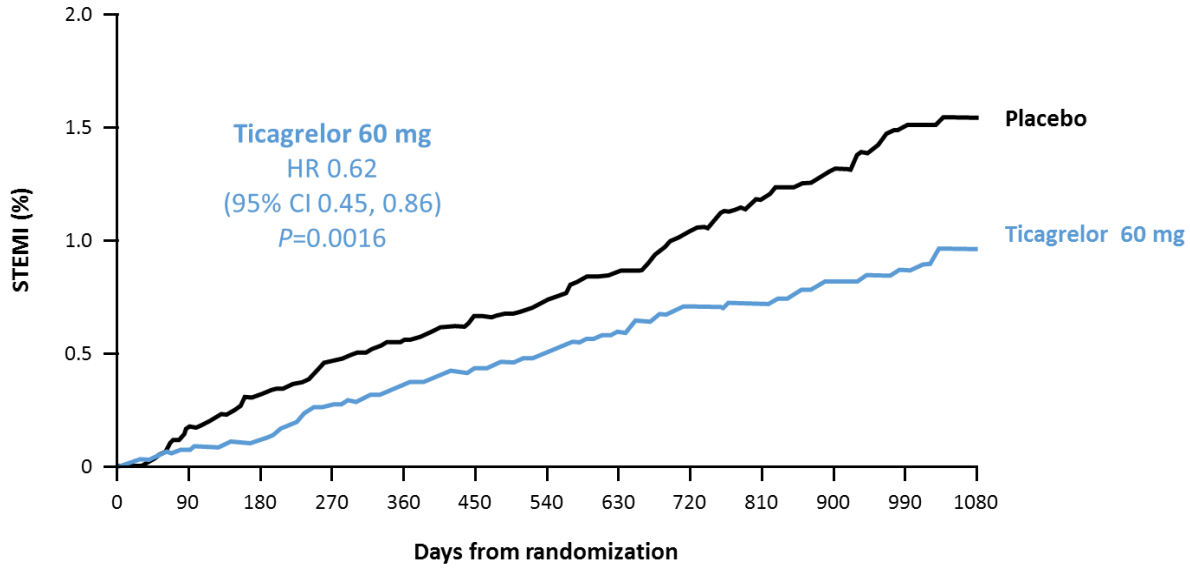
CI; confidence interval; HR: hazard ratio; KM: Kaplan Meier; MI: myocardial infarction; PCI: percutaneous coronary intervention; p values are nominal

Figure 14: Benefit of Ticagrelor by size of MI(69)



CI: confidence interval; HR: hazard ratio; KM: Kaplan Meier; MI: myocardial infarction; ULN = upper limit of normal; Tn = troponin; p values are nominal

Figure 15: Effect of Ticagrelor on STEMI(69)



CI: confidence interval; HR: hazard ratio; STEMI: ST-elevation myocardial infarction; p value is nominal

In PEGASUS-TIMI 54, in addition to reducing CV death and stroke, ticagrelor 60mg BID consistently reduced the incidence of MI, across subtypes, degrees of troponin elevation, and STEMI

12 month Landmark analysis

The efficacy of ticagrelor 60mg BID was examined for the first year of therapy and then as a landmark including all patients alive at 1 year (defined as 360 days from randomisation). The objective was to investigate the consistency of the efficacy of ticagrelor over time. The rate of CV death/MI/stroke was analysed for ticagrelor 60mg BID compared to placebo, i) for the first year of observation, and then ii) as a landmark analysis beginning after the first year, in all patients alive at that time point. In this 'landmark 'analysis (Table 30), the RRR for Ticagrelor 60 mg was similar from 1 to 360 days ([redacted]) and from 361 days and onwards with no apparent diminution in effect through to the end of treatment ([redacted]). Ticagrelor reduces ischaemic risk with consistent efficacy early (within 1 year) and late (beyond 1 year) after initiation in patients with history of MI.

This analysis therefore supports the prolonged usage of ticagrelor 60mg BID therapy in high risk post-MI patients to reduce atherothrombotic events.

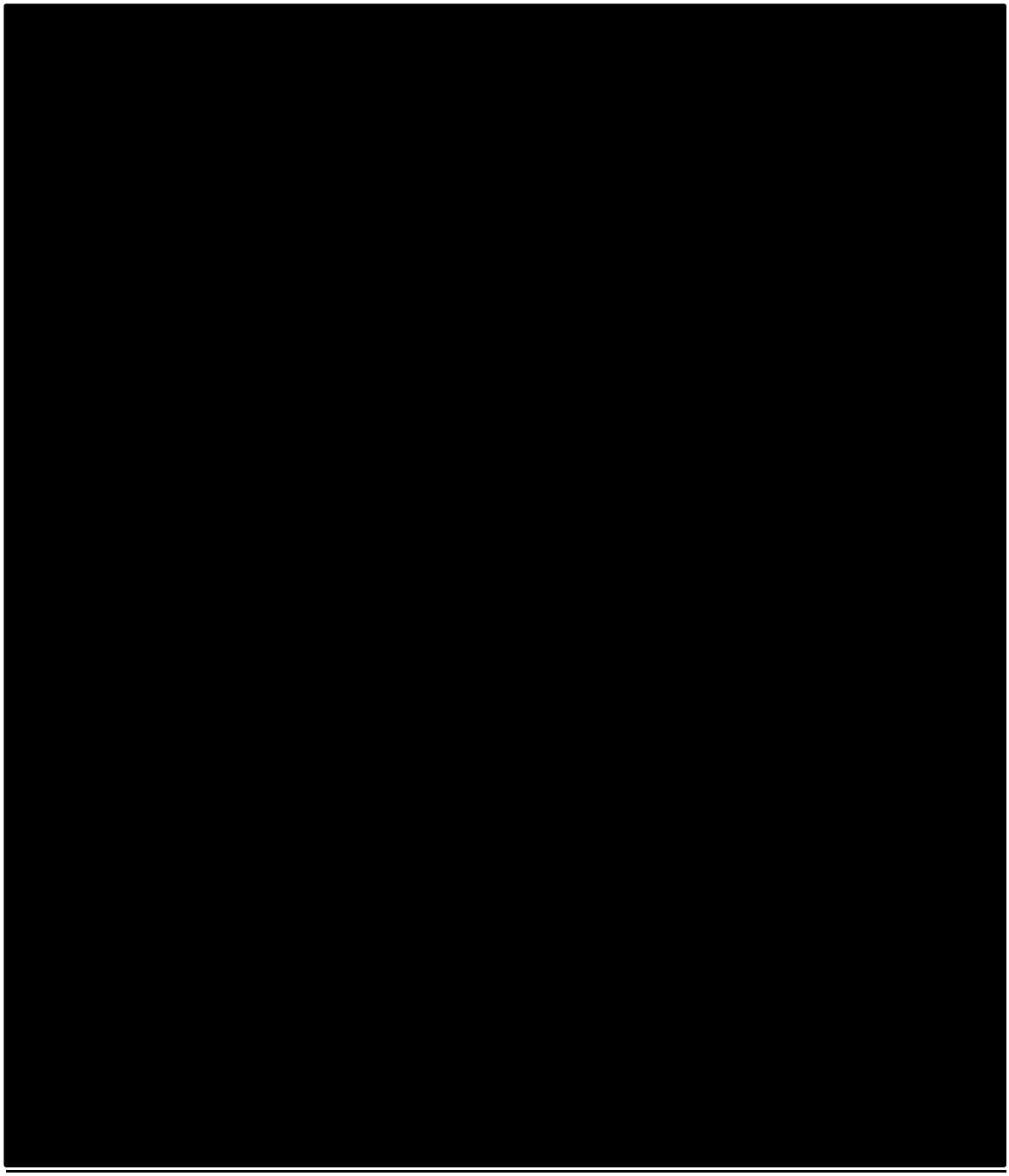
Table 30: Landmark analysis of primary efficacy endpoint: composite of CV death/MI/stroke (full analysis set)(62)

Time interval	Characteristic	Dose	
		Ticagrelor 60 mg	Placebo
1–360 days	n	[redacted]	[redacted]
	Patients with events (%)	[redacted]	[redacted]
	KM% at 12 months	[redacted]	[redacted]
	Hazard Ratio (95% CI)	[redacted]	
≥361 days	n[a]	[redacted]	[redacted]
	Patients with events (%)	[redacted]	[redacted]
	KM% at 24 months[b]	[redacted]	[redacted]
	KM% at 36 months[b]	[redacted]	[redacted]
	Hazard Ratio (95% CI)	[redacted]	

CI: Confidence interval; HR: Hazard ratio; KM: Kaplan-Meier; n: Number of patients in category or analysis; N: Number of patients in treatment group

a Only patients who are event-free in the first period (days 1-360) are included in the second period (day 361 and onwards). b Cumulative percentage from day 1 to 360 days after randomization and from day 361 to day 720 and 1080 respectively.

Figure 16: Kaplan-Meier plot of primary clinical endpoint from 1-360 days, and from 361 days and onwards (full analysis set)



On treatment (OT) analysis of the key efficacy endpoints

In PEGASUS TIMI-54 an ITT analysis was used for the analysis of all efficacy variables and included all patients randomized to study treatment, irrespective of their protocol adherence and exposure to study treatment. In contrast, the pre-planned exploratory OT efficacy analysis included all patients from the time from first administration of study drug until 7 days after the last dose of study drug (i.e. after permanent discontinuation).(62)

Both the ITT and OT analyses provide important information about the clinical study results. The ITT analysis should be viewed as the primary analysis of efficacy endpoints in a superiority study, such as PEGASUS-TIMI 54. However the OT analysis provides important information about efficacy, particularly in studies of a longer duration where there is considerable treatment discontinuation and where the rate of discontinuation differs between treatment groups, as in PEGASUS-TIMI 54. Similarity between these analyses is considered to be an indicator of the robustness of the study. The number of efficacy events in the ITT and OT analyses are presented in Table 31.

Table 31: Number of efficacy events in the ITT and OT analyses(70)

Endpoint	Analysis	Ticagrelor 60 mg BID n of events (36 month KM%)	Placebo n of events (36 month KM%)
CV death, MI or stroke	ITT OT	487 (7.77) 337 (6.8)	578 (9.04) 465 (8.4)
CV death	ITT OT	174 (2.86) 88 (1.8)	210 (3.39) 129 (2.4)
MI	ITT OT	285 (4.53) 206 (4.1)	338 (5.25) 274 (4.9)
Stroke	ITT OT	91 (1.47) 66 (1.4)	122 (1.94) 98 (1.8)
All-cause mortality	ITT OT	289 (4.69) 115 (2.4)	326 (5.16) 162 (3.1)

OT: on treatment; ITT: intention to treat; BID: twice daily; Kaplan Meier

In PEGASUS TIMI-54, the ITT and OT analyses showed similar results; both analyses demonstrated a statistically significant reduction in the primary endpoint: For ticagrelor 60 mg BID;

- The ITT analysis demonstrated a 1.27% ARR at 36 months versus placebo (KM estimates of 7.77% versus 9.04%), 16% RRR; HR=0.84 (95% CI 0.74 – 0.95), p=0.004

- The OT analysis demonstrated a 1.62% ARR at 36 months versus placebo (KM estimates of 6.8% versus 8.4%), 22% RRR; HR=0.78 (95% CI 0.68 – 0.90) p<0.001

The greater magnitude of effect in the OT analysis relative to the ITT analysis, is a consequence of a higher number of efficacy endpoints occurring off-treatment in patients randomised to ticagrelor, itself, a consequence of the higher number of patients who discontinued study medication in the ticagrelor arm of the study. (see section 4.12).(62)

It is important to bear in mind that the OT analysis selects patients and censor data based on post-randomization factors. Treatment discontinuation does not occur at random; it may be associated with the risk of the outcome event and may thus confer bias in the OT analysis and render interpretation difficult. However, it may also be a more accurate representation of efficacy in patients taking the medication. The OT analysis shows that the ischaemic risk was robustly reduced in patients continuing ADP receptor inhibition.

4.8 Subgroup analysis

A wide range of pre-specified subgroup analyses (Table 32) were conducted to examine the influence of patient characteristics on the primary endpoint. The results of these subgroup analyses for patients receiving 60 mg ticagrelor BID and placebo are presented in Figure 17 and Figure 18.(62)

The treatment effect was consistent across most pre-defined patient subgroups. There was no apparent heterogeneity in the efficacy of ticagrelor 60 mg BID with respect to the risk of the primary composite endpoint across major subgroups; the differences observed in hazard ratio point estimates were as expected given the large number of patient characteristics analysed.(62)

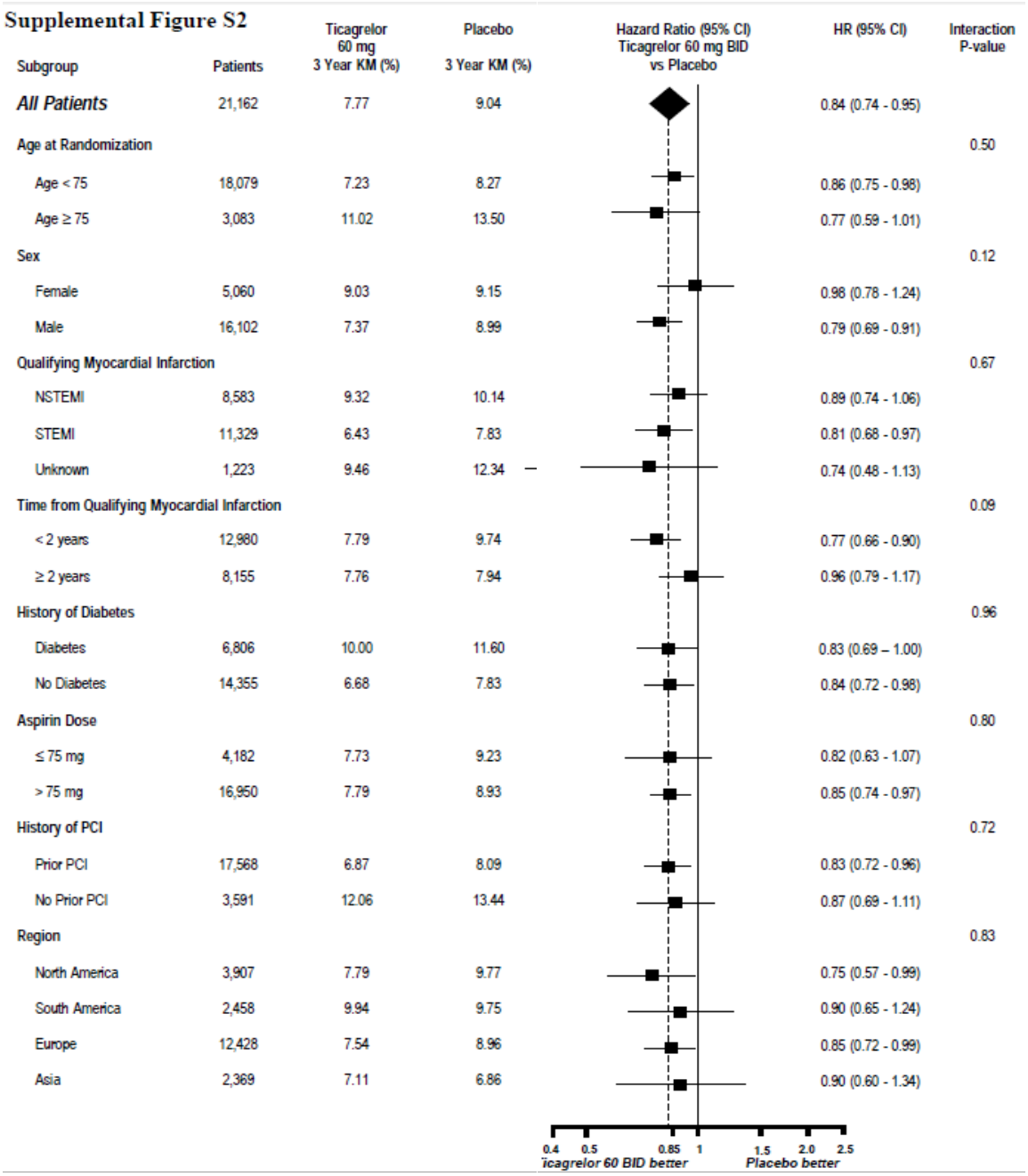
Table 32: Characteristics and categories for sub-group analysis of the primary composite endpoint(62)

Characteristic	Categories
Age (years)	<65, 65–75, >75
Sex	Male, Female
Race	Caucasian, Not Caucasian
Weight (kg)	<70, 70–90, >90
BMI (kg/m^2)	<30, ≥30
Geographic region	Asia and Australia • Australia, China, Japan, the Philippines, Republic of South Korea Europe and South Africa • Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Norway, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Turkey, UK, Ukraine North America • Canada, US South America • Argentina, Brazil, Chile, Colombia, Peru
History of more than 1 MI (≥1 year prior to randomisation)	Yes, No
Time from qualifying MI to randomisation(years)	<2, ≥2
Type of qualifying MI	STEMI, NSTEMI
Diabetes Mellitus	Yes, No
Multi vessel Coronary Artery Disease	Yes, No
Creatinine clearance (Cockroft Gault) at enrolment (mL/min)	<60, ≥60
History of PCI	Yes, No
History of coronary stent implantation	Yes, No
Type of stent	Any DES (including patients with both DES and BMS), BMS only
History of Angina	Yes, No
Current smoker	Yes, No
Time since previous treatment with ADP receptor blocker	<30 days, 30 days to 12 months, >12 months
ASA dose at randomisation (mg)	≤75, >75

ADP: Adenosine diphosphate; ASA: Acetyl salicylic acid; BMI: Body mass index; BMS: Bare metal stent; DES: Drug eluting stent; MI: Myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction

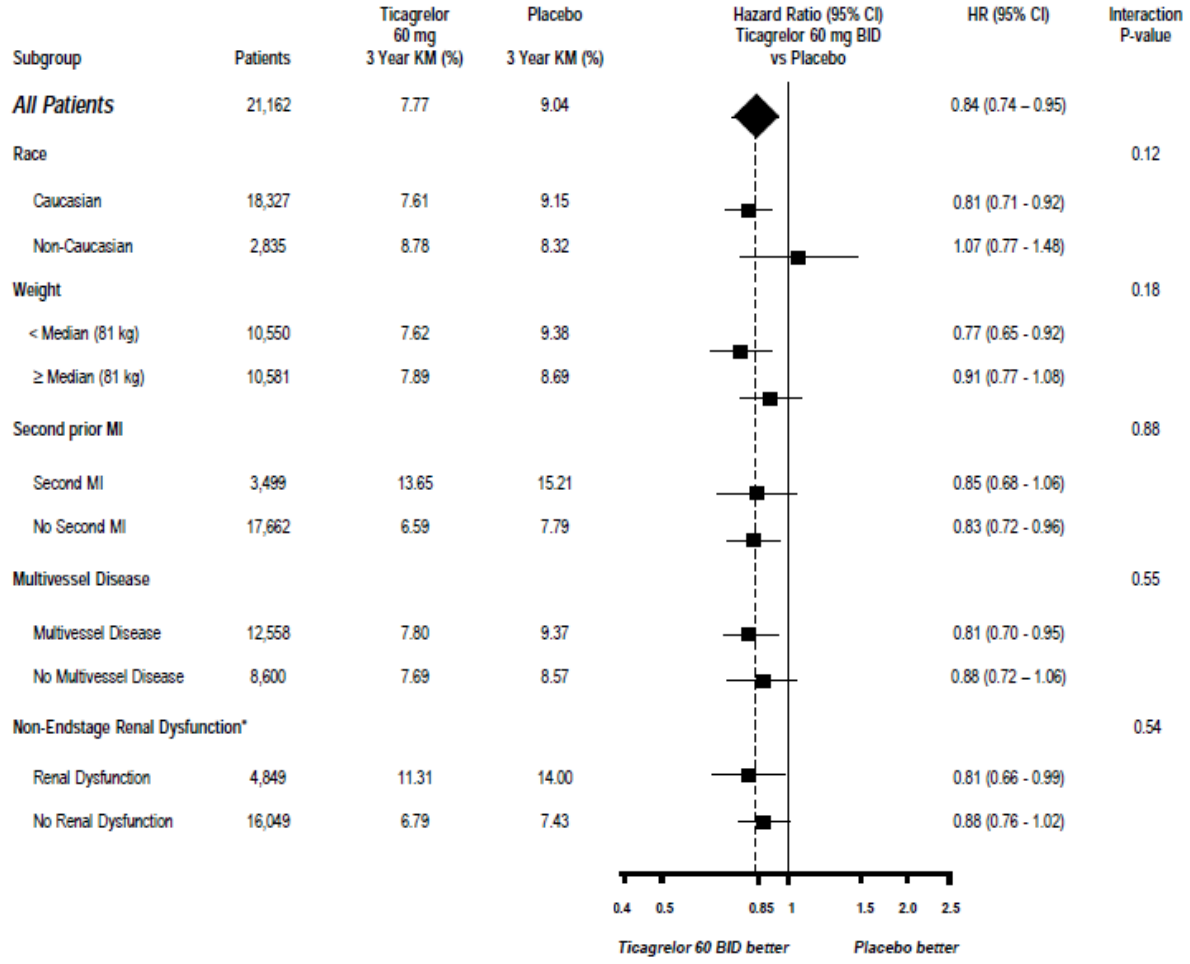
Figure 17: Primary efficacy endpoint across patient subgroups (modified from Bonaca et al 2015)(63)

Supplemental Figure S2



CI: confidence interval; HR: hazard ratio; KM: Kaplan Meier; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction

Figure 18: Continued primary efficacy endpoint across patient subgroups (modified from Bonaca et al 2015)[63]



CI: confidence interval; HR: hazard ratio; KM: Kaplan Meier; MI: myocardial infarction

Although there was no apparent heterogeneity in the efficacy of ticagrelor 60 mg BID with respect to the risk of the primary composite endpoint across major subgroups (Figure 17 and Figure 18), there was a numerically greater reduction in the ARR observed in patients with certain PEGASUS-like risk factors compared with those without.(60)

- Age:
  - 23% RRR (2.48% ARR) in the group aged ≥75 years
  - 14% RRR (1.04% ARR) in the group aged <75 years
- Multi-vessel CAD:
  - 19% RRR (1.57% ARR) in the group with multi-vessel CAD

    - 12% RRR (0.88% ARR) in the group without multi-vessel CAD
- Non-end stage renal disease:
    - 19% RRR (2.69% ARR) in the group with renal dysfunction
    - 12% RRR (0.64% ARR) in the group without renal dysfunction
- Diabetes:
    - 17% RRR (1.60% ARR) in the group with diabetes
    - 16% RRR (1.15% ARR) in the group without diabetes
- History of PCI:
    - 17% RRR; 1.22% ARR in the group with prior PCI
    - 13% RRR; 1.38% ARR in the group without prior PCI

Time from qualifying MI analysis

A pre-specified analysis of the PEGASUS-TIMI 54 was undertaken to determine whether the time from qualifying MI was associated with ischaemic risk and whether those patients with more recent MI derived greater benefit from long-term ticagrelor therapy. Patients were categorized according to the time from qualifying MI to randomization into 2 pre-specified groups (MI <2 years n= 8664; MI ≥2 years n= 5428).

Patients in the placebo arm who were less than 2 years from their MI were at higher risk for cardiovascular death, MI, or stroke (9.7% at 3 years) when compared with those who were at least 2 years from their MI before randomization (7.9% at 3 years). With regards to the primary efficacy endpoint, patients treated with ticagrelor 60 mg BID <2 years from their MI had HRs of 0.77 (95% CI 0.66–0.90, p=0.001) with an ARR of 1.9% (Table 33). It is estimated that, for every 10,000 patients who began treatment and were less than 2 years from their MI, 63 primary end-point events per year would be prevented with ticagrelor 60 mg BID compared to placebo.(33)

No clear benefit was seen in stable patients who were more than 2 years from their MI, with HRs of 0.96 (95% CI 0.79–1.17, p=0.6945) and an ARR of 0.1.

Table 33: Composite and individual component primary efficacy endpoint for patient subgroup: Time from qualifying MI as 3-year Kaplan-Meier estimates (full analysis) (62)

Sub group		Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID vs placebo		
	Patients	KM %	KM %	HR (95% CI)	p value	p value for interaction
CV death, MI or Stroke						
MI <2 years ago	8,664	7.8	9.7	0.77 (0.66, 0.90)	0.0010*	
MI > 2 - 3 years ago	5,428	7.8	7.9	0.96 (0.79, 1.17)	0.6945*	0.0868
CV death						
MI <2 years ago	8,664	[redacted]	[redacted]	[redacted]	[redacted]	
MI > 2 - 3 years ago	5,428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI						
MI <2 years ago	8,664	[redacted]	[redacted]	[redacted]	[redacted]	
MI > 2 - 3 years ago	5,428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke						
< MI <2 years ago	8,664	[redacted]	[redacted]	[redacted]	[redacted]	
MI > 2 - 3 years ago	5,428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All cause mortality						

ARR: absolute risk reduction; BID: twice daily; CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier; MI: myocardial infarction

* Nominal p-value

In summary, patients enrolled closest to their latest MI were at heightened ischaemic risk and therefore derived greater benefit from long-term ticagrelor therapy, whereas patients who remained event-free for an extended period were at relatively lower risk and derived no clear benefit from the addition of ticagrelor. These observations contributed to EMA's decision on the final wording of the license extension in this indication as discussed in Section 2.2. For clinicians considering a strategy of prolonged ADP receptor inhibitor therapy in high-risk patients, these data suggest greater benefit in the continuation of ticagrelor 60 mg BID without interruption after MI, rather than re-initiating ticagrelor 60 mg BID in patients who have remained stable for an extended period.

Time from ADP receptor inhibitor withdrawal analysis

A further pre-specified analysis assessed the effect of ticagrelor on CV death, MI or stroke by time from ADP receptor inhibitor withdrawal (<30 days, 30 days – 1 year and >1 year) exploring the question of whether the time interval between ADP receptor inhibitor cessation and the re-introduction of $P2Y_{12}$ inhibition using ticagrelor 60 mg BID influenced the anti-ischaemic benefit of the drug.

Patients in the placebo arm who had discontinued their ADP receptor inhibitor within 30 days of randomisation were at higher risk for cardiovascular death, MI, or stroke (10.0% at 3 years) when compared with those who had discontinued 30 days to 1 year prior (8.7%) and those who stopped more than 1 year before randomization (6.8%).

Patients treated with ticagrelor 60 mg BID after a brief interruption (<30 days) from ADP receptor inhibitor therapy derived the greatest reduction in CV death, MI or stroke versus placebo: HR 0.76; 95% CI 0.62 to 0.93; 24% RRR; 1.9% ARR. Patients treated with ticagrelor 60 mg BID after a longer period of withdrawal (30 days to 1 year) derived a more modest reduction in CV death, MI or stroke versus placebo: HR 0.81; 95% CI 0.65 to 1.01; 19% RRR; 1.6% ARR. In contrast, patients treated with ticagrelor 60 mg BID after surviving event-free >1 year on aspirin monotherapy experienced no reduction in CV death, MI or stroke versus placebo: HR 1.08; 95% CI 0.82 to 1.42; -8% RRR; -0.2% ARR and therefore derived no clear benefit from the addition of ticagrelor 60 mg BID (Table 34 and Figure 19).

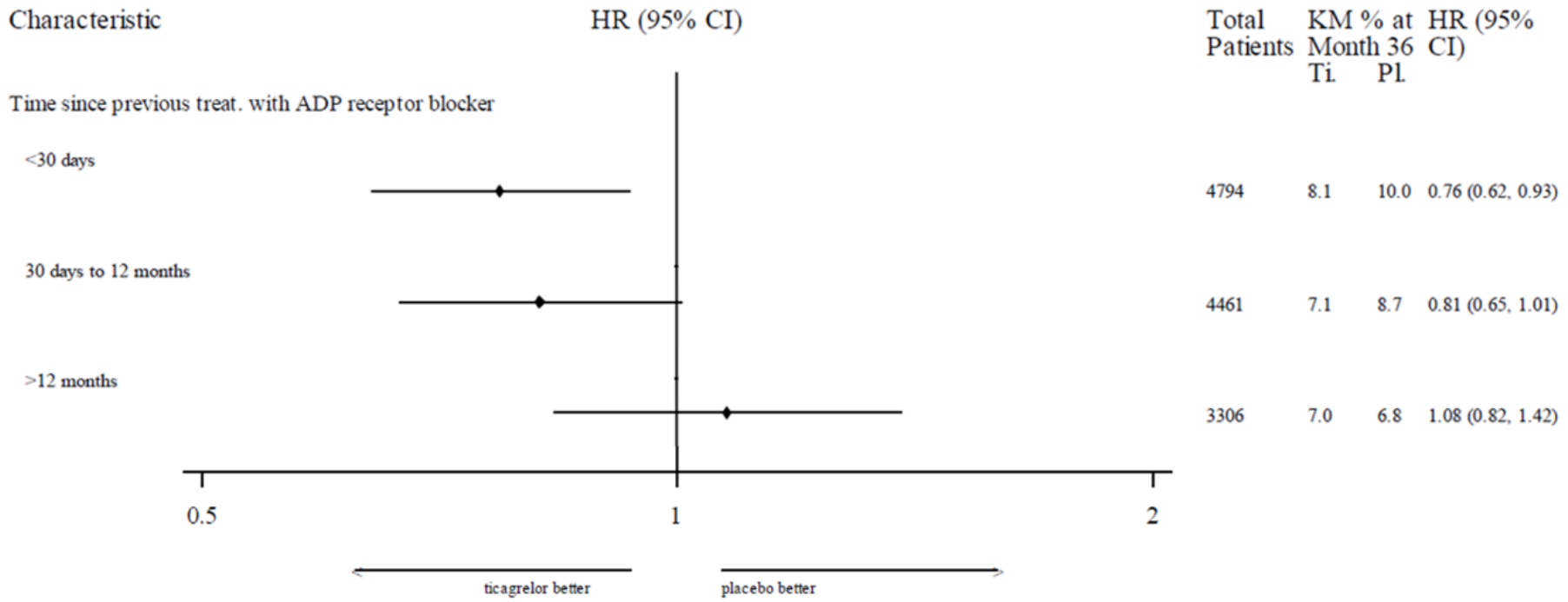
Table 34: Composite and individual component primary efficacy endpoint for patient subgroup: Time since previous ADP receptor inhibitor as 3-year Kaplan-Meier estimates (full analysis), (62)

Sub group		Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID vs placebo		
	Patients	KM %	KM %	HR (95% CI)	p value	p value for interaction
CV Death, MI or Stroke						
<30 days	4794	8.1	10.0	0.76 (0.62, 0.93)	0.0075	
30 days to 1 year	4461	7.1	8.7	0.81 (0.65, 1.01)	0.0584	
>1 year	3306	7.0	6.8	1.08 (0.82, 1.42)	0.5726	0.1067
CV death						
<30 days	4794	2.5	3.0	0.75 (0.52, 1.10)	0.1395	
30 days to 1 year	4461	2.2	3.1	0.68 (0.46, 1.01)	0.0535	
>1 year	3306	2.8	2.2	1.47 (0.93, 2.34)	0.1016	0.0292
MI						
<30 days	4794	5.3	6.4	0.77 (0.60, 0.99)	0.0455	
30 days to 1 year	4461	4.5	5.1	0.89 (0.67, 1.17)	0.3960	
>1 year	3306	4.2	4.5	0.96 (0.68, 1.35)	0.7995	0.5780
Stroke						
<30 days	4794	1.6	2.1	0.70 (0.44, 1.11)	0.1325	
30 days to 1 year	4461	1.4	2.0	0.75 (0.46, 1.22)	0.2449	
>1 year	3306	1.2	1.3	1.05 (0.56, 1.97)	0.8747	0.5739

ARR: absolute risk reduction; BID: twice daily; CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier; MI: myocardial infarction

* Nominal p-value

Figure 19: Primary efficacy endpoint in ticagrelor 60 mg BID compared to placebo by time from ADP receptor inhibitor withdrawal



The ischaemic risk was robustly reduced for ticagrelor 60 mg BID particularly in those patients continuing ADP receptor inhibition or restarting after a brief interruption (<30 days). These observations contributed to the EMA's decision on the wording of the posology section of the licence extension (see Section 2.2).

Additional Subgroup analyses specified in the Decision Problem

The final scope of the decision problem (Section 1.1) requests subgroup data for patients with or without diabetes and with or without a history of revascularization. It should be noted that the PEGASUS-TIMI 54 trial did not record or stratify patients according to revascularization specifically. However, primary analysis was stratified according to a history of percutaneous coronary intervention (PCI) and the results of the primary efficacy endpoint for these, as well as those according to diabetes status in the full PEGASUS-TIMI 54 population are presented in Figure 17 and Figure 18.

The licensed population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically sound as the trial was not powered to draw conclusions about (non-pre-specified) subgroups of subgroups. However, in order to provide evidence for these specific subgroups of patients aligned with the base case for this submission and within the limits of the marketing authorisation, we present subgroup analyses of composite and components of the primary efficacy endpoint for patients who experienced an MI <2 years ago, with or without diabetes, and with or without a history of PCI. Caution is advised when interpreting these results for the reasons set out above.

Table 35: Key efficacy endpoints for patient subgroup: (full analysis set; patients with MI <2 years ago, with and without diabetes)

Characteristic		Diabetes		No Diabetes	
		Ticagrelor 60mg BID	Placebo	Ticagrelor 60mg BID	Placebo
		(N=1419)	(N=1322)	(N=2912)	(N=3011)
Composite of CV death/MI/Stroke	Patients with events	128 (9.0%)	144 (10.9%)	165 (5.7%)	231 (7.7%)
	KM %	10.50%	12.10%	6.50%	8.70%
	Hazard Ratio (95% CI)	0.82 (0.64, 1.04)		0.73 (0.60, 0.89)	
	p-value	0.096		0.0023	
CV death	Patients with events	47 (3.3%)	64 (4.8%)	47 (1.6%)	73 (2.4%)
	KM %	3.70%	5.50%	2.00%	2.90%
	Hazard Ratio (95% CI)	0.68 (0.47, 0.99)		0.66 (0.46, 0.96)	
	p-value	0.0447		0.0286	
MI	Patients with events	79 (5.6%)	76 (5.7%)	101 (3.5%)	145 (4.8%)
	KM %	6.80%	6.40%	3.90%	5.40%
	Hazard Ratio (95% CI)	0.96 (0.70, 1.32)		0.72 (0.55, 0.92)	
	p-value	0.7984		0.0098	
Stroke	Patients with events	21 (1.5%)	33 (2.5%)	36 (1.2%)	46 (1.5%)
	KM %	1.70%	2.70%	1.40%	1.90%
	Hazard Ratio (95% CI)	0.59 (0.34, 1.02)		0.81 (0.52, 1.25)	
	p-value	0.0574		0.3365	

Table 36: Key efficacy endpoints for patient subgroup: (full analysis set; patients with MI <2 years ago, with and without a history of PCI)

Characteristic		History of PCI		No History of PCI	
		Ticagrelor 60mg BID	Placebo	Ticagrelor 60mg BID	Placebo
		(N=3638)	(N=3623)	(N=692)	(N=709)
Composite of CV death/MI/Stroke	Patients with events	218 (6.0%)	277 (7.6%)	75 (10.8%)	98 (13.8%)
	KM %	6.90%	8.50%	12.10%	15.80%
	Hazard Ratio (95% CI)	0.78 (0.65, 0.93)		0.76 (0.56, 1.02)	
	p-value	0.0059		0.0717	
CV death	Patients with events	51 (1.4%)	81 (2.2%)	43 (6.2%)	56 (7.9%)
	KM %	1.60%	2.60%	7.10%	9.50%
	Hazard Ratio (95% CI)	0.63 (0.44, 0.89)		0.77 (0.52, 1.14)	
	p-value	0.009		0.1929	
MI	Patients with events	148 (4.1%)	182 (5.0%)	32 (4.6%)	39 (5.5%)
	KM %	4.80%	5.50%	5.20%	6.30%
	Hazard Ratio (95% CI)	0.81 (0.65, 1.00)		0.82 (0.51, 1.31)	
	p-value	0.0517		0.404	
Stroke	Patients with events	44 (1.2%)	54 (1.5%)	13 (1.9%)	25 (3.5%)
	KM %	1.30%	1.70%	2.40%	4.40%
	Hazard Ratio (95% CI)	0.81 (0.55, 1.21)		0.51 (0.26, 1.00)	
	p-value	0.3062		0.0517	

4.9 Meta-analysis

Please see section 4.10.

4.10 Indirect and mixed treatment comparisons

Search strategy

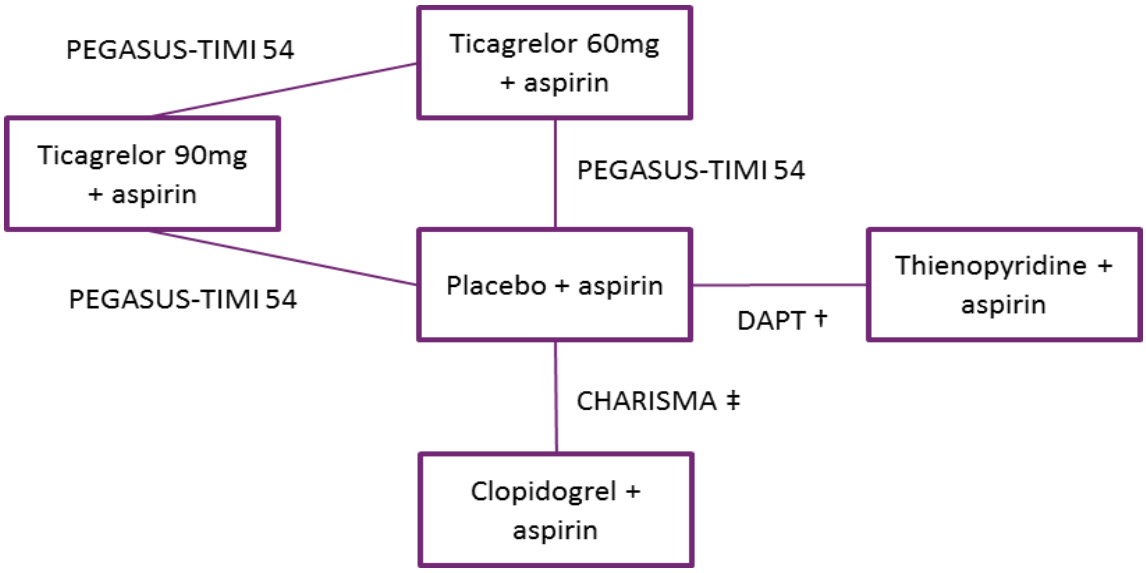
The objective of the search was to identify studies that could potentially be used to generate a robust indirect comparison to clopidogrel + ASA (in line with the appraisal scope), given the absence of a head-to-head (H2H) study. Details of the search strategy are provided in Section 4.1.

Study selection

The 3 unique RCTs identified in the systematic literature review were considered potentially useful for a network meta-analysis or assessment of indirect or mixed treatment comparison. Such comparison is only recommended given that the trials share a common comparator and are broadly homogenous with regard to their trial and patient characteristics to ensure analyses are not misleading and produce erroneous conclusions (71).

Based on an initial assessment of meta-analysis feasibility it was possible to produce a base-case evidence network as seen in Figure 20. This base-case network was constructed regardless of the study design, patient populations and outcomes reported across the three RCTs and represents a “best-case scenario”. The best-case evidence network would allow for an indirect comparison of ticagrelor + ASA with thienopyridine + ASA and clopidogrel + ASA via the common comparator placebo + ASA.

Figure 20: Base case evidence network assuming prior treatment has no influence on treatment effect



† Using data reported in the Yeh (2015) publication (72)
‡ Using data reported in the Bhatt (2007) publication (50)

It is worth noting that patients enrolled in the thienopyridine + ASA treatment arm in the DAPT trial received either clopidogrel (66% of patients) or prasugrel (34% of patients). The majority of outcomes were reported for the combined thienopyridine plus ASA arm compared to placebo alone, with only the incidence of stent thrombosis, MI, and moderate or severe bleeding (on the GUSTO scale) available for the individual treatments (72, 73). A comparison between ticagrelor + ASA and clopidogrel + ASA would be feasible in the “best case” scenario as data were reported in the CHARISMA trial (50). To allow comparisons with the grouped treatment arm (thienopyridine + ASA) the assumption that clopidogrel and prasugrel have the same treatment effect is required.

Risk of bias

Results of the quality assessment, conducted using the Cochrane Collaboration’s tool for assessing risk of bias, are presented in Table 37.

Table 37. Results of quality assessment using the Cochrane Collaboration's tool for assessing risk of bias

Domain	Yeh 2015 (51) (supplemented by information reported in Mauri 2010 (73))		Bhatt 2007 (50)	
	Support for judgement	**Review authors' judgement**	**Support for judgement**	**Review authors' judgement**
Selection bias				
Random sequence generation.	A computer-generated randomisation schedule was used to assign subjects to treatment, stratified by DES/BMS use	Low risk	Patients were randomised but details of the sequence generation were not reported; insufficient information	Unclear risk
Allocation concealment.	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk
Performance bias				
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes).	Treating physicians, subjects, personnel at investigative sites, Clinical Events Committee, and all study staff and investigators, other than data safety monitoring board and one statistician and programmer, were blinded to treatment assignment	Low risk	Randomisation was double-blinded; no further details provided	Low risk
Detection bias				
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes).	Clinical Events Committee were blinded to treatment assignments	Low risk	Clinical events were validated by the Cleveland Clinic Clinical Events Adjudication Committee	Unclear risk
Attrition bias				
Incomplete outcome data	CONSORT diagram provided;	Low risk	Insufficient information to	Unclear risk

Domain	Yeh 2015 (51) (supplemented by information reported in Mauri 2010 (73))		Bhatt 2007 (50)	
	Support for judgement	**Review authors' judgement**	**Support for judgement**	**Review authors' judgement**
Assessments should be made for each main outcome (or class of outcomes).	missing outcome data appears balanced across groups and similar reasons for missing data across groups		permit judgement of 'Low risk' or 'High risk'	
Reporting bias				
Selective reporting.	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk
Other bias				
Other sources of bias.	The study appears to be free of other sources of bias	Low risk	The study appears to be free of other sources of bias	Low risk

BMS: bare metal stent; DES: drug-eluting stent.

Cochrane Collaboration tool for assessing risk of bias (68).

Study design

In the three included trials, the objective was to analyse the effect of prolonged DAPT (defined as greater than 12 months) in adult patients with risk factors for atherothrombotic disease. Treatment duration was reported to be 18 months in the DAPT trial (72), and was not explicitly reported in the CHARISMA and PEGASUS-TIMI 54 trials. Patients in the CHARISMA and PEGASUS-TIMI 54 trials were treated until study end and followed for a median of 28 months and 33 months respectively (50, 74).

The DAPT trial (73) reported that patients randomised to either thienopyridine + ASA or placebo + ASA had experienced no interruptions (defined as 14 days or less) to initial treatment prior to randomisation (72).

It is unclear in the CHARISMA trial (50, 58) how many patients received treatment prior to randomisation and whether there was a break in treatment; however the PEGASUS-TIMI 54 trial reported that 89% of patients were treated with an ADP blocker (72). The sub-analysis of the PEGASUS-TIMI 54 trial stratified patients by the duration of withdrawal from prior therapy before randomisation into three groups: <30 days, ≥30-360 days and >360 days prior to randomisation (74).

The results of the sub-analysis of the PEGASUS-TIMI 54 trial suggest that the time from ADP receptor inhibitor withdrawal impacts treatment effect, with the greatest benefit of extended DAPT beyond 1 year from the index MI seen in patients who withdrew from treatment ≤30 days prior to randomisation (74). This is an important source of heterogeneity to consider when combining studies in a meta-analysis. Based on the differences in study design, the patients from the sub-analysis of the PEGASUS-TIMI 54 trial (74) who stopped prior ADP inhibitor therapy <30 days prior to randomisation could be considered the most comparable with the patients reported in the sub-analysis of the DAPT trial (72) who presented with MI prior to enrolment in the DAPT trial.

Patient population: prior antiplatelet therapy

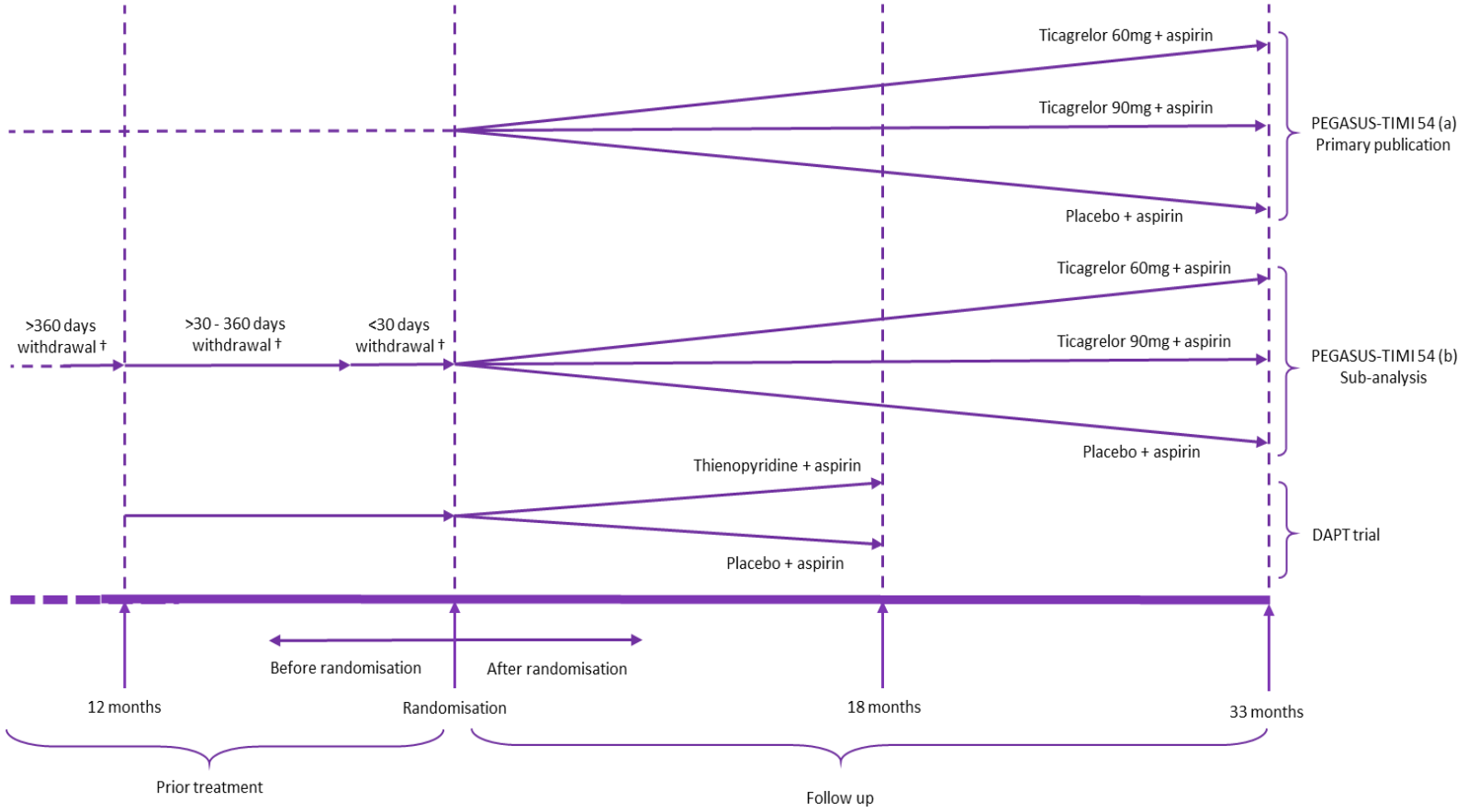
Whilst all patients in the included trials were randomised to either DAPT or placebo plus aspirin, patients in the DAPT trial had also received treatment with a ADP receptor inhibitor for 12 months prior to randomisation. Patients who tolerated this

treatment and did not experience an event, were then randomised to thienopyridine plus aspirin or placebo plus aspirin (15). This could introduce selection bias to the patient population and impact on the time to event, as patients who tolerate treatment could be considered a less ‘at risk’ population than those who experienced an event within the initial 12 months.

The detailed inclusion criteria of the PEGASUS-TIMI 54 trial state that patients may or may not have previously been on a ADP receptor inhibitor and could be randomised on cessation of ADP receptor therapy. It is reported that all patients included in the sub-analysis of the PEGASUS-TIMI 54 trial (89% of patients from the primary analysis) had received prior therapy with an ADP blocker at some point leading up to randomisation; however the precise duration of the prior treatment was not reported (14). There are no details reported regarding the prior treatment of patients enrolled in the CHARISMA trial (50).

A visual summary of the treatment regimens and duration is shown in Figure 21 and this highlights important differences between the studies.

Figure 21: Study design of the three publications of interest



The dashed line for the PEGASUS-TIMI 54 primary publication indicates that patients may or may not have received prior therapy, treatment duration is not reported
† It is not known how long patients were on prior treatment for, only when treatment was stopped prior to randomisation
‡ Median follow up time

Patient population: percutaneous coronary intervention

In addition to prior ADP receptor therapy it is important to note that all patients enrolled in the DAPT trial also received either a drug eluting stent (DES) or a bare metal stent (BMS) as a form of PCI prior to receiving DAPT. It has been shown that compared with BMS, DES might be associated with higher rates of stent thrombosis and the effect on other cardiovascular and cerebrovascular events is unclear (73). Eighty percent of patients enrolled on the PEGASUS-TIMI 54 trial had a history of PCI. Of these, 51% (n=8597) received a BMS and 49% (n=8294) a DES (75). The eligibility criteria detailed in the CHARISMA trial (58) included patients who had documented coronary artery disease, cerebrovascular disease, or PAD, or with multiple risk factors for atherothrombosis and therefore not all patients had received a PCI. The sub-analysis of the CHARISMA trial focused on patients with history of MI and only 26% of patients in both the clopidogrel + ASA and placebo + ASA treatment arms had received a PCI (50). This is an important source of heterogeneity to consider when assessing the feasibility of combining trials in a meta-analysis.

Patient population: Baseline characteristics

The main baseline characteristics of patients enrolled in the PEGASUS-TIMI 54, CHARISMA, and DAPT trials are summarised in Table 2. The baseline characteristics of patients who withdrew from prior therapy ≤30 days prior to randomisation across all treatment arms in the sub-analysis of the PEGASUS-TIMI 54 trial are also summarised in Table 38. It is important to note that the baseline characteristics in the CHARISMA trial for the subgroup of 3846 patients with a history of MI were not reported (50). The baseline characteristics are well balanced within both the PEGASUS-TIMI 54 and DAPT trials although there are differences between the included trials.

Time since prior MI is potentially an important risk factor for recurrent events (74, 76) and was reported in the PEGASUS-TIMI 54 trial to be a median of 1.7 years (IQR 1.2-2.3 years), 28.3 months in the prior MI subgroup of the CHARISMA trial, and was not reported in the sub-analysis of the DAPT trial for the subgroup of patients who had a prior MI. It can be assumed that the primary MI occurred >1 year before randomisation as patients were enrolled onto the DAPT trial within 72 hours after

placement of a stent (72). According to the NICE pathway for patients with MI with ST-segment elevation, PCI is recommended within 12 hours of onset of symptoms (77).

It is also noted in the inclusion criteria of the DAPT trial that patients were required not to have experienced an event (defined as MI, stroke or bleeding) for 12 months prior to randomisation (73). The inclusion criteria of the PEGASUS-TIMI 54 trial reported that patients had a history of MI 1-3 years prior to randomisation, therefore patients were also event free for 12 months prior to randomisation (78). The CHARISMA trial reported that the time since qualifying event (prior MI) and randomisation to the treatment arms was a median of 23.6 months, and patients may have had more than one prior event (PAD or stroke) with 443 patients falling into multiple categories. The different types of initial MIs experienced (STEMI or NSTEMI) are broadly comparable across the PEGASUS-TIMI 54 and DAPT trials however it is important to note that patients in the CHARISMA trial were excluded from enrolment if the patient required prolonged clopidogrel therapy, such as patients who have had a recent non–ST-segment elevation ACS (50).

A higher proportion of patients reported hypertension (78%) and diabetes (32-33%) as a comorbidity in the PEGASUS-TIMI 54 trial compared with patients enrolled in the DAPT trial (56-60% and 21% respectively). Whilst the prevalence of diabetes is associated with an aging population, both increased age and the presence of diabetes have been shown to be major risk factors for cardiovascular disease (79, 80) and are characteristics that need to be considered when evaluating the results of any comparisons.

Whilst the percentage of females enrolled in the trials was similar in the PEGASUS-TIMI 54 trial (24%) and the DAPT trial (21-22%), the age of the patients varied between the trials. The PEGASUS-TIMI 54 trial enrolled an older patient population, with a mean age of between 65.2 and 65.4 years, compared with 57.7 and 57.9 years in the DAPT trial. The age of the patients specifically with prior MI was not reported in the CHARISMA trial.

The smoking status and weight of the patients also showed differences between the included trials with approximately double the proportion of patients being current

smokers in the DAPT trial (41%) compared with the PEGASUS-TIMI 54 trial (16-17%).

The comparison of baseline characteristics highlighted a number of differences between the trials which may be considered important sources of heterogeneity. Many assumptions would be required when considering the equivalence of the patient populations of the included trials. Any comparisons between these patient populations require that such assumptions of comparability should be clinically validated prior to analysis.

Table 38: Study characteristics of publications included for feasibility

Study characteristics		PEGASUS-TIMI 54† (49) (n=21162)			Sub-analysis of PEGASUS-TIMI 54 (74) (n=18761)	Sub-analysis of DAPT (72) MI patients only (n=3576)		Sub-analysis of CHARISMA§ (50) MI patients only (n=3846)	
		Ticagrelor 90mg + aspirin††	Ticagrelor 60mg + aspirin	Placebo + aspirin	Patients stopped ≤30 days prior to randomisation across all treatment arms	Thieno-pyridine + aspirin	Placebo + aspirin	Clopidogrel + aspirin	Placebo + aspirin
No. of patients		7050	7045	7067	7181	1805	1771	1903	1943
Follow up (months)		33 (28-37)‡			3‡‡	18‡		NR	
Age (years)		65.4 ± 8.4	65.2 ± 8.4	65.4 ± 8.3	65 (58-71)‡	57.9 ± 10.5	57.7 ± 10.5	NR	NR
Sex (female)		1682 (23.9)	1661 (23.6)	1717 (24.3)	(22)	(22.4)	(21.2)	NR	NR
Type of MI	STEMI	3763 (53.4)	3757 (53.4)	3809 (54.0)	(55)	(46.8)	(47.2)	NR	NR
	NSTEMI	2898 (41.1)	2842 (40.4)	2843 (40.3)	(41)	(53.2)	(52.9)	NR	NR
	Other/unknown	382 (5.4)	436 (6.2)	405 (5.7)	(4)	(0)	(0)	NR	NR
Time since prior MI (years)		1.7 (1.2-2.3)‡	1.7 (1.2-2.3)‡	1.7 (1.2-2.3)‡	16 (13-24)‡ §§	NR¶	NR¶	NR	
Diabetes mellitus		2241 (31.8)	2308 (32.8)	2257 (31.9)	(33)	(20.8)	(21.0)	NR	NR
Hypertension		5462 (77.5)	5461 (77.5)	5484 (77.6)	(78)	(59.8)	(56.4)	NR	NR
Current smoker		1187 (16.8)	1206 (17.1)	1143 (16.2)	(17)	(41.8)	(41.8)	NR	NR
Weight (kg)		82.0 ± 16.7	82.0 ± 17.0	81.8 ±16.6	NR¶¶	89.7 ± 19.1	90.8 ± 19.0	NR	NR

No baseline characteristics were reported for the MI subgroup of the CHARISMA trial, values are mean ± SD or number of patients (%) unless otherwise stated

MI: myocardial infarction; No.: number; NR: not reported; NSTEMI: non-ST segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction
† The baseline characteristics have been obtained from the primary publication, baseline characteristics are similar to those presented in the PEGASUS-TIMI 54 sub-analysis (74) however they are stratified to those patients who withdrew from prior ADP receptor ≤30 days, ≥30-360 days and >360 days prior to randomisation

‡ Median (IQR), § Not all patients in the sub-analysis had prior MI, some patients experienced prior ischaemic, stroke, PAD or multiple events (specific type of MI not reported). ¶ Can assume ≥1 year prior to randomisation as patients were enrolled within 72 hours after placement of stent and were stratified by MI status, †† Unlicensed dose for patients requiring prolonged treatment, ‡‡ Reported in years (taken from the Kaplan Meier curves), §§ Reported in months

Conclusions

Eligible publications reporting on the PEGASUS-TIMI 54, CHARISMA and DAPT trials have been identified by the systematic literature review and could potentially allow for an indirect comparison of DAPT in patients with a history of MI. However, on review of the study designs and patient populations several important sources of heterogeneity have been identified. To proceed with an indirect comparison between the PEGASUS-TIMI 54, DAPT, and CHARISMA trials a number of assumptions would require clinical validation prior to performing analyses, including:

- Baseline characteristic data are not reported for the subgroup of interest (history of MI) in the CHARISMA trial and therefore it is assumed there were no important differences between the baseline characteristics across all included trials.
- Patients who experienced multiple different prior atherothrombotic events (MI, stroke or PAD) have the same response to treatment regardless of the prior event.
- There is a class effect of thienopyridines (clopidogrel and prasugrel) in the DAPT study.
- The relative treatment effects of prolonged treatment with dual antiplatelets (i.e. clopidogrel, prasugrel or ticagrelor with low-dose ASA) are NOT impacted by the following:
    - The selection bias in patients who had tolerated treatment in the first 12 months of the DAPT trial
    - Prior duration of antiplatelet therapy
    - Time since cessation of prior antiplatelet therapy
    - Time since prior MI
    - The type of MI experienced (STEMI or NSTEMI)
    - Known risk factors for cardiovascular events including age, smoking, diabetes status, incidence of hypertension
    - Previous PCI (and the type of stent)
    - Treatment duration of 18 months (DAPT), and assumed follow-up of 28 months (CHARISMA) and 33 months (PEGASUS-TIMI 54) can be considered comparable

(assuming that relative treatment effects remain constant over time).

In summary, there is currently a lack of evidence regarding prolonged treatment use (defined as greater than 12 months) in this patient population. Three RCTs were considered for inclusion in the network of evidence, examining the following treatments: ticagrelor plus ASA, clopidogrel plus ASA, and thienopyridine plus ASA with the common comparator of placebo plus ASA. However, the network of evidence is not considered to be robust due to the many assumptions required to conduct the analysis. Therefore, analysis using methods of indirect comparison or network meta-analysis (NMA) have not been performed. The rationale for this decision has been supported by an advisory board of clinical and statistical experts.

4.11 Non-randomised and non-controlled evidence

An observational study of 1676 patients in England (treated between 2005 and 2010) surviving one year after an acute MI and meeting the inclusion and exclusion criteria for PEGASUS-TIMI 54 demonstrated an 18.8% risk of recurrent MI, stroke of CV death in the following 3 years, twice the risk seen in the placebo arm of PEGASUS-TIMI 54. These 'target patients' were identified using linked primary and secondary care electronic health records from CALIBER (ClinicAl research using LInked Bespoke studies and Electronic health Records).

Patient characteristics of the target population were compared with the PEGASUS-TIMI 54 trial participants and a number of differences were identified. The target population was 12 years older and included proportionately more women and more patients with NSTEMI compared with the PEGASUS-TIMI-54 trial population. Analysis of the trial high-risk inclusion criteria showed that age ≥65 characterized 90% of CALIBER's target population compared with 55% of the PEGASUS-TIMI-54 trial population. Similarly, renal dysfunction (eGFR <60ml/min/1.73m^2) was also more prevalent in the target population but other risk factors including second prior MI and diabetes were less prevalent compared with the trial. Baseline utilisation of aspirin, beta-blockers and statins was seen to be lower in the target population compared with the trial (Table 39).

Table 39. Baseline characteristics of the history of MI survivor populations defined in this study and the equivalent characteristics from the PEGASUS-TIMI-54 trial.

Baseline characteristics	Target CALIBER data from England population	PEGASUS-TIMI-54 trial Placebo
N	**1676**	**7067**
Age, years, mean (SD)	77.0 (9.6)	65.4 (8.3)
Female	814 (48.6%)	1717 (24.3)
White race	1350 (95.7%)	6124 (86.7)
Weight, kg, mean (SD)	74.8 (17.4)	81.8 (16.6)
Hypertension	1090 (65.0%)	5484 (77.6)
Hypercholesterolemia	N/A	5451 (77.1)
Current smoker†	162 (10.6%)	1143 (16.2)
Diabetes mellitus	392 (24.4%)	2257 (31.9)
Multivessel coronary artery disease	N/A	4213 (59.6)
History of PCI*	391 (23.3%)	5837/7066 (82.6)
>1 myocardial infarction	191 (11.4%)	1188 (16.8)
Peripheral arterial disease	101 (6.0%)	404 (5.7)
eGFR<60ml/min/1.73m^2 †	797 (52.3%)	1649 (23.6)
Qualifying event		
Median years since MI	1.0	1.7
Interquartile range	1-1	1.2–2.3
Index myocardial infarction		
STEMI	599 (35.7%)	3809 (54.0)
NSTEMI	1077 (64.3%)	2843 (40.3)
Medications at study entry		
Any aspirin	1,250 (74.6%)	7057 (99.9)
Statins	1,335 (79.7%)	6583 (93.2)
Beta-blockers	1,065 (63.5%)	5878 (83.2)
ARBs/ACEIs	1,283 (76.6%)	5697 (80.6)

SD: standard deviation; PCI: percutaneous coronary intervention; eGFR: estimated glomerular filtration rate; STEMI: ST elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; ARBs: angiotensin II receptor blockers; ACEIs: angiotensin-converting-enzyme inhibitorsPCI in the last 365 days

† weight information was available for 65% CALIBER patients, smoking status was available in 94% patients and eGFR information available for 88% patients in CALIBER.

In CALIBER's target population the 3-year Kaplan-Meier rates for a composite outcome of MI, stroke or fatal CVD were 18.8% (16.3-21.8%), compared with 9.04% in the trial placebo group. Applying 3-year relative risk reduction for trial participants treated with ticagrelor 60mg BID, resulted in 101 (87-117) ischaemic events prevented per 10,000 treated per year. The 3-year rates of fatal-or-intracranial bleeding in the target population was approximately twice the 0.6% rate in the trial. Applying 3-year relative risk increase for the full trial population treated with ticagrelor 60mg BID, the excess fatal, severe or intracranial bleeds caused per 10,000 treated per year was calculated to be 75 (50-110). For fatal-or-intracranial bleeding, excess events per 10,000 treated per year were 10 (6-18) (Table 40).

Table 40: Observed cumulative event rate % of clinical outcomes and number of event prevented or harm caused, applying trial results to the UK history of MI patients populations defined in the study (with 95% CI).

	Met trial inclusion & exclusion criteria 'Target '	**PEGASUS-TIMI-54 Trial Placebo arm**
	n=1676	**n=7067**
MI/stroke/fatal CVD death		
3-year cumulative risk (%)	18.8 (16.3,21.8)	9.04
Number events prevented per year per 10,000 patients treated applying risk reduction in PEGASUS-TIMI-54 trial[1]	101 (87-117)	
Fatal, severe or intracranial bleeding		
3-year cumulative risk (%)	3.0 (2.0,4.4)	1.26[2]
Number excess harms per year per 10,000 patients treated applying risk increase in PEGASUS-TIMI-54 trial[1]	75 (50-110)	
Fatal or intracranial bleeding		
3-year cumulative risk (%)	1.5 (0.8,2.7)	0.6
Number excess harms per year per 10,000 patients treated applying risk increase in PEGASUS-TIMI-54 trial[2]	10 (6-18)	

1 PEGASUS-TIMI 54 trial estimates [ticagrelor 60 mg vs. placebo; intention to treat estimates] for CV death, stroke or MI [hazard ratio: 0.84, main report], TIMI major bleeding [relative risk: 1.75, appendix E], were used to calculate CV events prevented and harms caused per 10,000 treated per year; 2TIMI-Major bleeding.

2Based on applying the trial on-treatment relative risks of the ticagrelor 60 mg vs. placebo comparison: 1.20 (fatal or intracranial bleeding) to the CALIBER population.

The cardiovascular risk in this “target” population was high compared to the trial population, with approximately twice the rate of non-fatal and fatal cardiovascular events in the subsequent 3 years. The analysis indicated that addition of ticagrelor to the treatment regimen of these patients may prevent 101 of these events per year for every 10,000 patients treated, at the cost of 75 major bleeds. This ratio is almost identical to the calculation reported in the main trial results (42 vs 31), although the absolute magnitude of potential net benefit of 26 is greater in the real world data.

The main strength of this study was in its use of CALIBER’s linked Electronic Health Records (EHRs) to assemble a large target population for comparison with participants in a major randomised trial. The CALIBER dataset also enhanced the ascertainment of CVD outcomes in this understudied group of patients surviving ≥1 year after an MI. It was a limitation of the study that the authors were unable to compare coronary disease severity between the two populations since this information is unavailable in CALIBER. However, this is unlikely to have affected their conclusions as there was no apparent heterogeneity in the efficacy of ticagrelor with respect to the severity of coronary disease in the trial. It was a further limitation of their study that they were able to provide a precise match for only two of the TIMI major bleeding criteria (27), the third criterion, ≥5g/dl fall in haemoglobin concentration, required proxies: hospitalised bleeding with length of stay ≥7 days or need for blood transfusion. PEGASUS-TIMI-54’s other harm end-point – fatal or intracranial bleeding - was matched in the target population.

In summary, this novel comparative analysis has shown that patients surviving ≥1 year after AMI remain at substantial risk of further cardiovascular events. The PEGASUS-TIMI-54 trial was one of the first to inform management of this understudied group. This potential must be weighed against the bleeding risk and is likely to be greatest in high CV risk subgroups without prior stroke or recent anticoagulation therapy.

4.12 Adverse reactions

The safety objective of the PEGASUS-TIMI 54 study was to assess the safety and tolerability of long-term therapy with ticagrelor plus low dose aspirin compared with aspirin alone in patients with history of MI (1 to 3 years prior to randomisation) and at high risk of an atherothrombotic event.(62)

There were 3 safety objectives in the study with 2 objectives specifically related to bleeding, an expected side effect of antiplatelet therapy due to the mechanism of action.

Specific focus was on:

- Time to the first TIMI Major bleeding event following the first dose of study drug, as well as time to the first TIMI Major or Minor bleeding event
- Time to discontinuation of study drug due to any bleeding event
- Evaluation of adverse events (AEs)

The safety assessment was based on the safety analysis set, defined as all patients who received at least 1 dose of ticagrelor or placebo.(62) The primary analysis approach was an on-treatment analysis where patients were censored 7 days after their last dose of study drug.(62) For bleeding events and AEs of special interest, Kaplan-Meier time-to-event analyses were performed. Cumulative incidences at 36 months were presented as event rates for these analyses.(62)

Bleeding events were classified using the TIMI, PLATO, GUSTO, and ISTH definitions, although this study focused primarily on the TIMI bleeding scale, as follows:

- TIMI Major bleeding is defined as any of the following:
    - **Fatal bleeding** – A bleeding event that directly led to death within 7 days.
    - **Intracranial haemorrhage**
    - **Other TIMI Major bleeding** – Clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥5 g/dL, or when Hgb is not available, a fall in haematocrit (Hct) of ≥15%.
- TIMI Minor bleeding is defined as bleeding that is clinically apparent with 3 to <5 g/dL decrease in Hgb, or when Hgb is not available a fall in Hct of 9 to <15%.

Efficacy results for the full PEGASUS-TIMI 54 population are presented initially. Results for the base case of patients who had an MI <2 years ago are found in Section 4.8.

Primary safety endpoint (TIMI Major bleeding)

As expected, there was an increase in the rate of TIMI major bleeding versus placebo. Of the 21,162 patients randomised into the PEGASUS-TIMI 54 study, “TIMI major bleeding events” on treatment were reported for 115 patients on ticagrelor 60mg BID and 54 patients on placebo, corresponding to Kaplan-Meier percentages at 36 months of 2.30% in the ticagrelor 60 mg BID cohort and 1.10% in the placebo cohort (HR 2.32; 95% CI 1.68 to 3.21; p<0.0001). The KM curves show a fairly constant risk of bleeding over time for both ticagrelor and placebo with a constant relative risk for ticagrelor compared with placebo (Figure 22).

Figure 22: Kaplan-Meier plot of the cumulative percentage of patients with TIMI major bleeding events – on treatment (safety analysis set)(62)

CI: confidence interval; HR: hazard ratio; KM: Kaplan Meier; m: month; P: placebo; T: ticagrelor

The rates of fatal bleeding or nonfatal intracranial haemorrhage were low (<1% over 3 years) and did not differ significantly between ticagrelor and placebo (37) Fatal

bleeding events were reported in 11, and 12 patients on ticagrelor 60 mg BID, and placebo, respectively, corresponding to Kaplan-Meier percentages at 36 months of 0.3%, and 0.3%: HR 1.00 (95% CI 0.44, 2.27) (Table 41). Most fatal bleeding events were spontaneous and the most frequently reported anatomical location was intracranial. Intracranial haemorrhage events were few and reported in, 28, and 23 patients on ticagrelor 60 mg, and placebo, respectively, corresponding to Kaplan-Meier percentages at 36 months of 0.6%, and 0.5%:HR 1.33 (95% CI 0.77, 2.31) for ticagrelor 60 mg (Table 41).

The observed increased risk of TIMI Major bleeding with Ticagrelor 60 mg BID was driven by a higher frequency of Other TIMI Major bleeding events; a total of 83 patients in the Ticagrelor 60 mg BID cohort and 25 patients in the placebo group; corresponding to KM % at 36 months of 1.6% and 0.5%, for Ticagrelor 60 mg BID and placebo, respectively (Ticagrelor HR 3.61; 95% CI 2.31 to 5.65; p<0.0001).(62)

The observed higher frequency in Other TIMI Major bleeding for ticagrelor treatment was driven by gastrointestinal events: 51 (0.7%), and 12 (0.2%) patients had events in the ticagrelor 60 mg BID, and placebo groups, respectively Table 41).(37)

In patients with Other TIMI Major bleeding events:

- the majority of patients continued on study drug. Permanent treatment discontinuation was reported in similar proportions in the 2 treatment groups:, 33.7% (28/83), and 40.0% (10/25) for ticagrelor 60 mg bid and placebo, respectively (Table 41).

- transfusions were common and reported in similar proportions in the two treatment groups: [redacted] for ticagrelor 60mg and placebo respectively (Table 41)

- hospitalisations were common and slightly higher in patients on ticagrelor compared with placebo: [redacted] for, ticagrelor 60 mg BID and placebo, respectively (Table 41).).

Although ‘Other TIMI major bleeding’ events are important as they cause morbidity and require care, they are still manageable clinically and do not cause irreversible harm.

It is estimated that, for every 10,000 patients who began treatment with ticagrelor 60 mg BID (i.e. the ITT study population), 31 TIMI major bleeding events would be caused compared to placebo.

Table 41: Analysis of bleeding events using TIMI definitions - on treatment (safety analysis set)

	Ticagrelor 60 mg BID (N=6958)				Placebo (N=6996)	
Characteristic	**Patients (%) with events**	**KM%**	**HR (95% CI)**	**p-value**	**Patients (%) with events**	**KM%**
TIMI Major bleeding	115 (1.7%)	2.3%	2.32 (1.68, 3.21)	<.0001	54 (0.8%)	1.1%
Fatal	11 (0.2%)	0.3%	1.00 (0.44, 2.27)	1.0000	12 (0.2%)	0.3%
ICH	28 (0.4%)	0.6%	1.33 (0.77, 2.31)	0.3130	23 (0.3%)	0.5%
Other Major	83 (1.2%)	1.6%	3.61 (2.31, 5.65)	<.0001	25 (0.4%)	0.5%
• Gastrointestinal	51 (0.7%)				12 (0.2%)	
Other Major bleeding events leading to:						
• Discontinuations	28/83 (33.7%)				10/25 (40%)	
• Hospitalisations	[redacted]				[redacted]	
• Transfusions	[redacted]				[redacted]	
TIMI Major or Minor bleeding	168 (2.4%)	3.4%	2.54 (1.93, 3.35)	<.0001	72 (1.0%)	1.4%

Other safety bleeding endpoints (TIMI Major or Minor bleeding events)

The analysis of TIMI Major or Minor bleeding events is summarised below:

- TIMI Major or Minor bleeding events were reported for 168 and 72 patients on Ticagrelor 60 mg BID and placebo respectively, corresponding to a KM% at 36 months of 3.4%, and 1.4% (Ticagrelor HR 2.54; 95% CI 1.93 to 3.35; p <0.0001; Table 41)

- Kaplan-Meier curves show a fairly constant risk of bleeding over time for both ticagrelor and placebo with a constant relative risk for ticagrelor compared with placebo over time (Figure 23).

Figure 23: Kaplan-Meier plot of the cumulative percentage of patients with TIMI Major or Minor bleeding events - on treatment (safety analysis set)

Table 42: Non-fatal non-ICH TIMI major bleeding events by system organ class (on treatment)(62)

SOC/preferred term	Total number of bleeding events		First Bleeding Event	
	Ticagrelor 60 mg (n=6,958)	Placebo (n=6,996)	Ticagrelor 60 mg (n=6,958) (%)	Placebo (n=6,996) (%)
Patients with at least 1 non-fatal non-ICH TIMI major bleed	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]

ICH: intracranial haemorrhage; TIMI: thrombolysis in myocardial infarction; SOC: system organ class

This table includes adverse events with an onset date on or after the date of first dose and up to and including 7 days following the date of last dose of study drug.

* Adverse events with a bleeding event documented by the investigator and adjudicated as a non-fatal non-ICH TIMI major bleeding event

Adverse events (non-bleeding)

Adverse events reported in the PEGASUS-TIMI 54 trial were consistent with the existing evidence base for ticagrelor. Overall AEs were reported more frequently in the ticagrelor group than on placebo with frequencies of 76.3% and 70% for ticagrelor 60mg BID and placebo respectively. Rates of overall adverse events, serious adverse events and non-cardiovascular causes of death are listed in Table 44 and Table 45. The most commonly reported AEs on ticagrelor were dyspnoea, epistaxis and increased tendency to bruise (Table 43).

Table 43: Most common AEs (including bleeding) by preferred term (with frequency >1%) - on treatment (safety analysis set)

	Ticagrelor 60 mg BID (N - 6958)		Placebo (N = 6996)	
Preferred term	**Number of patients (%)**	**Event rate (per 100 pt years)**	**Number of patients (%)**	**Event rate (per 100 pt years)**
Patients with any AE	5268 (75.7%)	35.93	4837 (69.1%)	30.55
Dyspnoea	865 (12.4%)	5.9	309 (4.4%)	1.94
Epistaxis	422 (6.1%)	2.88	156 (2.2%)	0.98
Increased tendency to bruise	419 (6.0%)	2.86	62 (0.9%)	0.39
Contusion	349 (5.0%)	2.38	108 (1.5%)	0.68
Nasopharyngitis	347 (5.0%)	2.37	349 (5.0%)	2.19
Non-cardiac chest pain	341 (4.9%)	2.33	374 (5.3%)	2.35
Dissiness	290 (4.2%)	1.98	261 (3.7%)	1.64
Spontaneous haematoma	218 (3.1%)	1.49	41 (0.6%)	0.26
Hypertension	282 (4.1%)	1.92	290 (4.1%)	1.82
Bronchitis	187 (2.7%)	1.28	180 (2.6%)	1.13
Diarrhoea	228 (3.3%)	1.55	173 (2.5%)	1.09
Back pain	226 (3.2%)	1.54	226 (3.2%)	1.42
Traumatic haematoma	160 (2.3%)	1.09	45 (0.6%)	0.28
Headache	175 (2.5%)	1.19	182 (2.6%)	1.14

Dyspnoea-related adverse events:

In previous studies (PLATO, DISPERSE, and DISPERSE2), ticagrelor has been shown to cause dyspnoea in some patients; this was generally brief, resolving with continued ticagrelor treatment. There appears to be a relationship with ticagrelor dose. Extensive evaluation in these studies has demonstrated no impact of ticagrelor on pulmonary or cardiac function. In PEGASUS TIMI 54 study, dyspnoea AEs were reported for 986, and 382 patients on ticagrelor 60 mg, and placebo, respectively, corresponding to Kaplan-Meier percentages at 36 months of 15.9%, and 6.4%: HR 2.82 (95% CI 2.50, 3.17).

Most dyspnoea AEs were assessed as mild to moderate in severity and were transient in nature and the majority of patients with dyspnoea AEs had only 1 episode regardless of treatment group. Discontinuations due to dyspnoea AEs were reported for 296, and 51 patients in the ticagrelor 60 mg, and placebo treatment groups, respectively, corresponding to Kaplan-Meier percentages at 36 months of 4.5%, and 0.8%: HR 6.04 (95% CI 4.48, 8.12). The time to onset of first dyspnoea AE was shorter in the ticagrelor treatment groups: 28.0%, and 8.1% of patients with dyspnoea AEs in ticagrelor 60 mg, and placebo groups, respectively, reported a dyspnoea AE within 3 days from start of treatment. Median times to first dyspnoea AE were 29, and 240 days, respectively.

Bradyarrhythmic adverse events

In PEGASUS TIMI 54 study there were no notable differences between ticagrelor 60 mg BID and placebo in the rates of bradyarrhythmic adverse events. Bradyarrhythmic AEs were reported for, 121, and 105 patients on ticagrelor 60 mg BID, and placebo, respectively, corresponding to Kaplan-Meier percentages at 36 months of 2.3% and 2.0%: HR 1.25 (95% CI 0.96, 1.63). The most commonly reported bradyarrhythmic AEs were bradycardia, sinus bradycardia, and atrioventricular block first degree.

Renal related adverse events

There were no notable differences between ticagrelor 60 mg BID in the rates of renal adverse events. Mean values for absolute from baseline in creatinine increased slightly over time in the ticagrelor 60mg BID group but values at the follow-up visit were similar in the ticagrelor and placebo groups.

Adverse events related to gout or urate nephropathy

Adverse events of gout and gouty arthritis were infrequent but significantly more common with ticagrelor 60 mg BID than with placebo. There were no reports of urate nephropathy. An increase in serum uric acid levels from baseline to last observation on treatment was found for ticagrelor 60 mg BID, but this was reversible.

Table 44 Safety endpoints as 3-year Kaplan-Meier estimates (on-treatment)(60)

AE	Ticagrelor 60 mg BID (n=6,958)	Placebo (n=6,996)	Ticagrelor 60 mg vs placebo	
	n (%)	n (%)	HR (95% CI)	p value[a]
Dyspnoea	987 (15.84)	383 (6.38)	2.81 (2.50–3.17)	<0.001
Event leading to study drug discontinuation	297 (4.55)	51 (0.79)	6.06 (4.50–8.15)	<0.001
Serious AE	23 (0.45)	9 (0.15)	2.70 (1.25–5.84)	0.01
Renal event	173 (3.43)	161 (2.89)	1.17 (0.94–1.45)	0.15
Bradyarrhythmia	121 (2.32)	106 (1.98)	1.24 (0.96–1.61)	0.10
Gout	101 (1.97)	74 (1.51)	1.48 (1.10–2.00)	0.01

AE: adverse event; BID: twice daily; CI: confidence interval; HR: hazard ratio; TIMI: thrombolysis in myocardial infarction

Note: there are minor differences between numbers for discontinuations due to bleeding and dyspnoea between this table from NEJM and the KM plots that follow (taken from the CSR)

a Safety endpoints were evaluated on an exploratory basis; the p-values for these endpoints were considered descriptive and not indicative of statistical significance.

Table 45: Adverse events reported in the PEGASUS-TIMI 54 trial (60 mg BID dose)(63)

AE	Ticagrelor 60 mg BID	Placebo
	n (%)	n (%)
On treatment patient population	**(n=6,958)**	**(n=6,996)**
Any AE (serious and non-serious)*	5,311 (76.3)	4,899 (70.0)
Leading to discontinuation of study drug	1,139 (16.4)	621 (8.9)
Most common AEs leading to discontinuation		
• Bleeding[†]	354 (5.1)	86 (1.2)
• Dyspnoea	297 (4.3)	51 (0.7)
• Arrhythmia	103 (1.5)	96 (1.4)
Any serious AE	1,650 (23.7)	1,676 (24.0)
Leading to discontinuation of study drug	273 (3.9)	231 (3.3)
ITT population	**(n=7,045)**	**(n=7,067)**
All-cause mortality	299 (4.2)	336 (4.8)

Non-CV death	117 (1.7)	115 (1.6)
• Accident/trauma	2 (0.03)	4 (0.06)
• Infection/sepsis	25 (0.36)	24 (0.34)
• Malignancy	64 (0.92)	53 (0.76)
• Pulmonary failure	9 (0.13)	9 (0.13)
• Renal failure	4 (0.06)	4 (0.06)
• Other	13 (0.19)	21 (0.30)

AE: adverse event; BID: twice daily; ITT: intention-to-treatment

* Excludes patients who stopped drug due to an efficacy event with no associated bleeding

† Bleeding as confirmed by the Clinical Events Committee

Discontinuations

In the study, patients who prematurely permanently discontinued treatment with study drug, but did not withdraw from the study, continued to be followed up for SAEs and study endpoint events. Of the patients who received study drug, permanent discontinuations occurred more frequently in the ticagrelor 60 mg BID (28.7%; n=1999) group than in the placebo group (21.4%; n=1496). The most common reasons for permanent discontinuation of study drug were AEs/ SAEs (16.1% (n = 1257) of patients receiving ticagrelor 60mg BID, compared to 11.2% (n = 784) of patients receiving placebo) and patient decision (9.1% (n = 635) of patients receiving ticagrelor 60mg BID, compared to 8.4% (n = 590) of patients receiving placebo).

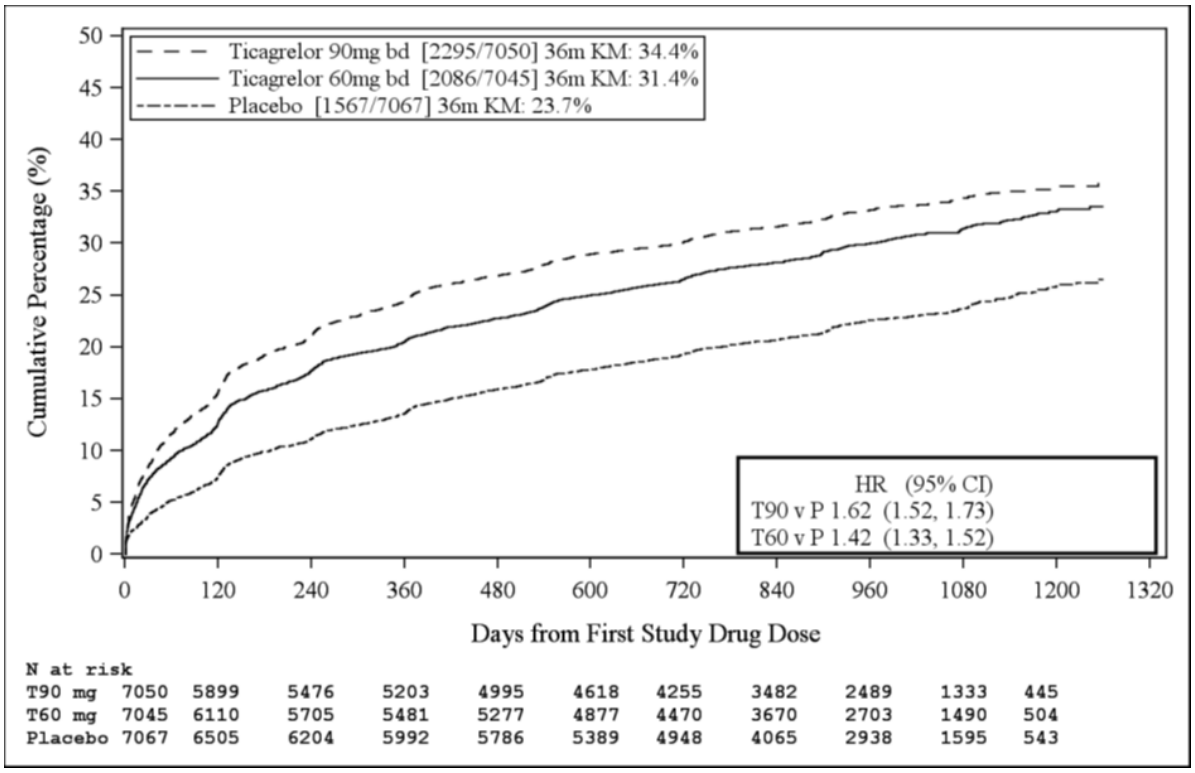
While most of the difference in discontinuation rates between the treatment groups accumulated soon after randomisation, the annual permanent discontinuation rate, based on a mean follow-up time of 31.8 months, was 10.8%/year, and 8.1%/year in the ticagrelor 60 mg BID, and placebo groups, respectively. Most of the differences in discontinuation rates accumulated in the earlier part of the study; approximately half of the discontinuations with ticagrelor 60 mg BID occurred within the first 150 days (Figure 24). The difference in rate of discontinuation between the ticagrelor and placebo groups decreased over time.

The higher proportion of patients prematurely permanently discontinued from study drug in the ticagrelor group compared to the placebo group resulted in lower mean total duration of exposure in the ticagrelor group. For ticagrelor 60 mg BID, and

placebo groups, mean total duration of exposure to study drug (first dose to last dose) was 25.3, and 27.3 months, respectively.

The impact of permanent discontinuations on the efficacy results is discussed in the context of the 'on treatment' exploratory analysis in section 4.7

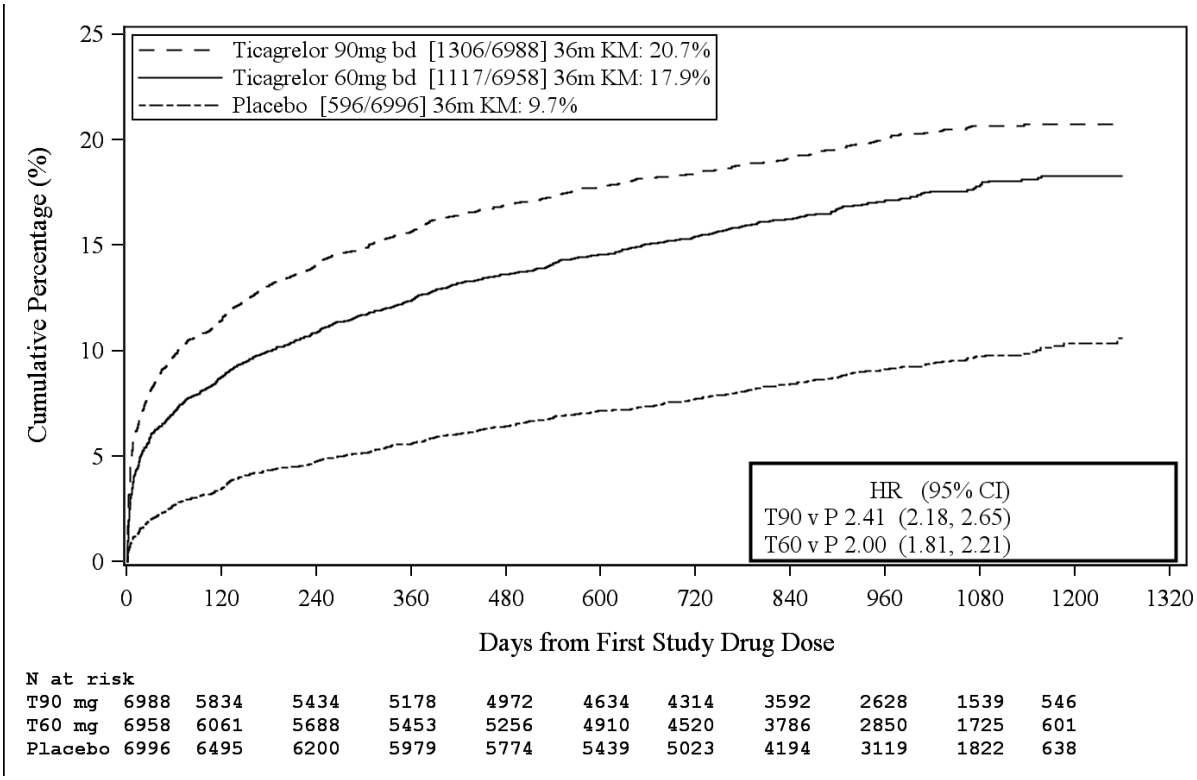
Figure 24: Kaplan-Meier plot of the cumulative percentage of patients with premature permanent discontinuation of study drug (safety analysis set)(62)



CI: confidence interval; HR: hazard ratio

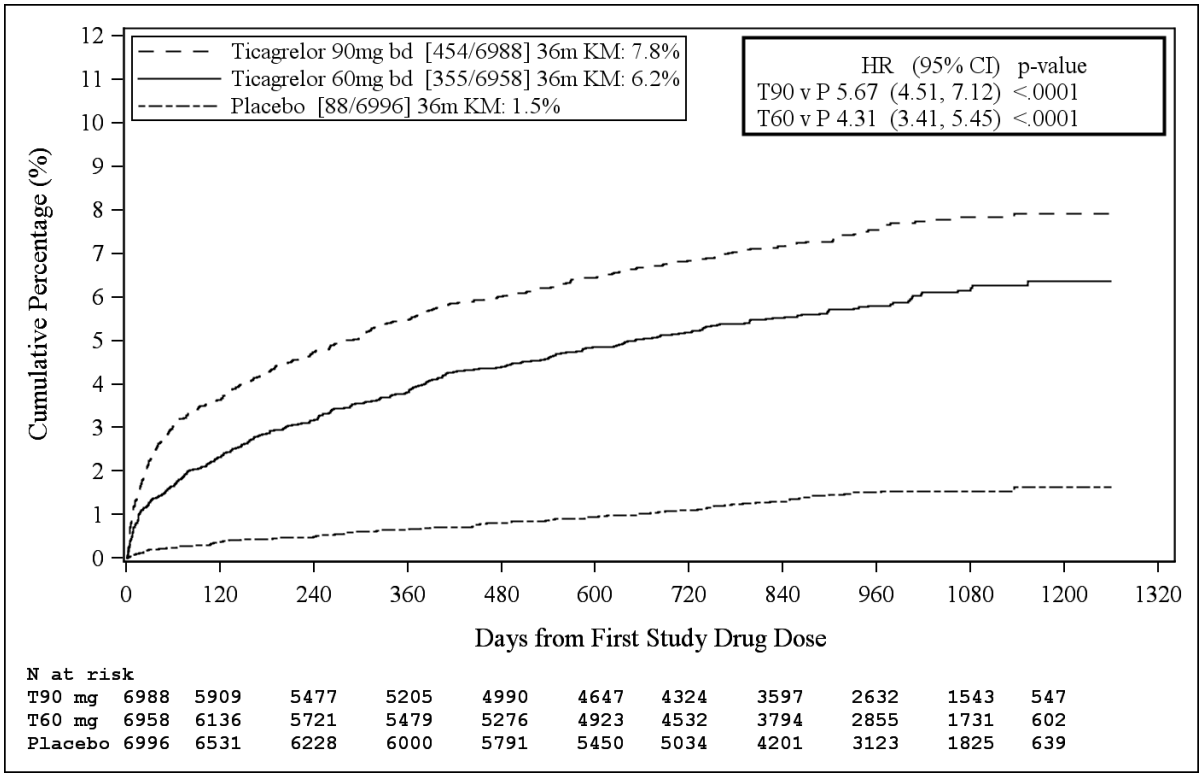
Overall, 16.4% of patients in the ticagrelor 60 mg BID group discontinued treatment due to AEs, compared with 8.9% of patients in the placebo group.(63) The primary cause of the higher rates of permanent discontinuation in the ticagrelor treatment groups compared with the placebo group were discontinuations due to bleeding events(5.1% in the ticagrelor 60 mg group vs 1.2% in the placebo group) and dyspnoea(4.3% in the ticagrelor 60 mg group vs 0.7% in the placebo group).(62) Discontinuation of ticagrelor was driven by non-severe AEs (primarily mild to moderate dyspnoea and non-major TIMI bleeding).

Figure 25: KM estimate of time to premature permanent discontinuation of study drug due to adverse event (safety analysis set)(37)



Bleeding AEs which led to discontinuation were reported for 355 and 88 patients on ticagrelor 60 mg BID and placebo, respectively. These corresponded to Kaplan-Meier percentages at 36 months of 6.2% for ticagrelor 60 mg (HR 4.31; 95% CI 3.41 to 5.45; p<0.0001) and 1.5% for the placebo group.(62) KM curves show an increased risk of discontinuations due to bleeding from the start of treatment with ticagrelor, which is most pronounced during the first months of treatment (Figure 26), but similar to placebo during the latter part of the study.(62) The most common bleeding AEs leading to discontinuation were; increased tendency to bruise, epistaxis and spontaneous haematoma.

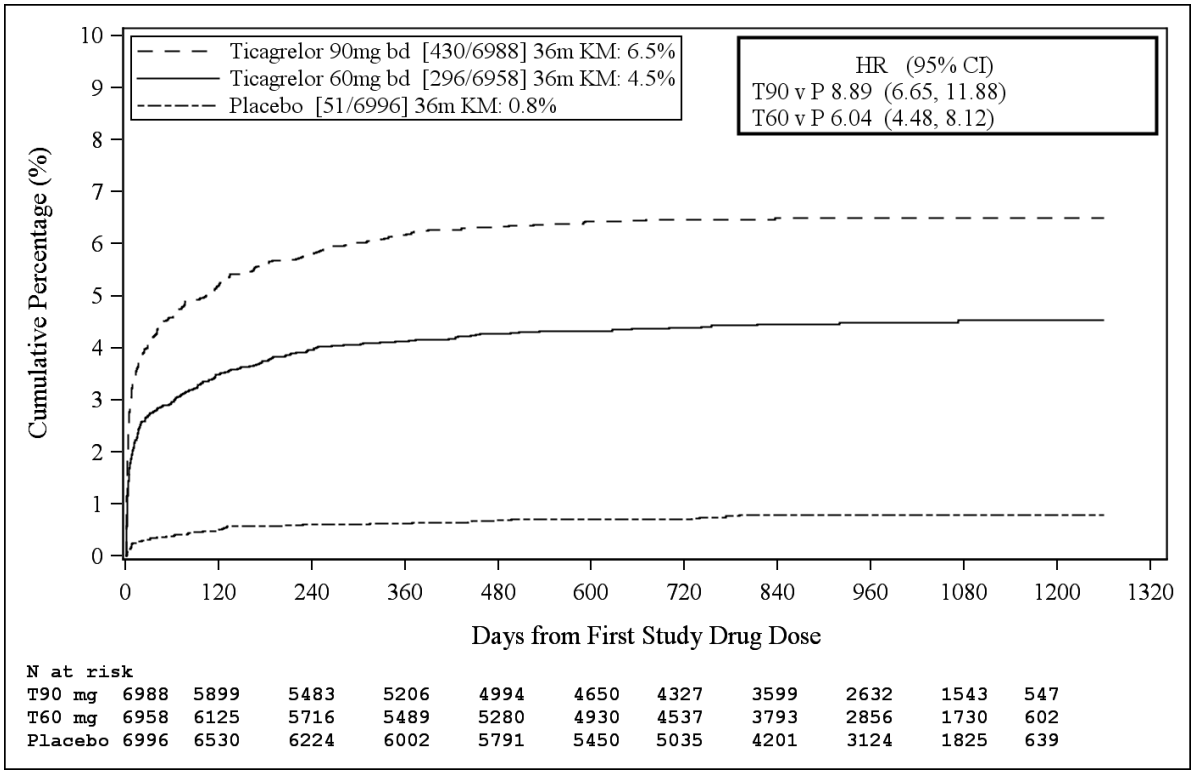
Figure 26: KM estimate of time to premature permanent discontinuation of study drug due to bleeding (safety analysis set)(62)



AE: adverse event; CI: confidence interval; HR: hazard ratio; P: placebo; T: ticagrelor

Discontinuations due to dyspnoea AEs were reported for 296, and 51 patients in the ticagrelor 60 mg BID and placebo treatment groups, respectively. Corresponding to Kaplan-Meier percentages at 36 months of 4.5% for ticagrelor 60 mg BID (HR 6.04; 95% CI 4.48 to 8.12) and 0.8% for the placebo group. Discontinuations due to dyspnoea for patients treated with ticagrelor generally occurred early during study treatment and in the longer term the rates were similar between treatment groups (Figure 27).(62)

Figure 27: Kaplan-Meier plot of the cumulative percentage of patients with discontinuation due to dyspnoea AE - on treatment (safety analysis set)(62)

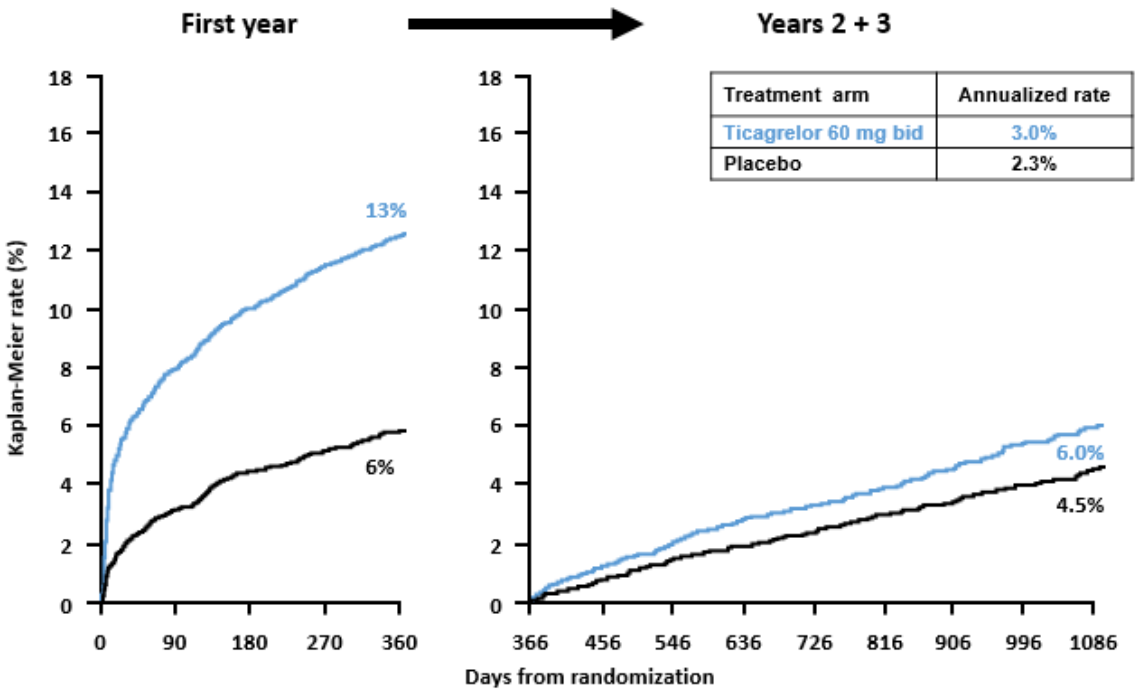


AE: adverse event; CI: confidence interval; HR: hazard ratio; P: placebo; T: ticagrelor

In PEGASUS TIMI 54, discontinuation of newly started ticagrelor among stable outpatients with prior MI was driven by adverse events of bleeding and dyspnoea. Although significant enough to prompt discontinuation, the majority of dyspnoea was non-serious and only mild–moderate in intensity and bleeds were non-major TIMI bleeding.

Importantly, patients who tolerated 1 year of ticagrelor therapy had lower rates of drug discontinuation thereafter, and these were similar to placebo (Figure 28). Translation of PEGASUS-TIMI 54 into clinical practice would more likely be in the form of continuing in patients already tolerating ticagrelor 90mg BID for 1 year after their MI; consequently, if a patient was tolerating the treatment at 12 months, continuing ticagrelor beyond 12 months would not be expected to trigger a new episode of dyspnoea or further increase the risk of bleeding events.

Figure 28: Drug discontinuation in first year compared to subsequent years (81)

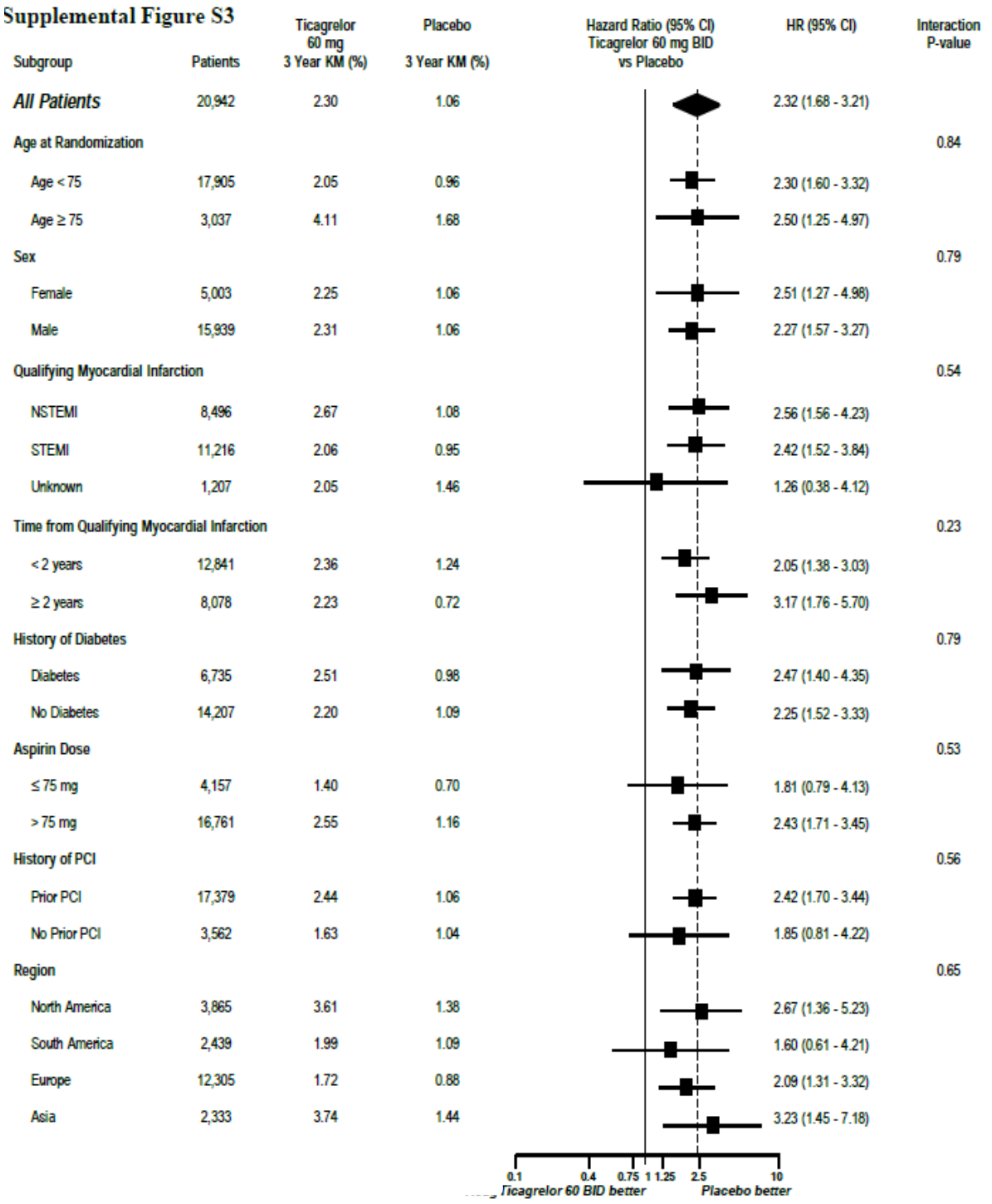


Subgroup analyses

There was no apparent heterogeneity in the primary safety endpoint among major subgroups (Figure **29**, Figure 30) (60) and the results did not suggest differential effects in the pre-defined subgroups. The differences observed in HR point estimates across subgroups were as expected given the large number of patient characteristics fanalysed.(62)

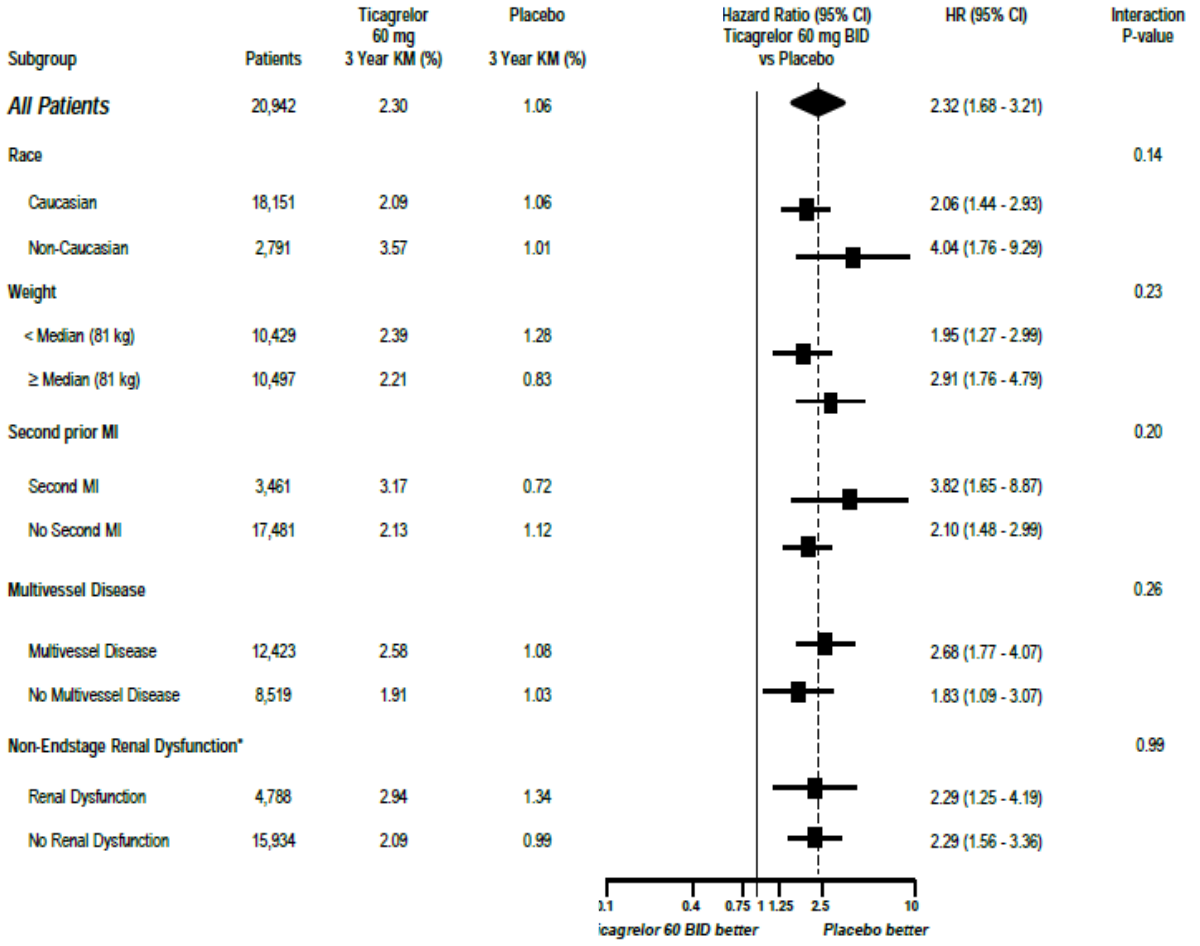
When analysed by patient subgroups the pattern of TIMI Major bleeding was consistent across all pre-defined patient subgroups for ticagrelor BID 60 mg compared with placebo (Figure **29**, Figure 30). There was no additional increased risk of TIMI Major bleeding in patients aged >75 years (ticagrelor KM % at 36 months 4.1; HR 2.50; 95% CI 1.17 to 5.30).

Figure 29: Primary safety endpoint (TIMI major bleeding) across patient subgroups (modified from Bonaca et al, 2015)(63)



CI: confidence interval; HR: hazard ratio; KM: Kaplan Meier; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction

Figure 30: Continued primary safety endpoint (TIMI major bleeding) across patient subgroups (modified from Bonaca et al, 2015)(63)



CI: confidence interval; HR: hazard ratio; KM: Kaplan Meier

Pre-specified analysis

Time from qualifying MI analysis

With regards to TIMI major bleeding, patients treated with ticagrelor 60mg BID < 2 years from their MI had HR of 2.05 (95% CI 1.38–3.03, p=0.0004) with an ARI of 1.2%. For those who were ≥2 years from their MI, the HR for TIMI Major Bleeding was 3.17 (1.76–5.70, p=0.0001) with an ARI of 1.5% (Table 0.47).

It is estimated that, for every 10,000 patients who began treatment with ticagrelor 60 mg BID and were <2 years since their MI, 23 TIMI major bleeding events would be caused compared to placebo.

Taken with the efficacy results for the same subgroup (Table 33), this suggests a favourable benefit:harm profile for long-term treatment of patients who are <2 years from their qualifying MI.

In patients who are more than 2 years from their MI and have survived event-free without an ischaemic complication, re-initiation of therapy increases the risk of bleeding without an appreciable ischaemic risk reduction.

Table 46: Primary safety endpoint for patient subgroup: Time from qualifying MI event

		MI <2 years		MI >=2 years	
Characteristic		**Ticagrelor 60mg BID**	**Placebo**	**Ticagrelor 60mg BID**	**Placebo**
		(N=4279)	**(N=4287)**	**(N=2671)**	**(N=2700)**
TIMI Major bleeding	Patients with events	72 (1.7%)	38 (0.9%)	43 (1.6%)%)	15 (0.6%)
	KM %	2.40%	1.20%	2.2%	0.7%
	Hazard Ratio (95% CI)	2.05 (1.38, 3.03)		3.17 (1.76, 5.70)	
	p-value	0.0004		0.0001	
TIMI Major or Minor Bleeding	Patients with events	[redacted]	[redacted]	[redacted]	[redacted]
	KM %	[redacted]	[redacted]	[redacted]	[redacted]
	Hazard Ratio (95% CI)	[redacted]		[redacted]	
	p-value	[redacted]		[redacted]	

Time since previous treatment with ADP receptor inhibitor

In this analysis, an increase in TIMI major bleeding was observed with ticagrelor compared to placebo regardless of time from last dose of ADP inhibitor receptor (Table 0.48). The hazard ratios for TIMI Major bleeding were 3.37 (95% CI 1.85, 6.16, p=0.0001, ARI = 2.0%) for patients within 30 days since their last ADP receptor inhibitor, 2.92 (95% CI 1.65 - 5.19, p=0.0003, ARI = 1.5%) for patients who were more than 30 days, but less than 1 year from their previous ADP receptor inhibitor and 2.12 (95% CI 1.05 - 4.25, P 0.0355, ARI = 1.0%) for patients who have been stable for more than a year without an ADP receptor inhibitor as part of their treatment strategy (Table 46).

Table 47: Primary safety endpoint for patient subgroup: Time since previous treatment with ADP receptor inhibitor

		<30 days since ADP receptor inhibitor		≥30 days – 1 year since ADP receptor inhibitor		>1 year since ADP receptor inhibitor	
Characteristic		**Ticagrelor 60mg BID**	**Placebo**	**Ticagrelor 60mg BID**	**Placebo**	**Ticagrelor 60mg BID**	**Placebo**
		(N=2354)	**(N=2373)**	**(N=2212)**	**(N=2209)**	**(N=1641)**	**(N=1629)**
TIMI Major bleeding	Patients with events	44 (1.9%)	14 (0.6%)	43 (1.9%)	16 (0.7%)	23 (1.4%)	12 (0.7%)
	KM %	2.7%	0.7%	2.7%	1.2%	1.9%	0.9%
	Hazard Ratio (95% CI)	3.37 (1.85, 6.16)		2.92 (1.65, 5.19)		2.12 (1.05, 4.25)	
	p-value	<0.0001		0.0003		0.0355	
TIMI Major or Minor Bleeding	Patients with events	68 (2.9%)	20 (0.8%)	61 (2.8%)	22 (1.0%)	30 (1.8%)	16 (1.0%)
	KM %	4.2%	1.1%	3.8%	1.6%	2.5%	1.2%
	Hazard Ratio (95% CI)	3.65 (2.22, 6.01)		3.01 (1.85, 4.90)		2.06 (1.12, 3.77)	
	p-value			<0.0001		0.3679	

Additional Subgroup analyses specified in the Decision Problem

The final scope of the decision problem (Section 1.1) requests subgroup data for patients with or without diabetes and with or without a history of revascularization. It should be noted that the PEGASUS-TIMI 54 trial did not record or stratify patients according to revascularization specifically. However, patients were stratified according to a history of percutaneous coronary intervention (PCI) and the results of the primary safety endpoint for these, as well as those according to diabetes status in the ITT analysis population are presented

The licensed population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically sound as the trial was not powered to draw conclusions about (non-pre-specified) subgroups of subgroups. However, in order to provide evidence for these specific subgroups of patients within the limits of the marketing authorization, we present subgroup analyses of composite and individual primary endpoints for patients who experienced an MI <2 years ago, with or without diabetes and with or without a history of PCI. Caution is advised when interpreting these data for the reasons set out above.

Table 48: Primary safety endpoint for patient subgroup: (on treatment analysis; patients with MI <2 years ago, with and without diabetes)

		Diabetes		No Diabetes	
Characteristic		**Ticagrelor 60mg BID**	**Placebo**	**Ticagrelor 60mg BID**	**Placebo**
		(N=1402)	**(N=1310)**	**(N=2877)**	**(N=2977)**
TIMI Major bleeding	Patients with events	27 (1.9%)	8 (0.6%)	45 (1.6%)	30 (1.0%)
	KM %	2.80%	0.70%	2.10%	1.50%
	Hazard Ratio (95% CI)	3.32 (1.51, 7.31)		1.69 (1.07, 2.68)	
	p-value	0.0029		0.0258	

Table 49: Composite primary safety endpoints for patient subgroup: (on treatment analysis; patients with MI <2 years ago, with and without a history of PCI

		History of PCI		No History of PCI	
Characteristic		**Ticagrelor 60mg BID**	**Placebo**	**Ticagrelor 60mg BID**	**Placebo**
		(N=3595)	**(N=3585)**	**(N=684)**	**(N=701)**
TIMI Major bleeding	Patients with events	62 (1.7%)	31 (0.9%)	10 (1.5%)	7 (1.0%)
	KM %	2.50%	1.20%	1.80%	1.20%
	Hazard Ratio (95% CI)	2.17 (1.41, 3.34)		1.55 (0.59, 4.06)	
	p-value	0.0004		0.3767	

12 month Landmark analysis of Bleeding events

The objective of this analysis (81) was to investigate the consistency of the safety of ticagrelor 60 mg BID over time. The rate of TIMI major bleeding was analysed for ticagrelor 60 mg BID compared to placebo, i) for the first year of observation, and then ii) as a landmark analysis beginning after the first year, in all patients alive at that time point. TIMI major bleeding was increased with ticagrelor 60 mg BID within the first year (HR 3.22, 95% CI 1.86- 5.57, p < 0.001), but numerically less after the first year (HR 1.91, 95% CI 1.27 – 2.86, p = 0.0018). After 1 year of therapy, ticagrelor 60 mg BID increased TIMI major bleeding by 0.34% per year, with no increase in ICH or fatal bleeding.

Taken with the efficacy results of the same analysis, these data support the prolonged use of ticagrelor therapy in high risk post MI patients to reduce atherothrombotic events.

Figure 31: Annualised rate of TIMI major bleeding(81)

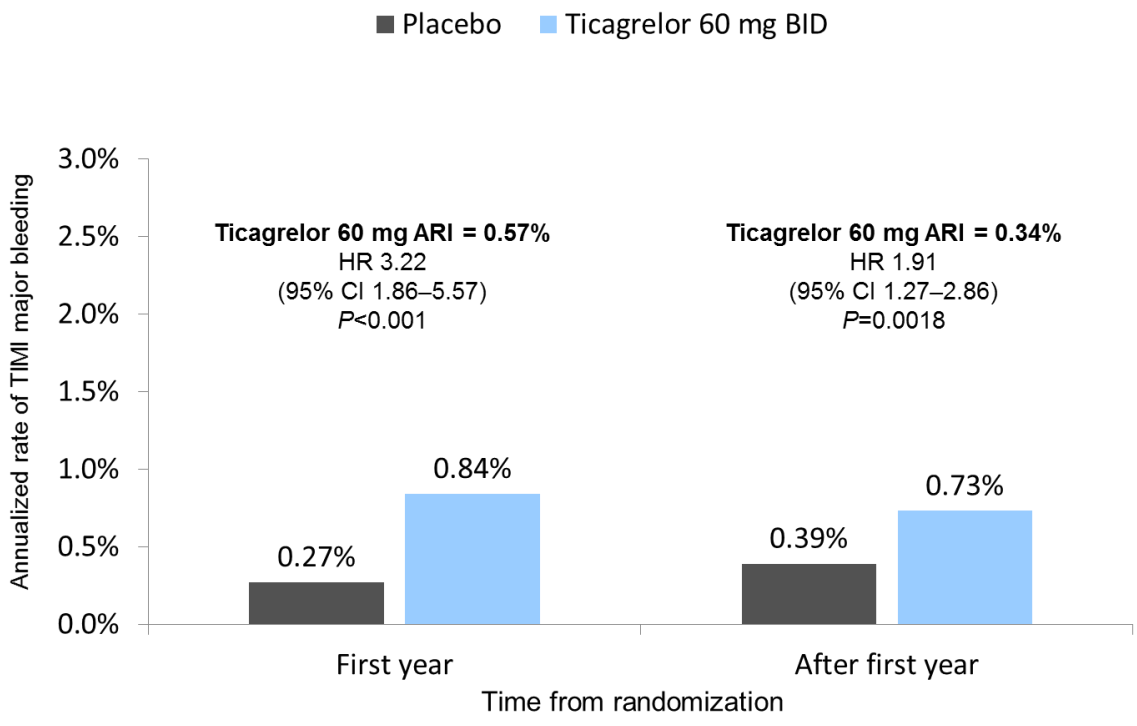
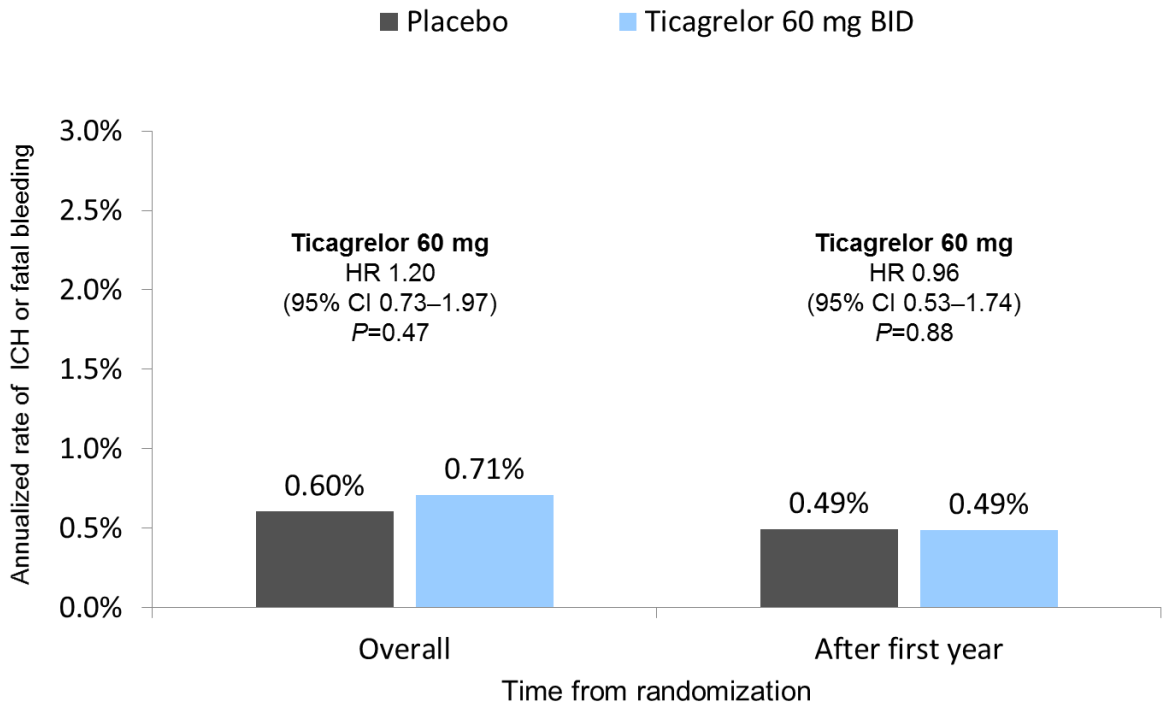


Figure 32: Annualised rate of ICH or fatal bleeding (81)



4.13 Interpretation of clinical effectiveness and safety evidence

Patients who have suffered an MI are at heightened risk of CV death and recurrent ischaemic events. In some registries, as many as 1 in 5 patients who remain event-free 1 year after an MI will experience another MI, a stroke, or suffer CV death in the subsequent 3 years (26, 82, 83), suggesting that this population may benefit from more intensive secondary prevention.

PEGASUS-TIMI 54 is the first prospective, appropriately powered, randomised controlled clinical trial to demonstrate the benefit of long-term DAPT in patients who are more than 1 year from their MI. The study demonstrated that the addition of ticagrelor 60 mg BID to low-dose aspirin significantly reduced the primary composite endpoint of CV death, MI or stroke in patients with prior spontaneous MI and a high risk of further atherothrombotic events and each component contributed to the reduction in the primary composite endpoint, including CV death. MI and stroke represent irreversible loss of organ function with important medical consequences. The clinical relevance of the results is further supported by the consistent findings over time, across multiple endpoints, and across patient subgroups. The benefits of

ticagrelor were also seen consistently across a number of other pre-defined exploratory efficacy endpoints, providing further support for the benefit of ticagrelor 60 mg compared with placebo.

There was a higher frequency of study drug discontinuation in the ticagrelor group than in the placebo group .The effects of the lower exposure time on the outcome of the primary composite endpoint were explored in a pre-specified ‘on treatment’ analysis. The results were consistent with the primary ITT analysis, and demonstrated a greater magnitude of effect as a consequence of a higher number of CV major events occurring off-treatment in patients randomised to ticagrelor and who discontinued study medication. It is important to note that the OT analysis may be a more accurate representation of efficacy in patients taking the medication.

In the trial, discontinuation of ticagrelor was driven by non-severe AEs (primarily mild to moderate dyspnoea and non-major TIMI bleeding) and occurred early in the study. Patients who tolerated 1 year of ticagrelor therapy had lower rates of drug discontinuation thereafter, and similar to placebo. However, translation of PEGASUS-TIMI 54 into clinical practice would more likely be in the form of continuing in patients already tolerating ticagrelor 90mg BID for 1 year after their MI. Consequently in clinical practice, if a patient was tolerating the treatment at 12 months, continuing ticagrelor beyond 12 months would not be expected to trigger a new episode of dyspnoea or further increase the risk of bleeding events.

The safety profile was consistent with the current evidence base for ticagrelor. Bleeding is a known and expected side effect of antiplatelet therapy, owing to the mechanism of action, as expected, there was an increase in TIMI major bleeding with both ticagrelor 60 mg bid versus placebo, but the rates of intracranial haemorrhage or fatal bleeding were low (<1% over 3 years) and were similar between treatment arms. The difference between ticagrelor and placebo was driven by ‘other TIMI major bleeding’ (mainly gastrointestinal bleeds). The results did not suggest differential effects on bleeding in pre-defined patient subgroups; of special note, there was no additional increased risk of TIMI Major bleeding in elderly patients.

Other TIMI Major bleeding events with ticagrelor are serious and important, but are clinically manageable events. These contribute to morbidity and risk for patients, and need to be balanced against the significant and clinically important reduction in CV events obtained with ticagrelor. The primary efficacy and safety endpoints present an initial perspective on the benefit-harm profile. For every 10,000 patients who began treatment (i.e., in an intention-to-treat analysis), 42 primary end-point events per year would be prevented with ticagrelor 60 mg BID and 31 TIMI major bleeding events per year would be caused.

Two pre-specified analyses assessed the overall benefit:harm profile;

- Net clinical benefit (defined as time from randomisation to first occurrence of any event from the composite of: CV death, MI, stroke or TIMI major bleeding)

- Irreversible harm (defined as time from randomisation to first occurrence of any event from the composite of: CV death, MI, stroke, intracranial bleeding or fatal bleeding)

Analysis of the net clinical benefit suggested that the risks associated with ticagrelor 60mg BID are marginally outweighed by the benefits (HR = 0.95, 95% CI; 0.85 – 1.06). However, this analysis gives equal weighting to TIMI major bleeds and CV death, MI or stroke – an importance and weighting that may not be considered appropriate by patients. An alternative assessment of the benefit:harm profile, focused on events with the most severe consequences, i.e. endpoints that measure the risk of death or irreversible harm to the patient. This analysis demonstrated a numerical reduction in the event rate for ticagrelor 60mg BID compared with placebo: HR 0.86 (95% CI 0.77, 0.97).

Two pre-specified subgroup analyses related to time since qualifying MI and time from ADP receptor inhibitor withdrawal indicate that the benefit of ticagrelor may be greatest in patients <2 years from their last MI or in patients continuing on or re-starting after only a brief interruption of ADP receptor inhibition. The ischaemic risk was robustly reduced, particularly in those continuing $P2Y_{12}$ inhibition or restarting after a brief interruption (≤30 days). The increase in bleeding events with ticagrelor

60 mg BID versus placebo was consistent regardless of time since MI or withdrawal of previous ADP receptor inhibitor.

Consequently, the analysis of the net clinical benefit in patients with MI <2 years ago showed that the risks associated with ticagrelor 60mg BID are outweighed by the benefits ([redacted]). Assessment of the most severe consequences (i.e. CV death, MI, stroke, fatal bleeding and intracranial haemorrhage) demonstrated a clinically relevant reduction in the irreversible harm event rate for ticagrelor 60mg BID compared with placebo: [redacted]. For every 10,000 patients with MI <2 years ago who began treatment, [redacted] primary end-point events per year would be prevented with ticagrelor 60 mg BID and [redacted] TIMI major bleeding events per year would be caused.

In these analyses patients who have survived, event-free on aspirin monotherapy without an ischaemic complication more than 1 year from stopping $P2Y_{12}$ inhibition and in general over 2 years from their MI appear to be a group at lower risk where re-initiation of therapy provided no appreciable ischaemic risk reduction and increased the risk of bleeding. These analyses supported the final wording in the EMA licence for the post MI indication.

These results support the use of ticagrelor 60 mg BID, when initiated for up to 3 years treatment duration in conjunction with aspirin, in patients with a history of MI (<2 years ago) and a high risk of developing an atherothrombotic event, including use as continuation therapy after the initial one year of dual antiplatelet treatment with ticagrelor 90 mg BID or another ADP receptor inhibitor. Coupled with PLATO, PEGASUS-TIMI 54 provides consistent evidence of the benefit ticagrelor can bring to patients with CAD in acute and chronic secondary prevention.

Table 50: Analyses of Net Clinical Benefit and Irreversible harm

		Ticagrelor 60 mg bid versus placebo		
	Characteristic	**RRR**	**HR (95%CI)**	***P* value**
Full PEGASUS-TIMI 54	Net clinical benefit: CV death, MI, stroke, or TIMI major bleeding	5%	0.95 (0.85–1.06)	0.3412

population	Irreversible harm: CV death, MI, stroke, ICH and fatal bleeding	14%	0.86 (0.77–0.97)	0.0160
Base case: MI <2 years ago	Net clinical benefit: CV death, MI, stroke, or TIMI major bleeding	[redacted]%	[redacted]	[redacted]
	Irreversible harm: CV death, MI, stroke, ICH and fatal bleeding	[redacted]%	[redacted]	[redacted]

This technology does not meet the end-of-life criteria

4.14 Ongoing studies

AstraZeneca is not aware of any studies likely to provide additional evidence in the next 12 months for this indication, i.e. in patients <2 years from an MI and at high risk of further atherothrombotic events.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

Identification of studies

Strategies used to retrieve cost-effectiveness studies

A systematic review of the published literature was conducted to identify cost-effectiveness studies assessing prolonged (>18 months) DAPT (ticagrelor, clopidogrel, prasugrel, vorapaxar, and rivaroxaban in combination with aspirin) in adult patients with a history of MI. A wide range of DAPT-based therapies were incorporated, owing to the NICE scope not having been finalised at the time of the literature search. Studies which met the eligibility criteria of the review, but which considered DAPT for a duration of <18 months were tagged.

The following electronic databases were searched via the Ovid platform on the 1st December 2015: MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE, Embase, and the Cochrane Library, incorporating the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA), and the NHS Economic Evaluation Database (NHS EED).

The electronic searches were supplemented by hand searching of the following sources: reference lists of included publications and relevant conference proceedings from the last available three years.

Full details of the search and review methodology are provided in Appendix 11. Quality assessment of economic evaluations was undertaken using the criteria described in Appendix 11 of the NICE single technology assessment (STA) specification for manufacturer submission of evidence (June 2012), as adapted from Drummond and Jefferson (1996)(84).

Description of identified studies

Brief overview of each cost-effectiveness study relevant to decision-making in England

In total, 833 papers were identified through the electronic searches. Upon the removal of duplicate papers, 780 titles and abstracts were reviewed. Following first pass, 140 publications were ordered for full paper review, 132 of which were excluded. Three additional publications were identified via hand searching; one was eligible for inclusion, and two were tagged. This resulted in five relevant papers for final inclusion and six tagged publications which met the eligibility criteria of the review, but considered treatment of patients for 12 months only.

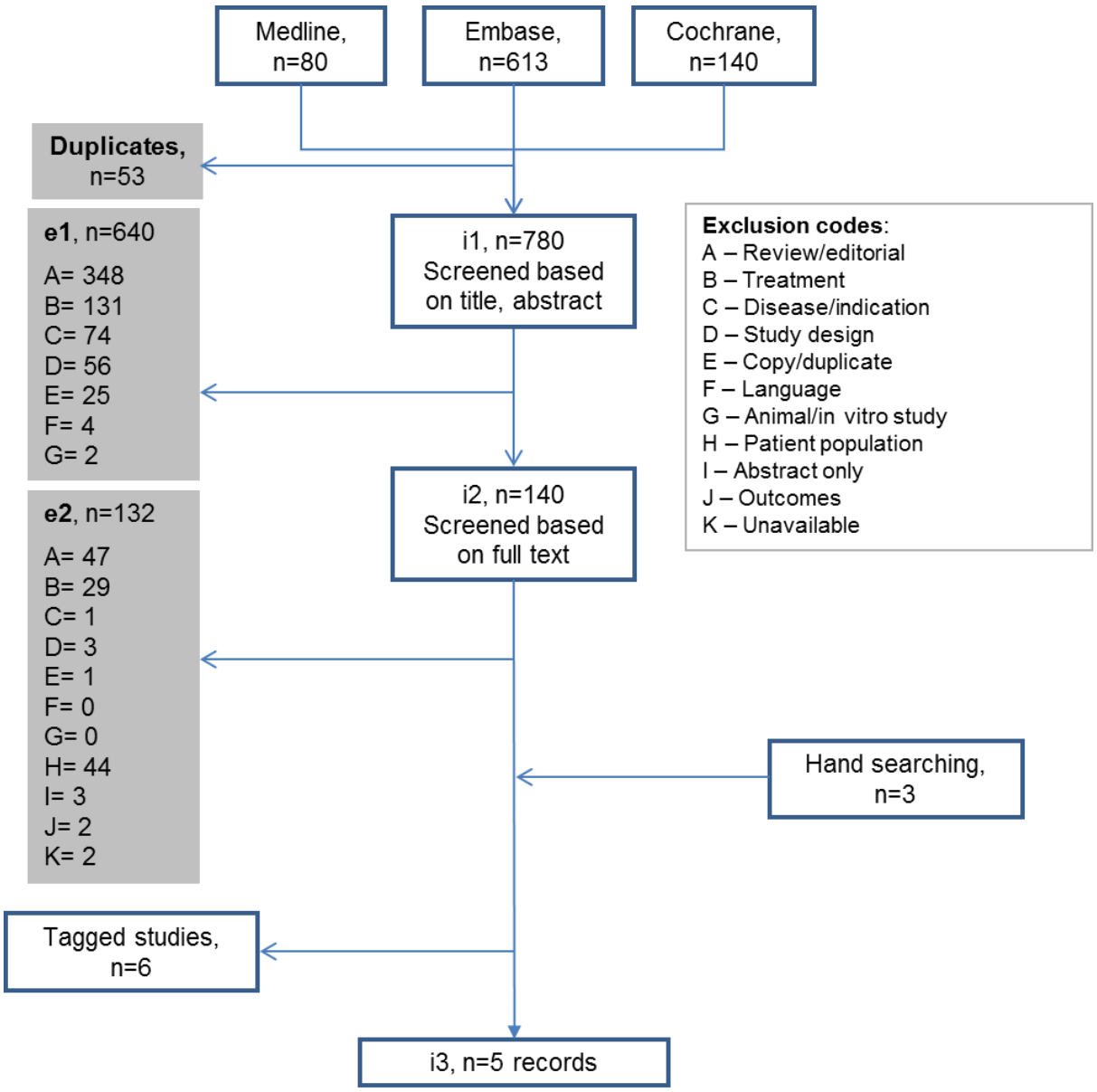
The flow of the studies through the review is shown in the PRISMA flow chart in Figure 33. A list of the five included studies, and the six tagged publications are provided in Table 15 and Table 16 (Appendix 11), respectively. A list of the studies excluded from the review on the basis of full publication is provided in Table 17 (Appendix 11), along with a rationale for exclusion (Appendix 11). Results of the quality assessment of the included studies are provided in Appendix 12.

A total of five studies met the eligibility criteria of the review, all of which were full publications (85-89). Countries from which the economic data were derived included: Canada (n=2) (85, 88); Sweden (n=1) (86); and the US (n=2) (87, 89).

No relevant UK-based cost-effectiveness analyses were identified and none of the five studies considered the cost-effectiveness of ticagrelor 60mg BID + low dose ASA in patients with a history of MI.

Of the five studies identified, three were cost-utility analyses (85, 86, 89) reporting incremental costs per quality adjusted life year (QALY) gained, and two were cost-effectiveness analyses (88), reporting incremental costs per life year gained (LYG).

Figure 33. PRISMA flow diagram for the economic evaluation review



The included studies considered the following patient populations for their analyses: adult patients with a diagnosis of ACS or peripheral vascular disease (PVD) (85); adult post-ACS patients with elevated cardiac biomarkers (86); patients with established cardiovascular (CV) disease or patients with risk factors for CV events (87, 88); adult patients with coronary disease which developed during a specific time frame and who survived the first month after diagnosis (89). It was unclear in each of the included studies whether all patients had previously experienced a MI, however, two studies reported sub-group analysis results specifically for patients with prior MI (87, 88);. Additionally, all five included studies specifically stated that treatment was for the secondary prevention of CV events (85-89). The interventions investigated in

the included studies included: clopidogrel in combination with aspirin versus aspirin monotherapy (n=4) (85, 87-89); and rivaroxaban plus standard anti-platelet therapy (ST-APT; defined as aspirin monotherapy or aspirin in combination with clopidogrel or ticlopidine) versus ST-APT alone (n=1) (86). The duration of treatment in the studies ranged from a maximum of 2 years (85, 86) to 28 months (87, 88). In one study, treatment duration was not explicitly stated, however, interventions with benefits were modelled for up to three years (89).

With regard to the model structures used, two studies constructed Markov models (85, 86), two studies conducted trial-based analyses (87, 88), and one study used a computer simulation model (89). The cycle length of the Markov models ranged from 12 weeks (for the first 2 years of the model) (86)(56)(Begum, Stephens et al. 2015) to one year (85). Health states considered in the Markov models considered the occurrence of single or multiple CV events over time. In Banerjee et al, 2015 (85) the model for ACS patients consisted for 6 health states: (i) qualifying/new MI (a new MI and the 12 month period afterward, during which time the patient is at greatest risk of another event); (ii) post-new MI (the period beyond the first 12 months after a MI); (iii) new stroke (a new stroke and the first 12 months afterwards); (iv) post-new stroke (the period beyond the first 12 months after a stroke); (v) vascular death; and (iv) non-vascular death (90). The analysis by Begum et al, 2015 (86) consisted of 16 health states representing the occurrence of single or multiple CV events over time. Events included MI, ischaemic stroke (IS), haemorrhagic stroke (HS), intracranial haemorrhage (ICH) and death (vascular or non-vascular) (86). This study also included an event free health state and considered transient health states for bleeding and revascularisation (86).

The analyses were conducted from the perspective of the payer in three studies (85, 87, 88), and from a societal perspective in one study (86). One study did not report the perspective adopted for the analysis (89). The time horizon of the analysis was reported in four studies (85, 86, 89), and ranged from 25 years (89) to a lifetime (85-87). Four studies stated that costs and health outcomes were discounted (85, 86, 88, 89), and the rate ranged from 3.0% (86, 89) to 5.0% (85, 88).

Study details of the included economic evaluations are summarised in Table 51; a summary of the main results from the analyses is provided in Table 52; and a summary of the key model assumptions in each study are presented in Table 53.

Table 51. Summary of study details of included economic evaluations (n=5)

Study, Country	Study design	Population	Interventions and comparators	Treatment duration	Outcomes reported	Study perspective	Model summary	Model inputs (clinical, costs, QoL)
Gaspoz, 2002 (89) US	CUA	US patients aged 35-84 years in whom coronary disease developed during or before 2003 to 2027 and who survived their first month after diagnosis	Six secondary prevention strategies (A-F): A - Zero utilisation B - Current use of aspirin (85%) C - Aspirin for all eligible patients D - Aspirin for all eligible patients and clopidogrel for remaining 5.7% E - Clopidogrel for all patients F - Combination of clopidogrel for all patient plus aspirin for eligible patients	Unclear (interventions with benefits were modelled for up to three years)	Costs and QALYs	NR	Computer simulation model, 25 year time horizon, 3% discount rate of costs and health outcomes	Clinical: data for the initial model were obtained from a literature review, the National Vital Statistics reports, the National Hospital Discharge Survey, the National Health Interview Surveys, the Framingham Heart Study, and variety of clinical and observational trials Costs: Medical Economics Staff, Stinnett et al (91), Weinstein et al (92), Scandinavian Simvastatin Survival Study QoL: non-coronary HRQL weights were based on observational data from the Beaver Dam Health Outcomes Study

Study, Country	Study design	Population	Interventions and comparators	Treatment duration	Outcomes reported	Study perspective	Model summary	Model inputs (clinical, costs, QoL)
Chen, 2009 (87) US	CEA	Patients with either established coronary, cerebrovascular or PAD, or with multiple risk factors for CV events, as outlined in the CHARISMA trial (number of patients with prior MI: clopidogrel + aspirin, 40.7%; aspirin, 41.9%)	Clopidogrel + aspirin Aspirin monotherapy	Duration of treatment was assumed to be a median of 28 months, as in the CHARISMA trial	Costs and LYG	Payer – US healthcare system	Trial-based analysis (based on CHARISMA trial), lifetime horizon, discounting not stated	Costs: estimated by multiplying counts of resource utilisation in CHARISMA by price weights derived from comparable populations of US patients; indirect costs obtained from Reduction of Athero-thrombosis for Continued Health Registry Life expectancy: data from CHARISMA trial and analysis of the Saskatchewan Health Database
Chen, 2011 (88) Canada	CEA	Patients with established CV disease or patients with multiple CV risk factors	Clopidogrel + aspirin Aspirin monotherapy (+ placebo)	Mean duration of treatment was assumed to be 28 months, as in the	Costs and LYG	Payer – Canadian healthcare system	Trial-based analysis, time horizon not stated, 5.0% discount rate for costs and life expectancy	Costs: Ontario Case Costing Initiative's Costing Analysis Tool for 2006-2007, Ontario Drug Benefit Formulary/ Comparative Drug Index No. 41 Life expectancy: data from CHARISMA trial and analysis of the Saskatchewan Health

Study, Country	Study design	Population	Interventions and comparators	Treatment duration	Outcomes reported	Study perspective	Model summary	Model inputs (clinical, costs, QoL)
		(number of patients with prior MI: clopidogrel + aspirin, 40.7%; aspirin, 41.9%)		CHARISMA trial				Database
Banerjee, 2015 (85) Canada	CUA	Adult patients with a diagnosis of ACS or PVD; the reference group had an average age of 60 years	Clopidogrel + aspirin Aspirin monotherapy Clopidogrel monotherapy	Base case: ACS: treatment duration was assumed to be one year for interventions, followed by lifetime of aspirin treatment PVD: treatment duration was assumed to be 2 years for interventions, followed	Costs and QALYs	Payer – Canadian provincial ministry of health	Separate Markov models for ACS (6 health states) and PVD (7 health states), considers MI within and beyond 12 months, one year cycle length, only relevant direct medical costs were included, 40 year time horizon (lifetime), 5% discount rate for costs and outcomes[†]	Transition probabilities: based on approach by Karnon et al (93) revised with Canadian specific mortality data Costs: Ontario Drug Benefit Formulary Comparative Drug Index, the British Columbia Ministry of Health formulary, PATH research institute, Alberta case cost report 2005-2006 QoL: utilities for stroke, MI, and PVD states were derived from two US studies of chronic conditions

Study, Country	Study design	Population	Interventions and comparators	Treatment duration	Outcomes reported	Study perspective	Model summary	Model inputs (clinical, costs, QoL)
				by lifetime of aspirin treatment				
Begum, 2015 (86) Sweden	CUA	Adult post-ACS patients with elevated cardiac biomarkers and without a prior history of stroke or TIA; the reference cohort had an average age of 62 years	Rivaroxaban + ST-APT[§] ST-APT alone[§]	Base case: Rivaroxaban was assumed to be prescribed for a maximum of two years Clopidogrel and ticlopidine were assumed to be discontinued after one year	Costs and QALYs	Societal	Markov model, 16 health states representing the occurrence of single and multiple CV events over time (MI, IS, HS/ICH, and death), 12 weekly cycles from 0-2 years and 6 month cycles from 2-40 years, 40 year (lifetime) horizon, 3.0% discount rate for all costs and health outcomes[‡]	Transition probabilities: estimated from patient-level data from ATLAS ACS 2-TIMI 51 trial Costs: based on published literature including Heeg et al (94) and a paper estimating costs from a Swedish register (95) QoL: utility values for MI, IS and HS/ICH were taken from the PLATO trial, disutilities were based on literature and expert opinion

ACS, acute coronary syndrome; CAD, Canadian dollars; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CV, cardiovascular; DAPT, dual antiplatelet therapy; HS, haemorrhagic stroke; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; IS, ischaemic stroke; LYG, life years gained; MI, myocardial infarction; PAD, peripheral artery disease; PVD, peripheral vascular disease; QALY, quality adjusted life year; QoL, quality of life; SEK, Swedish Krona; ST-APT, standard anti-platelet therapy; TIA, transient ischaemic attack; UK, United Kingdom; US, United States; USD, United States dollars.

† For ACS patients, one year of treatment with clopidogrel or clopidogrel + aspirin, followed by remaining lifetime of aspirin treatment, was assumed for the base case; for PVD patients, two years of treatment with clopidogrel or clopidogrel + aspirin, followed by remaining lifetime on aspirin treatment, was assumed in the base case.

‡ A maximum treatment duration of 2 years was assumed for rivaroxaban, and to comply with current clinical guidelines for ACS, the maximum treatment duration of clopidogrel or ticlopidine in both arms of the analysis was 1 year.

§ Standard anti-platelet therapy was defined as aspirin monotherapy or aspirin in combination with clopidogrel or ticlopidine

Table 52. Summary of results from included economic evaluations (n=5)

Study, country	Currency (ref year)	Intervention vs comparator	QALYs/LYG	Costs	Base case ICERs (cost per QALY/cost per LYG)	Relevance and limitations
Gaspoz, 2002 (89) US	USD (2000)	Five comparisons[†]: B vs A C vs B D vs C E vs D F vs D	QALYs gained from 2003 to 2027: A – 115,535,000 B – 121,768,000 C – 122,450,000 D – 122,906,000 E – 123,538,000 F – 124,343,000	Total cost from 2003 to 2027: A - $1,797,000 B - $1,867,000 C - $1,874,000 D - $1,888,000 E - $2,045,000 F - $2,071,000	ICER/QALY: B vs A, $11,000 C vs B, $11,000 D vs C, $31,000 E vs D, $250,000 F vs D, $130,000	It is unclear how representative the population in this analysis is of the population of interest; it is not clear if patients had prior MI, however, the analysis investigated treatment for secondary prevention of vascular events in patients with ACS Treatment duration is not explicitly stated, therefore it is unclear if the results reflect the cost-effectiveness of prolonged therapy in this indication US-based analysis; generalisability of results to a UK setting is unknown Does not provide cost-effectiveness evidence for ticagrelor 60mg BID + low dose ASA in a UK setting
Chen, 2009 (87) US	USD (2007)	Clopidogrel + aspirin vs aspirin monotherapy	Additional LYG with clopidogrel: Overall population, 0.072 Patients with prior MI, 0.130	Mean total cost per patient (overall): Clopidogrel + aspirin, $13,743 Aspirin monotherapy, $11,136 Cost difference:	ICER/LYG: Overall population, $36,343 Patients with prior MI, $20,413	Study population may be representative of population of interest; base case analysis results for sub-group of patients with prior MI are reported and considers DAPT over a period of 28 months; however, extension of findings to patients at higher or lower risk of CV events than those in the CHARISMA trial would require additional assumptions US-based analysis; generalisability of results to a UK setting is unknown

Study, country	Currency (ref year)	Intervention vs comparator	QALYs/LYG	Costs	Base case ICERs (cost per QALY/cost per LYG)	Relevance and limitations
				Overall population, $2,607 Patients with prior MI, $2,662		The life expectancy projections derived from historical Saskatchewan data may not directly applicable to current Us practice and outcomes Does not provide cost-effectiveness evidence for ticagrelor 60mg BID + low dose ASA in a UK setting
Chen, 2011 (88)(63)(Chen, Shi et al. 2011) Canada	CAD (2008)	Clopidogrel + aspirin vs aspirin monotherapy (+ placebo)	Additional LYG with clopidogrel: Overall population, 0.057 Patients with prior MI, 0.106 Additional QALYs with clopidogrel: Overall population, 0.07 Patients with prior MI, NR	Mean total cost per patient (overall): Clopidogrel + aspirin, $7,075 Aspirin monotherapy, $5,587 Cost difference: Overall population, $1,488 Patients with prior MI, $1,297	ICER/LYG: Overall population, $25,969 Patients with prior MI, $12,265 ICER/QALY gained: Overall population, $21,549 Patients with prior MI, NR	Study population may be representative of the population of interest; base case analysis results for sub-group of patients with prior MI are reported and the analysis considers DAPT over a period of 28 months Canadian-based analysis; generalisability of results to a UK setting is unknown Life expectancy estimates derived from historical Saskatchewan data may not be directly applicable to current Canadian practice and outcomes Does not provide cost-effectiveness evidence for ticagrelor 60mg BID + low dose ASA in a UK setting
Banerjee, 2015 (85) Canada	CAD (2009)	ACS: Clopidogrel versus aspirin Clopidogrel +	QALYs: ACS: Aspirin, 6.070	Costs: ACS: Aspirin, $36,498	ICER/QALY: ACS: Clopidogrel, dominated by	It is unclear how representative the results are of the population of interest as the number of patients with prior MI is not specified; the study title does, however,

Study, country	Currency (ref year)	Intervention vs comparator	QALYs/LYG	Costs	Base case ICERs (cost per QALY/cost per LYG)	Relevance and limitations
		aspirin vs aspirin PVD: Clopidogrel vs aspirin Clopidogrel + aspirin vs clopidogrel monotherapy	Clopidogrel, 6.032 Clopidogrel + aspirin, 6.095 PVD: Aspirin, 7.464 Clopidogrel, 7.538 Clopidogrel + aspirin, 7.526	Clopidogrel, $37,153 Clopidogrel + aspirin, $37,230 PVD: Aspirin, $71,120 Clopidogrel, $71,715 Clopidogrel + aspirin, $72,099	aspirin Clopidogrel + aspirin vs aspirin, $29,604 PVD: Clopidogrel vs aspirin, $8,106 Clopidogrel + aspirin, dominated by clopidogrel monotherapy	state that treatment is for secondary prevention of vascular events DAPT duration was assumed to be only 12 months for ACS patients, followed by a lifetime of aspirin monotherapy; the results for ACS patients therefore may not represent the true economic impact of prolonged DAPT >18 months The cost inputs for vascular death may be over-estimated as the costs for fatal stroke and MI came from patients with diabetes Canadian-based analysis; generalisability of results to a UK setting is unknown Does not provide cost-effectiveness evidence for ticagrelor 60mg BID + low dose ASA in a UK setting
Begum, 2015 (86) Sweden	SEK and € (2013) [Exchange rate: €1=SEK 8.8561]	Rivaroxaban + ST-APT vs ST-APT alone	QALYs: Rivaroxaban + ST-APT, 10.86 ST-APT alone, 10.72	Total costs: Rivaroxaban + ST-APT, SEK 562,911 (€63,562) ST-APT alone, SEK 552,911 (€64,433)	ICER/QALY: SEK 71,246 (€8,045)	It is unclear how representative the results are of the population of interest as it is unclear how many patients had previously experienced MI; the study does, however, specify that treatment is for the secondary prevention of ACS Swedish-based analysis; generalisability of results to a UK setting is unknown There is currently no data available on the real-life use of rivaroxaban in this patient population, therefore treatment discontinuation adjustments applied in the analysis are based on expert opinion

Study, country	Currency (ref year)	Intervention vs comparator	QALYs/LYG	Costs	Base case ICERs (cost per QALY/cost per LYG)	Relevance and limitations
						Does not provide cost-effectiveness evidence for ticagrelor 60mg BID + low dose ASA in a UK setting

Abbreviations: ACS, acute coronary syndrome; CAD, Canadian dollar; CV, cardiovascular; DAPT, dual anti-platelet therapy; ICER, incremental cost effectiveness ratio; LYG, life year gained; MI, myocardial infarction; NR, not reported; PVD, peripheral vascular disease; QALY, quality adjusted life year; SEK, Swedish Krona; ST-APT, standard anti-platelet therapy; UK, United Kingdom; US, United States; USD, United States dollar.

† See Table 51 for details of the treatment prevention strategies considered.

Table 53. Summary of key assumptions made in included economic evaluations (n=5)

Study, country	Key assumptions
Gaspoz, 2002 (89) US	Additional relative reductions were assumed for the rates of coronary events (8.7%) and deaths from non-coronary causes (5.0%) to model the effects of clopidogrel. In the base case analysis, aspirin was assumed to be used in 85% of patients with coronary heart disease in 2003; this is based on data on patients discharged after acute infarctions. The model assumed that 94.3% of patients were eligible for treatment with aspirin and 100% were eligible for treatment with clopidogrel. The cost of the combination of aspirin and clopidogrel was assumed to be the sum of the two individual drug costs. The incidence of gastrointestinal AEs and rash were assumed to be as reported for aspirin and clopidogrel; the incidence of stroke was assumed to be the incidence reported in pooled secondary statin trials.
Chen, 2009 (87) US	Actual duration of treatment was assumed to mirror that provided in the CHARISMA trial (a median of 28 months) as the precise effect of long-term therapy in the study population was unknown. Clopidogrel treatment was assumed to be discontinued at the end of the trial, and therefore, the base case analysis also assumed no further differences between the two treatment groups in the rates of subsequent CV events beyond the end of the trial.

Study, country	Key assumptions
	The analysis assumed no further treatment costs or benefit beyond the time frame of the trial. A friction cost approach was used to estimate days of work lost due to a fatal event in the secondary analyses; the duration of lost work was capped at 96 days, beyond which it was assumed that a replacement for the deceased worker would be found.
Chen, 2011 (88) Canada	Actual duration of treatment was assumed to mirror that provided in the CHARISMA trial (a median of 28 months) as the precise effect of long-term therapy in the study population was unknown. Clopidogrel treatment was assumed to be discontinued at the end of the trial, and therefore, the base case analysis also assumed no further differences between the two treatment groups in the rates of subsequent CV events beyond the end of the trial. A friction cost approach was used to estimate days of work lost due to a fatal event in the secondary analyses; the duration of lost work was capped at 96 days, beyond which it was assumed that a replacement for the deceased worker would be found.
Banerjee, 2015 (85) Canada	For ACS, one year of treatment with clopidogrel or clopidogrel + aspirin, followed by remaining lifetime on aspirin was assumed in the base case; for PVD, to years of treatment with clopidogrel or clopidogrel + aspirin, followed by remaining lifetime on aspirin was assumed in the base case. RR of non-vascular death for clopidogrel was unavailable and was assumed to equal 1; in PVD, population RRs for non-fatal stroke and non-fatal MI were unavailable, and were assumed equal to any stroke and any MI respectively. The cost of non-vascular death was assumed to be zero, as it is not a disease-related cost. A mean starting age of 60 years for patients and a discount rate of 5% for costs and outcomes were assumed in the base case analysis.
Begum, 2015 (86) Sweden	Treatment duration of rivaroxaban was assumed to be a maximum of 2 years (with an overall discontinuation rate of 81% in the second year), and to comply with clinical guidelines for ACS, the maximum treatment duration for clopidogrel or ticlopidine was 1 year. A half cycle correction was applied to reflect the continuous nature of the occurrence of transitions during each cycle by assuming that, on average, all transitions occurred halfway through any particular cycle. The model assumed there was no treatment effect associated with rivaroxaban or clopidogrel or ticlopidine after treatment discontinuation. In line with treatment guidelines, aspirin monotherapy was assumed to be continued after discontinuation of all other treatment(s) for the remainder of the model. As ticlopidine is not available in Sweden for the treatment of ACS patients, it was assumed that all patients who received

Study, country	Key assumptions
	ticlopidine in the ATLAS ACS 2-TIMI 51 clinical trial (<1% of patients) were subsequently treated with clopidogrel, without affecting the overall clinical outcomes. Revascularization and non-ICH bleeding events were assumed to only occur during the observation period (in accordance with the specified length of treatment in each arm) as the rates would be considered equal after rivaroxaban and ST-APT discontinuation, and their impact on the incremental outcomes negligible after the observation period. To capture long-term survival rates, transition probabilities on the effectiveness and safety of aspirin were extrapolated assuming constant rates in time. Patients who have experienced an ACS event are at an elevated risk of experiencing a subsequent event, typically within the first 6 months following an event, although this risk diminishes over time; the risk of suffering a second subsequent event after the first was assumed to be 1.5 times the risk of suffering a first subsequent event after the index event. In the absence of specific, separate costs for IS and HS/ICH, the costs were assumed to be the same for the stroke types.

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; MI, myocardial infarction; PVD, peripheral vascular disease; RR, relative risk; ST-APT, standard anti-platelet therapy; US, United States.

Complete quality assessment for each relevant cost effectiveness study identified.

Quality assessment is provided at Appendix 12.

5.2 De novo analysis

Patient population

As described at section 1.1, the patient population presented in the base case economic evaluation is a subgroup of the licensed indication (and population defined by the scope), corresponding to those patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event, who tolerate low dose aspirin, whose most recent MI occurred <2 years ago.

The base case population corresponds with the “MI <2 years” subgroup of the PEGASUS TIMI-54 trial and can be described more specifically as:

Patients with a history of myocardial infarction (MI), aged ≥50 years, whose most recent MI occurred <2 years ago, who tolerate low dose aspirin

and exhibit at least one of:

- Age ≥65 years
- Diabetes requiring medication
- >1 prior MI
- Multivessel Coronary Artery Disease
- Chronic renal disfunction

but do not exhibit:

- Planned use of PY12 antagonist, dipyridamole, cilostazol or anticoagulant
- Bleeding disorder
- History of ischaemic stroke, intracerebral hemorrhage, CNS tumour or vascular abnormality
- Recent GI bleed or major surgery
- Risk of bradycardia

- Dialysis or severe liver disease

The baseline characteristics for the base case population are shown in Table 20.

Model structure

The objective of the cost-effectiveness model was to reflect the outcomes of patients from the 'label' population within the PEGASUS-TIMI 54 trial. The trial involved a composite endpoint as the primary outcome. In the cost-effectiveness model, each of the individual components of the composite endpoint was modelled individually in a competing risk framework such as that used in the Scottish Cardiovascular Disease (CVD) Policy model (2). The principal advantage of using a competing risks framework is that it allows for different impacts (coefficients) of characteristics for each separate endpoint. For example, systolic blood pressure (SBP) may be expected to be more important for cerebrovascular disease than for coronary heart disease (CHD) outcomes, as was evident in the Scottish CVD Policy Model. For this reason, this approach was considered most appropriate to reflect the risks of each event in the PEGASUS-TIMI 54 trial. Furthermore, the risk equations are used to model events directly, rather than composite events which are then apportioned using the probability of that event being of a certain type. For this reason, fewer assumptions are made in the modelling process.

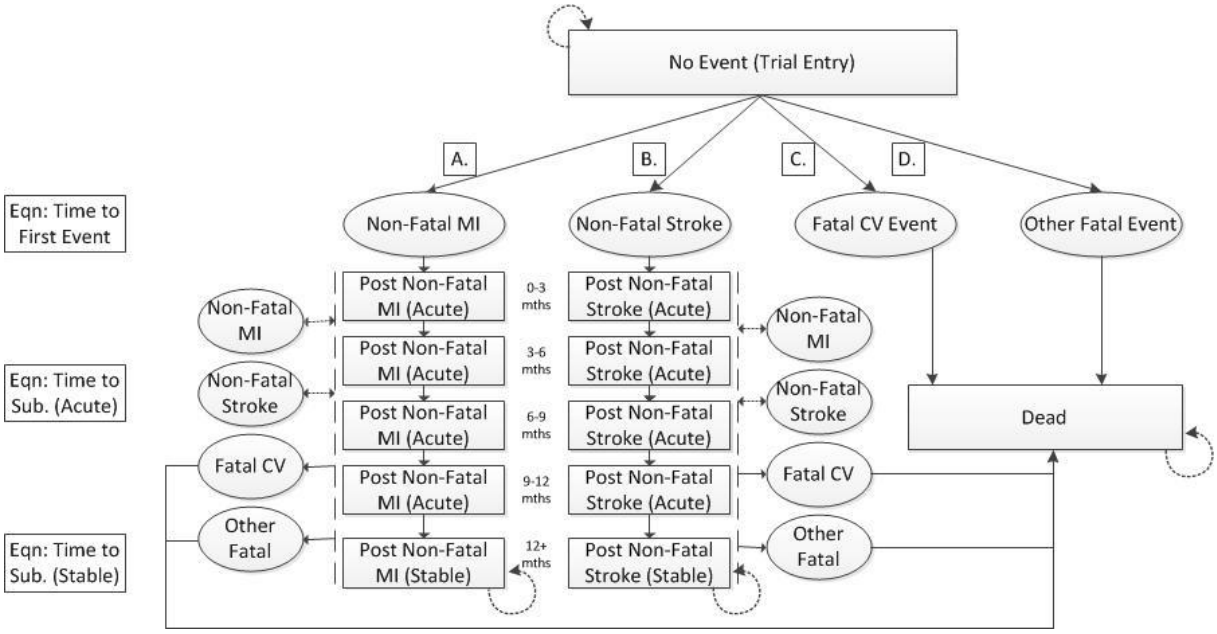
The main events of interest in PEGASUS-TIMI 54 were:

- first events, subsequent events (and ordering of events)
- hospitalisations
- dyspnoea (grade 1–2 and 3–4)
- TIMI bleeds (major and minor)
- EQ-5D responses
- permanent treatment discontinuation

A state transition diagram for the Markov model of the PEGASUS-TIMI 54 study is shown in Figure 34. Health states are represented in the diagram as rectangles, while events are represented as ovals. The model uses a 3-month cycle length, with

a maximum time horizon of 50 years (200 cycles) which can be varied between the observed trial time period (approximately 36 months) and the 50-year maximum (40 years in base case). Health state costs and utilities are half-cycle corrected by calculating the average proportion of the cohort in the states over the course of each model cycle.

Figure 34: State transition diagram of cost-effectiveness model



Note: All patients will have had a qualifying MI (ie patients in the 'No Event' health state will have had at least one MI and those with a 'first' event MI will have had at least two MIs). The model diagram does not include TIMI bleeds or dyspnoea, which are modelled as events that are conditional on the patient remaining on treatment

First events

The model structure was designed to reflect the PEGASUS-TIMI 54 trial as closely as possible. Patients enter the model in the 'No Event (Trial Entry)' state and are modelled to have an individual risk for their first event (non-fatal MI, non-fatal Stroke, fatal CV event or other fatal event). This is represented in Figure 34 as 'Eqn: Time to First Event', A, B, C, and D. Patients having a fatal event, enter an absorbing 'Dead' state, while those who have a non-fatal event, enter either a 'post non-fatal MI' or 'post non-fatal stroke' state depending upon the first event experienced.

Risk functions for all 'Eqn: Time to First Event' in Figure 34 were estimated using a competing risks survival analysis, where non-fatal MI, non-fatal stroke, fatal CV and other fatal events, compete to be the first event. Analysing trial data in this way more closely reflects the primary outcome of the trial (the composite endpoint for MI,

stroke and CV death), but allows for different assumptions for the underlying hazard to be applied (via different functional forms) for the extrapolation period.

This approach differs from other CV economic models which have directly modelled the time-to-first composite event using a risk equation and then applied a logistic function to determine the probability of the composite event being a non-fatal MI, non-fatal stroke or CV death.(96) The approach applied in the PEGASUS-TIMI 54 model improves on these previous methods, allowing flexibility for the underlying hazard of an event, and individual treatment effect and interaction effects to be applied for each outcome.

Subsequent events

Although patients can attain further events, those patients who enter a 'Post Non-Fatal MI' or 'Post Non-Fatal Stroke' state, remain in this health state until they die. Explicitly modelling repeat events over the relatively short time frame of the trial would add substantially to the complexity of the model (i.e. modelling multiple sets of tunnel states for acute phases), which would not be expected to alter estimates of life years or QALYs. While this is a simplification of reality, it is a structural assumption that will not significantly change overall health outcomes and associated costs.

Subsequent events, non-fatal MI, non-fatal stroke, fatal CV and other fatal are estimated using a second set of risk equations. To reflect the higher rate of subsequent events for the 12 months after the first event, five tunnel states are applied. The first four states track time since the first event with a diminishing risk for subsequent events: patients whose first event occurred 0–3 months prior, the second 3–6 months prior, the third 6–9 months prior and the fourth 9–12 months prior, for states one to four, respectively. The fifth state applies a constant risk for subsequent events from 12 months or more after the first event.

In Figure 34, solid lines illustrate the directional flow of patients through the Markov model, dotted lines indicate that patients may remain in a state either event-free or, for the 'Post Non-Fatal' states, with a subsequent event recorded.

TIMI bleeds and dyspnoea

Additional events, not illustrated in Figure 34, are included in the Markov model:

- TIMI bleeding events, major and minor
- dyspnoea, major (grade 3–4) and minor (grade 1–2)

These events are not modelled using health states, as they do not have a long-term impact on prognosis in terms of long-term mortality or permanent utility decrements. These events (TIMI bleeds and dyspnoea) are modelled as transient events that are conditional upon the patient remaining on treatment and they contribute to the costs and QALYs (via disutility) in the model.

Mortality (non-CV related)

The Markov model includes risk equations based on the PEGASUS-TIMI 54 trial for 'Other Fatal Events'. The risk equations allow for the total number of events observed in PEGASUS-TIMI 54, by treatment arm, to be replicated. However, as is often the case in clinical trials, inclusion and exclusion criteria applied to patients at the commencement of the trial result in a lower rate of 'other mortality' events than would be expected in the general population. To avoid underestimation of mortality in the base case the probability of non-CV related mortality was derived from UK life tables. A sensitivity analysis explored the use of probability of non-CV mortality derived from the PEGASUS-TIMI 54 trial.

Within the PEGASUS-TIMI 54 trial, the average time between MI or stroke events that led to a fatal CV event is 3 days, and therefore it was assumed that the costs associated with a MI or stroke event that led to a CV death would be captured by the inpatient cost applied to fatal events within the model.

Duration of treatment effect

The duration of treatment for ticagrelor 60 mg BID + low-dose ASA is set to 36 months in line with the duration of treatment specified at section 1.1 (there are limited data on the efficacy and safety of ticagrelor 60mg beyond 3 years of treatment). In the model, survival functions associated with ticagrelor 60 mg BID + low-dose ASA (including AEs) are applied only for the first 36 months. The subsequent time periods are modelled without treatment effects, and are akin to the

low-dose ASA treatment arm (i.e. the patient is assumed to discontinue ticagrelor 60mg BID and continue on ASA monotherapy).

Hospitalisations

Admissions to hospital were captured for every patient randomised at baseline in PEGASUS-TIMI 54 and recorded for the day that admission occurred. The Markov model applies a different rate of hospitalisation for patients who occupy each health state. All patients within a health state will accrue an outpatient and maintenance cost but only a proportion of patients will accrue an inpatient cost. For example, in a given cycle 10 patients have a fatal cardiovasular event as their first event. However, only a proportion of these patients are hospitalised. Therefore, a proportion of these patients will receive an inpatient cost.

Due to the low hospitalisation rates for MI, stroke and serious adverse events predicted by the regression model, which are unlikely to be represenative of clinical practice within the UK, we have assumed that all patients experiencing a non-fatal MI, non-fatal stroke or serious adverse event will be hospitalised.

Comparison to the reference case

Key features of the de novo analysis are detailed in Table 54.

Table 54: Features of the de novo analysis

Factor	Chosen values	Justification
Model structure	Markov model	See below
Time horizon	40 years	NICE reference case. All important differences in costs and outcomes are captured as 98.8% of patients have died by this time point in the model
Were health effects measured in QALYs; if not, what was used?	QALYs (measured using EQ-5D) and life years	NICE reference case
Discount of 3.5% for utilities and costs	3.5%	NICE reference case
Perspective (NHS/PSS)	NHS and PSS	NICE reference case
PSS, personal social services; QALYs, quality-adjusted life years		

Intervention technology and comparators

The following treatment arms are included in the de novo cost-effectiveness analysis:

Intervention: Ticagrelor 60mg BID + low dose (75mg) ASA daily

Comparator: Placebo + low dose (75mg) ASA daily

Additionally, the scope requests clopidogrel + ASA be considered a comparator for this appraisal. This comparator is not included in the de novo cost-effectiveness analysis, owing to the absence of a head-to-head trial in the population of interest and a lack of available trial evidence for clopidogrel + ASA that would facilitate a robust indirect comparison to the ticagrelor 60mg BID + low dose ASA arm of the PEGASUS TIMI-54 trial (or MI<2 years subgroup thereof). Further explanation in this regard is provided at section 4.10.

Continuation rule

A treatment continuation rule is not applied in the model.

5.3 Clinical parameters and variables

Clinical analyses versus economic analyses

Bonaca et al(6) used Kaplan–Meier plots and a simple Cox regression to report results for the primary outcome, time to a first composite event (CV death, MI, and stroke).

The key efficacy and safety outcomes for the full trial population, as reported by Bonaca et al(6) (excluding the ticagrelor 90 mg BID + low-dose ASA arm) are presented in Table 55.

Table 55: Clinical outcomes from PEGASUS-TIMI 54 (full population)

Clinical endpoint	**Placebo + low dose ASA (N=7,067)**	**Ticagrelor 60 mg BID + low-dose ASA (N=7,045)**	
	N	**N**	**HR (95% CI)**
Efficacy			
CV death, MI or stroke	578	487	0.84 (0.74–0.95)

CV death or MI	497	422	0.85 (0.74–0.96)
CV death	210	174	0.83 (0.68–1.01)
MI	338	285	0.84 (0.72–0.98)
Stroke: any	122	91	0.75 (0.57–0.98)
Stroke: ischemic	103	78	0.76 (0.56–1.02)
Death from any cause	326	289	0.89 (0.76–1.04)
Bleeding			
TIMI major bleed	54	115	2.32 (1.68–3.21)
TIMI minor bleed	18	55	3.31 (1.94–5.63)
Other adverse event			
Dyspnoea	383	987	2.81 (2.50–3.17)
Leading to discontinuation	51	297	6.06 (4.50–8.15)
Grade 3-4	9	23	2.70 (1.25–5.84)
Gout	74	101	1.48 (1.10–2.00)

For the purpose of this economic model the composite outcome (of CV death, MI or stroke) is disaggregated into its components, to accord with the model structure outlined in Figure 34. A competing risks approach is used to estimate hazard functions representing the time to first component of the composite outcome.

In addition, for the purpose of accurately modelling mortality and overall expected survival, any MI or stroke that occurred within 30 days of a CV death was applied in the modelas a CV death. Hospitalisation events and HRQL estimates were made in consideration of recoding, with hospitalisation events and HRQL allocated to the cycles where mortality events occurred.

A total of 139 events were reallocated across the three arms of the trial using the 30-day CV death rule including a total of 84 of 1042 (8.1%) MI events, and 55 of 344 (16%) stroke events. This reallocation of MI and stroke events does not impact the overall primary composite outcome of the trial (Table 56) but the total number of events modelled is reduced by 139 events across all three arms (Table 57).

Table 56: Composite outcome result comparison using 30-day CV death rule

Clinical endpoint	Ticagrelor 60 mg BID + low-dose ASA
Bonaca et al. (2015) (6)	0.84 (0.74–0.95)
Economic model	0.84 (0.74–0.95)

The average time between MI or stroke events and the fatal CV event is 3 days, and therefore it was assumed that the costs associated with a MI or stroke event that led to a CV death would be captured by the inpatient cost applied to fatal events within the model. Table 57 shows the reallocation of observed events. It should be noted that this includes first and subsequent events, and therefore cannot be compared directly to Table 55, which considers only the first clinical event.

Table 57: Reallocation of observed events using 30-day fatal CV rule

Trial events	**Modelled events**			
	Non-fatal MI	Non-fatal stroke	Fatal CV	**Total**
MI	958		84	**1,042**
Stroke		289	55	**344**

Table includes both first and subsequent events, for all three treatment arms

Risk equation methodology

The clinical results presented in Bonaca et al(6) represent an analysis using a Cox proportional hazard regression that accounts for the treatment administered. The economic model expands upon these analyses. Estimation of time-to-first-event analyses were completed using a competing risk approach, where four events (non-fatal MI, non-fatal stroke, fatal CV and fatal other) were competing to be the first event experienced by each patient. The approach generates four separate risk equations for each of the event types, where an individual treatment effect is incorporated into the equation. These risk equations therefore incorporate baseline characteristics as a tool to predict risk, accounting for overall patient heterogeneity.

A competing risk approach differs from standard survival analyses, as patients are censored from the ‘at-risk’ population when a competing event occurs. The methodology mirrors the primary analysis used in PEGASUS-TIMI 54, whereby the components of the composite outcome are unpacked into their individual outcomes. This process allows for a more accurate estimation of future events, as alternative function forms for survival curves can be applied for events, allowing for greater flexibility over the extrapolation period in the model.

All patients from PEGASUS-TIMI 54 (including those who received ticagrelor 90 mg BID + low-dose ASA) were used in the statistical analysis, leading to an ‘original’ regression and set of risk equations aligned with the anticipation that the licence

would reflect the entire trial population. These were revisited when, during the regulatory process, it became clear that the licence was to be targeted at patients with MI <2 years previously or within 1 year of previous ADP inhibitor treatment (henceforth referred to as the 'label population'). The original risk equations developed for the full PEGASUS-TIMI 54 population were used to analyse the effect of incorporating an interaction term for the label population into the risk equations. The advantage of including all patients and analysing the effect of an interaction term between the label population and the treatment effect, is that there is no loss of power or precision to estimate the risk equations, as there is when data for individuals not included in the label population are excluded.

The analysis of a risk difference between patients included or excluded from the label population was performed only for the time-to-first-event risk equations. The other risk equations within the model (time to subsequent event, hospitalisations, utility decrements, treatment discontinuation and AEs) were analysed based on the full population. The inclusion criteria for the label population contain MI <2 years previously, suggesting that being in the label population or not is irrelevant after an event. The most important prognostic factor at this point in this is the event that has just occurred. Therefore, there was no rationale to suggest that inclusion (or not) in the label population would impact on any of these other risks.

Baseline characteristics for inclusion in the risk equations were selected using a step-wise process (97). For survival models a Cox regression analysis was used to select variables while other regressions (e.g. generalised linear models; panel data analyses) used their intended functional form. The process used to empirically select baseline covariates was as follows:

1. Individually regress all available baseline characteristics against the outcome of interest, retaining all covariates that are statistically significant at the 0.05 level.

2. Perform a backward stepwise regression incorporating all covariates identified in step 1, and individually dropping covariates with a p-value >0.1.

3. Include each of the covariates not incorporated into the model, one by one, retaining the variable only if the p-value for the coefficient is <0.1.

4. Covariates were tested for the proportional hazards assumption (using a combination of tests using Schoenfeld residuals, log–log plots of survival and a plot of Kaplan–Meier and predicted survival). Interaction effects were examined if the proportional hazard assumption did not hold. Variables were excluded if proportionality was not observed and interaction effects could not be established.

The baseline characteristics used to estimate patients' underlying risk and their definitions are outlined in Table 58.

Table 58: Baseline variables used in models

Variable name	Definition
Tic60	Treatment effect variable (coded 1 if patient was randomised to receive ticagrelor 60 mg BID + low-dose, coded 0 otherwise)
age	Patient age (in years) at randomisation
sex	Patient sex (coded 1 for Males and 0 for Females)
weight	Patient weight in kg at randomisation
bmi	Patient BMI (kg/m^2) at randomisation
dmtype	Patient diabetes status at randomisation (coded 1 for type 1 or 2, coded 0 otherwise)
MI_HIST	Patient previous history of MI (coded 1 if patient had more than 1 previous MI at randomisation, coded 0 otherwise)
cadmult	Identifies whether patient has Multivessel Coronary Artery Disease at randomisation (coded 1 if present, coded 0 otherwise)
pci	Identifies whether patient has ever received a PCI at randomisation (coded 1 if history of PCI, coded 0 otherwise)
smk_his1	Identifies patient smoking status at randomisation (coded 1 if former smoker, coded 0 otherwise)
smk_his2	Identifies patient smoking status at randomisation (coded 1 if current smoker, coded 0 otherwise)
stentany1	Identifies whether patient ever received a stent (coded 1 if stent received, coded 0 otherwise)
anpect	Identified whether patient has a history of angina pectoris (coded 1 if postive history, coded 0 otherwise)
qevtyp2	Identifies whether the qualifying event was a STEMI or NSTEMI event (coded 1 if qualifying MI was a STEMI, coded 0 otherwise)
qev2rnd	Time from qualifying MI to randomisation (days)
MEDTDDOS_n	Dose of ASA being received at baseline (mg)
sbpsup	Patients supine SBP (mmHg) at randomisation
dbpsup	Patients supine DBP (mmHg) at randomisation
hyp	Identifies whether patient has hypertension requiring medical therapy at baseline (coded 1 if present,coded 0 otherwise).

hypchol	Identifies whether patient has hypercholesterolaemia requiring medical therapy at randomisation (coded 1 if present, otherwise coded 0)
cohdhist	Identifies whether patient has a family history of premature coronary heart disease (coded 1 if present, coded 0 otherwise)
cabg	Identifies whether patient has a history of CABG at randomisation (coded 1 if history,coded 0 otherwise)
stroke	Identifies patients with a history of stroke at randomisation (coded 1 if history, coded 0 otherwise)
tria	Identifies patients with history of transient ischaemic attack at randomisation (coded 1 if history, coded 0 otherwise)
prcerr	Identifies whether patient has received a prior cerebrovascular revascularisation (coded 1 if history, otherwise coded 0).
chf	Identifies whether the patient has congestive heart failure at randomisation (coded 1 if patient has history, coded 0 otherwise)
spbleed	Identifies if patient has a history of spontaneous bleeding that required hospitalisation at randomisation (coded 1 if history, coded 0 otherwise)
Asia_Australia	Identifies whether patient was located in Asia or Australia at randomisation (coded 1 if located either in Asia or Australia, coded 0 otherwise)
NthAmerica	Identifies whether patient was located in North America at randomisation (coded as 1 if located in North America, coded 0 otherwise)
SthAmerica	Identifies whether patient was located in South America at randomisation (coded as 1 if located in North America, coded 0 otherwise)
tADP_30d12m	Identifies time since the last ADP (coded 1 if patient received ADP blocker between 30 days and 12 months prior to randomisation, coded 0 otherwise)
tADP_12mplus	Identifies time since the last ADP (coded 1 if patient received ADP blocker more than 12 months prior to randomisation, coded 0 otherwise)
tClop_7dplus	Identifies time from last treatment with clopidogrel to randomisation (coded 1 if over 7 days prior to randomisation, coded 0 otherwise)
histPAD	Identifies whether the patient has a history of peripheral arterial disease (coded 1 if history, coded 0 otherwise)
creatinine_cl	Identifies patient creatinine clearance rate at randomisation (coded 1 if ≥60 mL/min, coded 0 otherwise)
offlabel	Identifies patients included or excluded from the label population (coded 1 if excluded i.e. off label, coded 0 if included)
t60offlabel	Interaction term. Patients receiving ticagrelor 60 mg BID + low-dose who are not included in the label population (coded 1 if received ticagrelor 60 mg BID + low-dose and is not in label population, coded 0 otherwise)
t90offlabel	Interaction term. Patients receiving ticagrelor 90 mg BID + low-dose who are not included in the label population (coded 1 if received ticagrelor 60 mg BID + low-dose and is not in label population, coded 0 otherwise)

Covariate selection for time-to-event analyses was completed using a Cox proportional hazards model, which does not impose a restriction or assumption with regard to the form of the underlying hazard. The covariates selected using this approach were incorporated into parametric functions, in which an assumption was made with respect to the form of the underlying hazard to allow for extrapolation beyond the observed trial period.

For each of the four 'time to first event' risk equations (non-fatal MI, non-fatal stroke, fatal CV, and other fatal) an interaction between the treatment effect and the label population was analysed.

The following stepwise approach was used to observe the influence of an interaction effect upon the 'time to first event' for patients in the label population:

1. Run the original regression models developed for the full PEGASUS-TIMI 54 population.

2. Insert the covariate coding for patients included or excluded from the label population (offlabel), and insert two interaction variables (t60offlabel and t90offlabel), to evaluate the interaction between the label population variable (offlabel) and the treatment effect variables (Tic60 and Tic90).

3. Where variables are suspected to be similar to the qualifying characteristics of the label population (e.g. variables encoding time from qualifying MI event or time since previous ADP treatment) the regression analysis was performed with the interaction effect between the label population variable (offlabel) and the treatment effect variables (Tic60 and Tic90), with similar variables dropped from the analysis to isolate the effect of being in the label population.

4. The two interaction terms were evaluated for their improvement in predictive value within the risk equation using a likelihood ratio (LR) test. If the interaction term resulted in a p-value of $p<0.05$, it was included in the model. If the p-value fell between 0.05 and 0.1, then the two separate interaction terms (t60offlabel and t90offlabel) were collapsed to one variable (i.e. a new interaction variable encoding ticagrelor of any dosage

and patients not included in the label population). An interaction effect was then analysed by the LR test approach using this collapsed variable, increasing the power to detect an interaction effect where one existed).

5. If, after performing steps 2–4, there was no evidence of an interaction effect, then the interaction term was dropped from the risk equations and the risk equations were re-estimated adjusting for the label population variable (offlabel) and treatment effects (Tic60 and Tic90), without the interaction term. These variables were evaluated separately for their inclusion in the model, with variables retained where the p-value was ≤0.05.

6. Where the interaction terms and label population variable were not significant, then the original risk equation from the full population was retained. Where the label population variable was included, either as an interaction term or added as another covariate, a backward stepwise regression was subsequently performed (using the covariate selection process described above) to identify any change in the covariate selection that should be included after the incorporation of either an interaction term or the label population variable.

Multicollinearity

Multicollinearity occurs when explanatory variables within the risk equation are associated with the outcome of interest, but are also highly associated with other explanatory variables. Given that the label population is based upon patient characteristics that are already captured by current variables included in some of the risk equations (i.e. ‘qev2rnd’ indicating time since previous MI, and ‘tADP_12mplus’ indicating patients receiving an ADP blocker more than 12 months ago), it was expected that multicollinearity would be observed when these variables were included in the same risk equation as the label population variable. Where multicollinearity was suspected to have occurred between the ‘offlabel’ variable and either the ‘qev2rnd’ or ‘tADP_12mplus’ variables, the label population variable was prioritised and retained in the model, and the collinear variables dropped as the label population variable was of greater importance.

Extrapolation beyond the trial

A key objective of constructing an economic model based on the PEGASUS-TIMI 54 trial was to allow the long-term projection of patient outcomes, beyond the trial period. For each of the time-to-event analyses (time to first event and time to subsequent events), five alternative survival functions were estimated.

For each function the AIC and BIC outputs are reported and provide an insight into how well the models fit the observed data. The order of the minimum values for AIC and BIC estimates provide similar outcomes for each function but the BIC estimate penalises complex models more heavily. As all of the survival functions use the same number of covariates, the BIC will only vary from AIC with respect to the exponential model which does not require the estimation of a shape variable.

As a starting point the preferred survival function was selected based on the minimum AIC value. However, caution is required, as the AIC and BIC functions provide only a measure of fit for observed data, and do not provide an insight into the appropriate function to use during the extrapolation period. The underlying assumptions for the log-logistic function are most likely to be in line with clinical expectations that the risk will be high initially following a CV event and diminish over time (e.g. the risk of an MI is higher 2 years after an intial MI, than it is 10 years after an initial MI – e.g. see Figure 3).

Risk equations for first events – non-fatal MI

Bonaca et al (6) reported time-to-event results for MI events (non-fatal and fatal MI combined). These outcomes differ from the non-fatal MI outcome used in the economic analysis due to the 30-day fatal CV reallocation rule, and the competing risk framework for the other remaining components of the composite outcome (i.e. non-fatal stroke). For the purpose of the economic analyses it is important to distinguish between MI and stroke events that immediately precede death and those from which a patient survives, to ensure that costs and quality of life are allocated appropriately.

Table 59 outlines the HR results from a Cox proportional hazard model. Bonaca et al (6) refers to time to first MI whereas ‘economic model’ refers to time to first non-fatal MI within a competing risk structure, with and without controlling for baseline risk

characteristics. Using a model that does not adjust for baseline risk, the HR of ticagrelor 60 mg BID + low-dose ASA is statistically significant at a 5% level. When adjusting for baseline risks, the HR and 95% confidence interval (CI) for ticagrelor 60 mg BID + low-dose ASA is unchanged.

Table 59: Cox proportional hazard ratios, time to first event: non-fatal MI

Scenario	Endpoint	HR (95% CI)
Bonaca et al (6)	Time to first MI	0.84 (0.72–0.98)
Economic model (Tx only)	Time to first non-fatal MI	0.83 (0.71–0.98)
Economic model (adjusted)	Time to first not-fatal MI	0.83 (0.71–0.98)

Tx=Treatment. Covariates used in the adjusted economic model are detailed in Appendix 16, Table 34.

Appendix 16, Table 34 demonstrates the models tested in the analysis based on the methodology detailed above. For non-fatal MI, there was no evidence of an interaction effect between ticagrelor 60 mg BID + low-dose ASA and patients not included in the label population (LR test: p=0.493 for separate treatment dosage interaction terms, p=0.292 for one ticagrelor treatment interaction). Although there was no significant treatment interaction observed, there was evidence of a difference in baseline risk of a non-fatal MI between patients included and not included in the label population, after adjusting for treatment arms and all other covariates in the regression model (HR: 0.776, p=0.004). This suggests that patients not included in the label population have a 22% lower risk of a non-fatal MI compared to those in the label population.

Schoenfeld residuals, the log–log plot, and Kaplan–Meier and predicted survival plots are detailed in Appendix 16, Table 35 and in Figure 1.

Table 60 presents the coefficients and p-values for the survival function that provides the best fit to the observed events (log–logistic).

Table 60: Time to first event: non-fatal MI

	Log–logistic	
Variable	**Coef.**	**p-value**
offlabel	0.2771	0.0048
Tic60	0.2057	0.0293
Tic90	0.1860	0.0482
age	-0.0130	0.181

dmtype	-0.4085	<0.0001
MI_HIST	-0.7613	<0.0001
cadmult	-0.3111	0.0003
smk_his1	-0.2321	0.0122
smk_his2	-0.5086	<0.0001
anpect	-0.3164	0.0001
qevtyp2	-0.1945	0.0150
sbpsup	-0.0102	<0.0001
Asia_Australia	0.3051	0.0465
NthAmerica	-0.4164	<0.0001
histPAD	-0.2420	0.0858
creatinine_cl	0.2789	0.0048
cabg	-0.8230	<0.0001
_cons	13.17	<0.0001
shape	0.0728	0.0250

shape variables take the following form: Log Logistic – ln(gamma)

Appendix 16, Table 36 presents the coefficients and p-values for all survival functions estimated for non-fatal MI using each of the five functional forms incorporated into the cost-effectiveness model. Metrics (AIC and BIC outcomes) and Cox–Snell residual plots for each of the five functional forms are detailed in Appendix 16, Table 37 and in Figure 2.

To aid with the comparison of the parametric functions, an average survival curve was estimated across the label population only (n=10,779) for each functional form (extrapolated), and plotted against the Kaplan–Meier curve for low-dose ASA alone and ticagrelor 60 mg BID + low-dose ASA (Figure 35 and Figure 36, respectively).

Figure 35: Low-dose ASA alone KM versus parametric functions, non-fatal MI

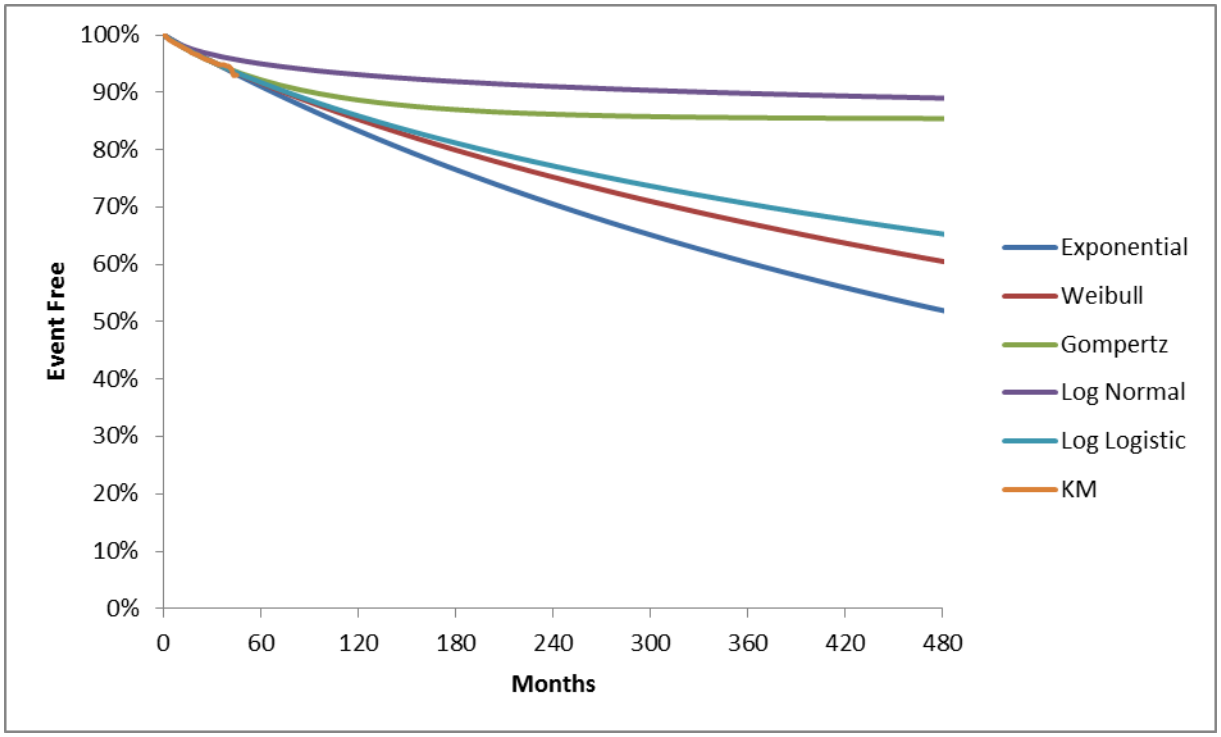
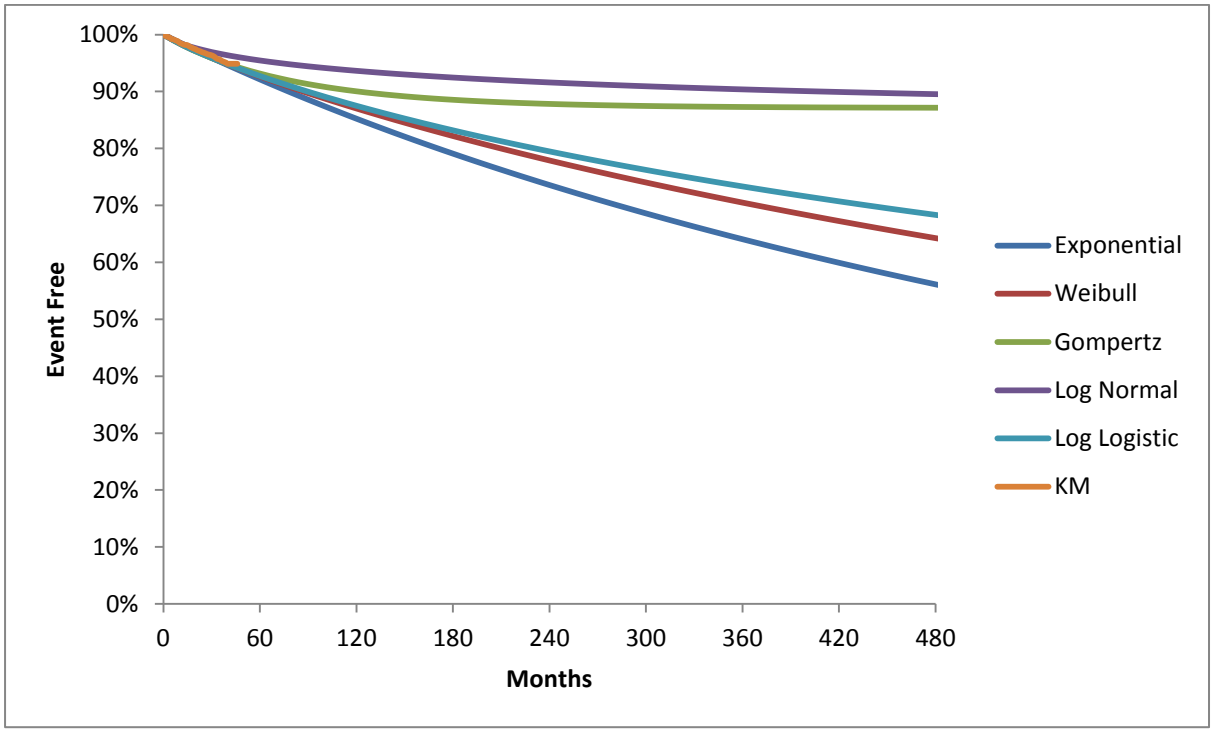


Figure 36: Ticagrelor 60 mg BID + low-dose ASA KM versus parametric functions, non-fatal MI



Risk equations for first events – non-fatal stroke

Analogous to the non-fatal MI outcome Bonaca et al(6) reported results for the time to non-fatal stroke. As with the economic analysis for non-fatal MI, it is important to distinguish between events that precede death and those from which a patient survives. Hence, the analyses that have been completed for the economic model differ from those in the clinical paper by adjusting for baseline risk, censoring for competing events, and applying the 30-day fatal CV event reallocation rule. While the results presented in Table 61 are not directly comparable to those in Table 55, there is an accord with respect to the magnitude and bounds of the 95% CI to the results from models with and without adjustments for baseline risks.

Table 61: Cox proportional hazard ratios, time to first event: non-fatal stroke

Scenario	Endpoint	HR (95% CI)
Bonaca et al (6)	Time to first stroke	0.75 (0.57–0.98)
Economic model (Tx only)	Time to first non-fatal stroke	0.77 (0.57–1.05)
Economic model (adjusted)	Time to first not-fatal stroke	0.79 (0.58–1.07)

Tx=Treatment. Covariates used in the adjusted economic model are detailed in appendix 16.

There was no evidence to support an interaction effect between the label population and the treatment effect for time to first non-fatal stroke. Furthermore, there was no evidence to suggest that adjusting for the label population was significant at $p<0.05$ (Appendix 16, Table 38). As such, the risk equation for non-fatal stroke for the label population is the same as for the full PEGASUS-TIMI 54 population. Outcomes from the statistical tests using Schoenfeld residuals (Appendix 16, Table 39) indicate that the proportional hazards assumption holds at the 5% level for the variables included in the risk functions.

Table 62 presents the coefficients and p-values for the survival function that provides the best fit to the observed events (log–logistic).

Table 62: Time to first event: non-fatal stroke

	Log–logistic	
Variable	**Coef.**	**p-value**
Tic90	0.1647	0.3338
Tic60	0.2674	0.1284
sex	-0.3845	0.0278
age	-0.0355	0.0004
dmtype	-0.3982	0.0069
smk_his2	-0.3579	0.0588
sbpsup	-0.0114	0.0151
hypchol	-0.4511	0.0330
stroke	-1.0763	0.0507
tria	-1.0498	0.0156
chf	-0.5899	0.0002
SthAmerica	-0.3865	0.0514
tADP_12mplus	0.3879	0.0361
histPAD	-0.6216	0.0084
creatinine_cl	0.5293	0.0033
_cons	16.20	<0.0001
shape	0.1054	0.0666

shape variables take the following form: Log Logistic – ln(gamma)

Appendix 16, Table 40 presents the coefficients and p-values for all the survival functions estimated for non-fatal stroke using each of the five functional forms incorporated into the cost-effectiveness model. Metrics (AIC and BIC outcomes) and Cox–Snell residual plots for each of the five functional forms are detailed in Appendix 16, Table 41 and in Figure 3.

To aid with the comparison of the parametric functions, an average survival curve was estimated across the label population only (n=10,779) for each functional form (extrapolated), and plotted against the Kaplan–Meier curve for low-dose ASA alone and ticagrelor 60 mg BID + low-dose ASA (Figure 37 and Figure 38, respectively).

Figure 37: Low-dose ASA alone KM versus parametric functions, non-fatal stroke

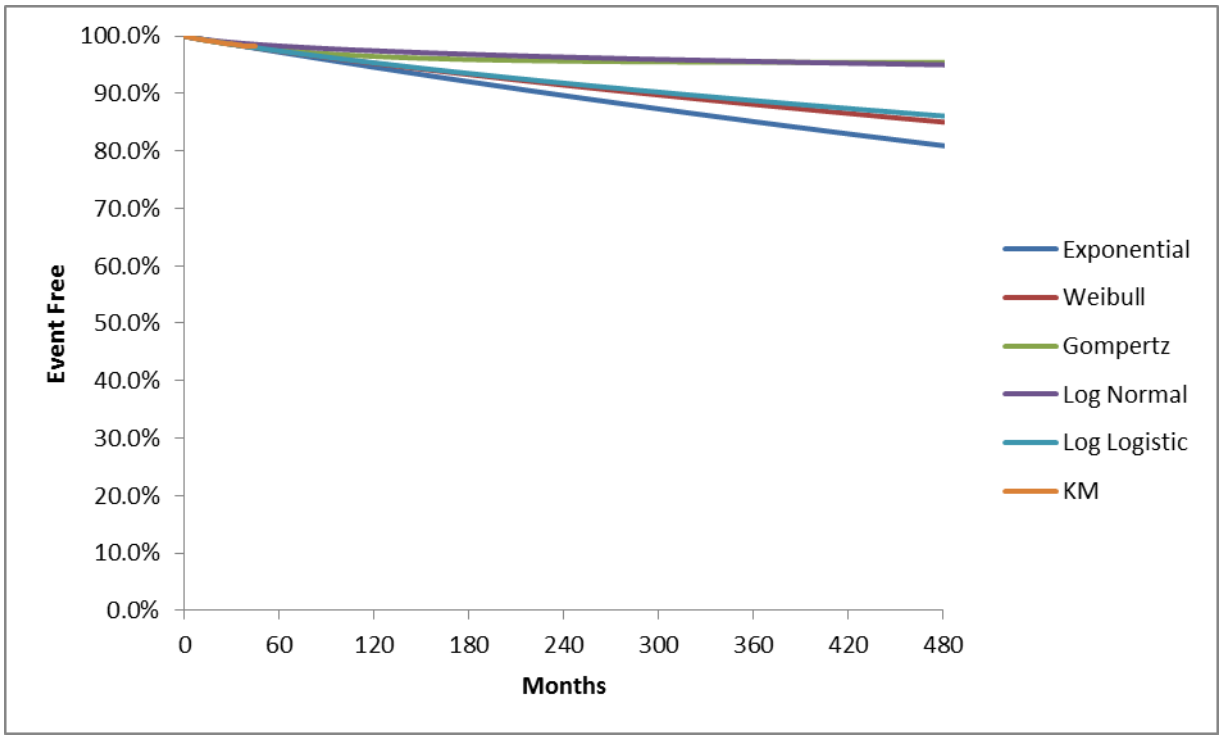
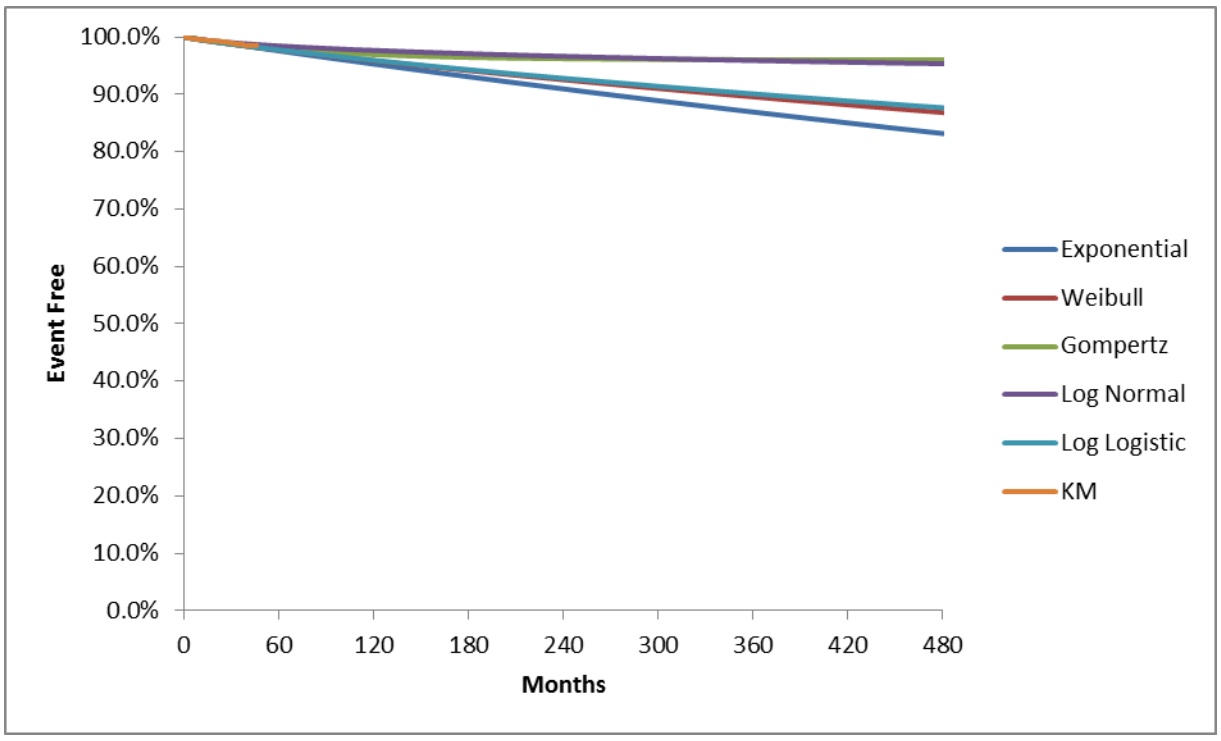


Figure 38: Ticagrelor 60 mg BID + low-dose ASA KM versus parametric functions, non-fatal stroke



Risk equations for first events – fatal CV

Bonaca et al (6) completed a number of predetermined analyses to assess whether any treatment effect modifiers were associated with patient characteristics. Data presented in the supplementary material shows [redacted].

For the 'original' regression analyses relating to the full PEGASUS-TIM 54 population, [redacted].

Table 63 outlines the hazard ratios from a Cox proportional hazard model, in which a time to first fatal CV event within a competing risk structure is applied, before incorporating the interaction term and adjusting for baseline risk. Hazard ratios for the 60 mg arm are slightly higher than those reported in Bonaca et al which is due to both the reallocation of fatal CV events and the competing risk approach used.

Table 63: Cox proportional hazard ratios, time to first event: fatal CV

Scenario	HR (95% CI)
Bonaca et al (6)	0.83 (0.68–1.01)
Economic model (Tx only)	0.88 (0.71–1.10)

Tx=Treatment. Covariates used in the adjusted economic model are detailed in Appendix 16.

[redacted], when considering the interaction between the treatment and label population.

Table 64 outlines the HRs from a Cox proportional hazard model, where a time to first fatal CV event within a competing risk structure is applied, adjusted for baseline risk, reallocated using the 30-day fatal CV rule and with an interaction term between the label population and the treatment effect incorporated into the analysis.

Table 64: Cox proportional hazard ratios, time to first event: fatal CV stratified by population

Scenario	HR (95% CI)	p-value
Label population	0.783 (0.608–1.009)	0.059
Non-label population	1.394 (0.910–2.135)	0.126

When incorporating the interaction term for the label population (Appendix 16, Table 42), the HR was 0.783 (95% CI 0.61–1.01, p=0.059) after adjusting for all other covariates. Outcomes from the statistical tests using Schoenfeld residuals (Appendix 16, Table 43) indicate that the proportional hazards assumption holds at the 5% level for the variables included in the risk functions.

Table 65 presents the coeffiecents and p-values for the survival function that provides the best fit to the observed events (log–logistic).

Table 65: Time to first event: fatal CV

	Log–logistic	
Variable	**Coef.**	**p-value**
offlabel	0.3194	0.0417
Tic60	0.2032	0.0629
Tic90	0.2092	0.0548
t60offlabel	-0.0255	<0.0001
t90offlabel	-0.4135	<0.0001
sex	-0.4003	<0.0001
age	-0.2248	0.0088
weight	-0.2262	0.0311
bmi	-0.6528	<0.0001
dmtype	0.4503	<0.0001
MI_HIST	-0.3830	0.0020
cadmult	-0.3269	0.0072
smk_his2	-0.6490	<0.0001
stentany1	-0.4157	0.0001
MEDTDDOS_n	-0.4924	0.0231
hyp	-0.3977	0.0683
chf	0.0115	0.0938
SthAmerica	-0.0447	0.0373
histPAD	0.8067	<0.0001
creatinine_cl	-0.0044	0.0218
_cons	12.6182	<0.0001
shape	-0.2010	<0.0001

Shape variables take the following form: Log–Logistic – ln(gamma);

Appendix 16, Table 44 presents the coefficients and p-values for the survival functions estimated for fatal CV using each of the five functional forms incorporated into the cost-effectiveness mode. Metrics (AIC and BIC outcomes) and Cox–Snell residual plots for each of the five functional forms are detailed in Appendix 16, Table 45 and in Figure 4.

To aid with the comparison of the parametric functions, an average survival curve was estimated across the label population only (n=10,779) for each functional form (extrapolated), and plotted against the Kaplan–Meier curve for low-dose ASA alone and ticagrelor 60 mg BID + low-dose ASA (Figure 39 and Figure 40,respectively).

Figure 39: Low-dose ASA alone KM versus parametric functions, fatal CV

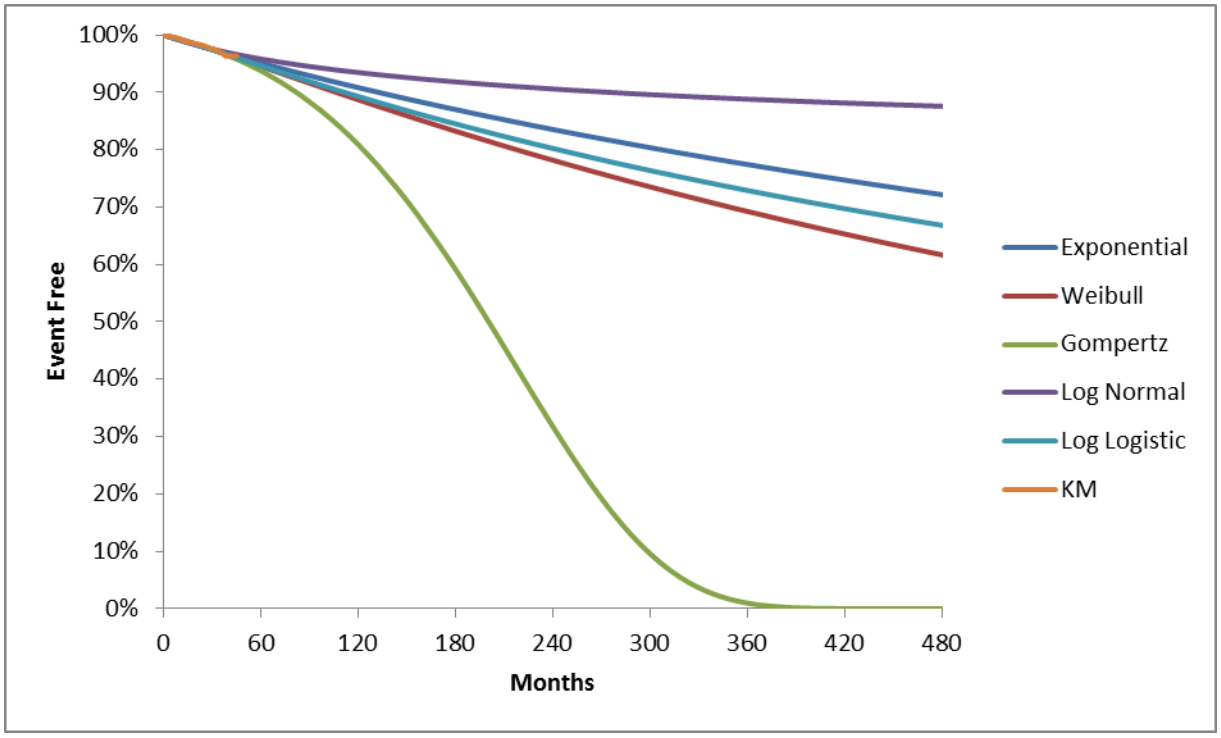
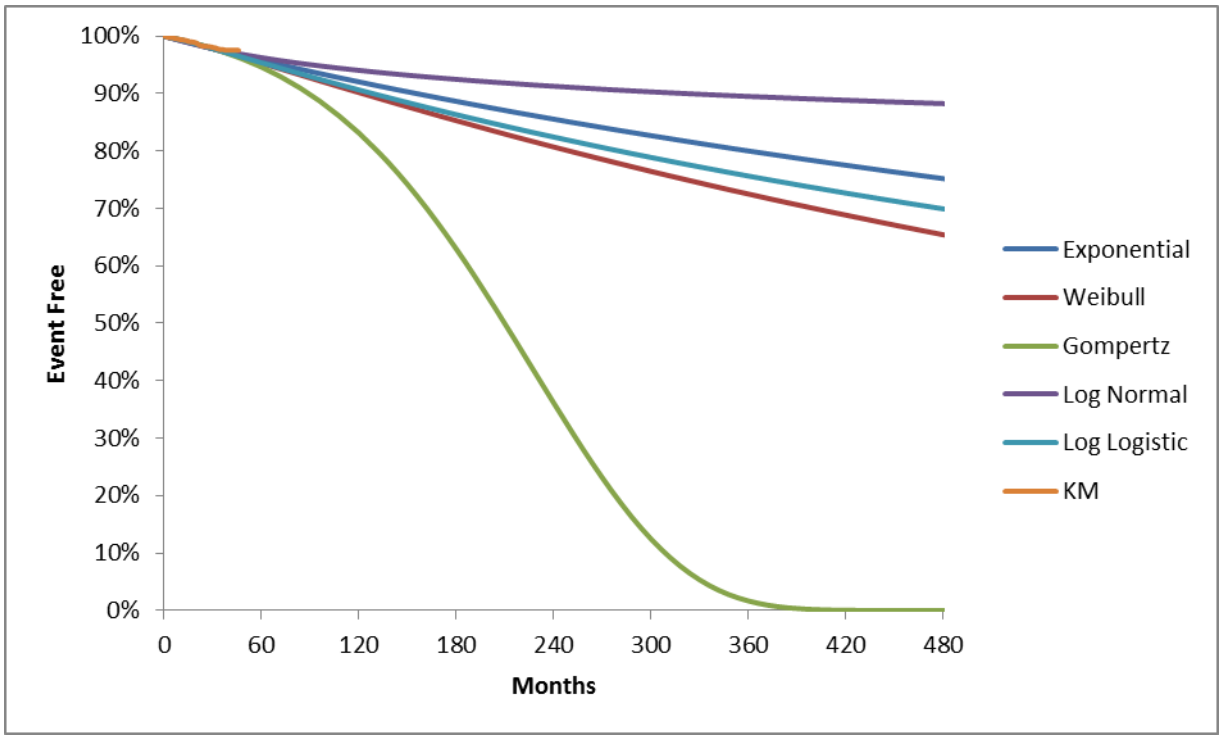


Figure 40: Ticagrelor 60 mg BID + low-dose ASA KM versus parametric functions, fatal CV



Risk equations for first events – fatal other

Treating patients with ticagrelor 60 mg BID + low-dose is not expected to influence the probability of death from causes other than a fatal CV event. Bonaca et al (6) confirms this to be the case, reporting time to death from any cause (CV and non-CV death) with a HR of 0.89 (95% CI: 0.76–1.04).

Table 66: Cox proportional hazard ratios, time to first event: fatal other

Scenario	Endpoint	HR (95% CI)
Bonaca et al (6)	Time to all cause death	0.89 (0.76–1.04)
Economic model (Tx only)	Time to non-CV death	0.97 (0.73–1.29)
Economic model (adjusted)	Time to non-CV death	n/a

Bonaca et al. (2015) analysed these outcomes as time to event, not time to first event. Furthermore, the authors analysed this outcome as a composite of all deaths, instead of a non-CV death, as applied in the economic model.

There was no evidence to support an interaction effect between the label population and the treatment effect for time to first fatal other events. Furthermore, there was no evidence to suggest that adjusting for the label population was significant at p≤0.05

(Appendix 16, Table 46). As such, the risk equation for fatal other for the label population is the same as for the full PEGASUS-TIMI 54 population.

Outcomes from the statistical tests using Schoenfeld residuals (Appendix 16, Table 47) indicate that the proportional hazards assumption holds for all variables with the exception of 'creatinine_cl' which requires further investigation. The log–log plot, and Kaplan–Meier and predicted survival plots are displayed in Appendix 16, Figure 5. As the proportional hazard assumption holds, the 'creatinine_cl ' variable has been retained.

Table 67 presents the coefficients and p-values for the survival function that provides the best fit to the observed events (log–logistic).

Table 67: Time to first event: fatal other

	Log–logistic	
Variable	**Coef.**	**p-value**
Tic90	-0.2276	0.0054
age	-0.0468	<0.0001
weight	-0.0136	0.0107
bmi	0.0462	0.0148
dmtype	-0.3006	0.0006
smk_his1	-0.2456	0.0114
smk_his2	-0.6724	<0.0001
anpect	0.1800	0.0612
chf	-0.1838	0.0773
NthAmerica	0.2294	0.0484
histPAD	-0.3635	0.0094
creatinine_cl	0.3555	0.0019
_cons	12.9254	<0.0001
shape	-0.3480	<0.0001

Shape variables take the following form: Log Logistic – ln(gamma)

Appendix 16, Table 48 presents the coefficients and p-values for the survival functions estimated for other fatal events using each of the five functional forms incorporated into the cost-effectiveness model. A treatment effect variable for patients treated with ticagrelor 90 mg BID + low-dose ASA has been incorporated into the models to replicate the observations from PEGASUS-TIMI 54. Metrics (AIC and BIC outcomes) and Cox–Snell residual plots for each of the five functional forms are detailed in Appendix 16, Table 49 and in Figure 6.

To aid with the comparison of the parametric functions, an average survival curve was estimated across the label population only (n=10,779) for each functional form (extrapolated), and plotted against the Kaplan–Meier curve for low-dose ASA alone and ticagrelor 60 mg BID + low-dose ASA (Figure 41 and Figure 42, respectively).

Figure 41: Low-dose ASA alone KM versus parametric functions, fatal other

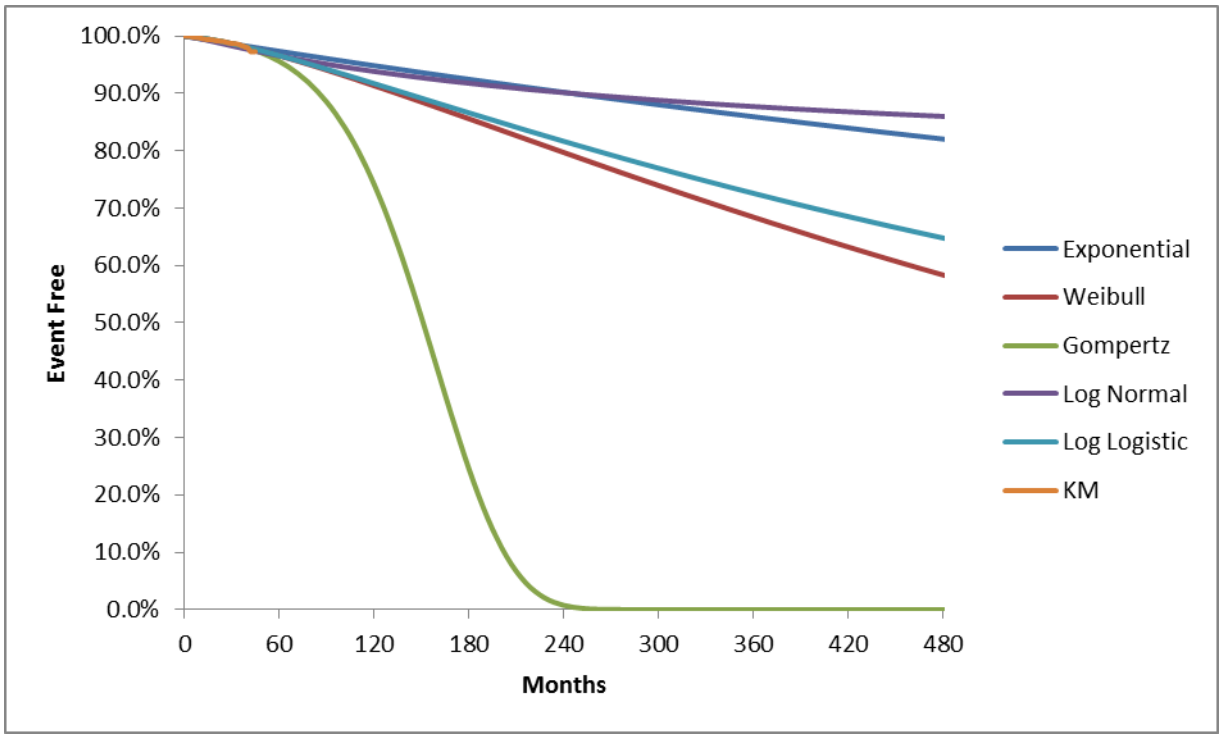
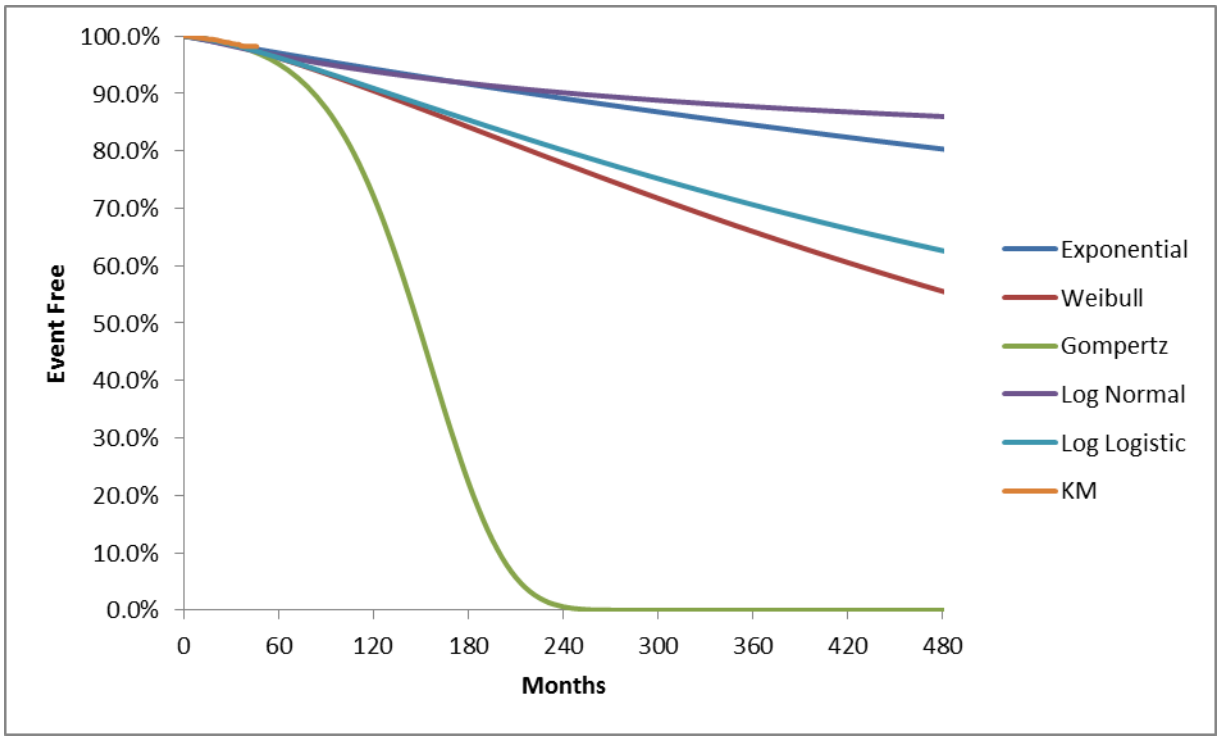


Figure 42: Ticagrelor 60 mg BID + low-dose ASA KM versus parametric functions, fatal other



Risk equations for subsequent events

Patients who experience a non-fatal event move from a stable post-MI or post-stroke state into an acute state where the risk of a subsequent event is elevated for 12 months. From 12 months post the first non-fatal event, patients enter a stable phase. These events are reflected in the economic model through the application of five tunnel states. The first four tunnel states (each of 3 months duration), represent the patient's acute phase where the risk of a subsequent event is elevated, while the fifth tunnel state is used to represent the long-term stable phase. In the fifth state patients still face the risk of events, but at lower probability than that associated with the first four tunnel states.

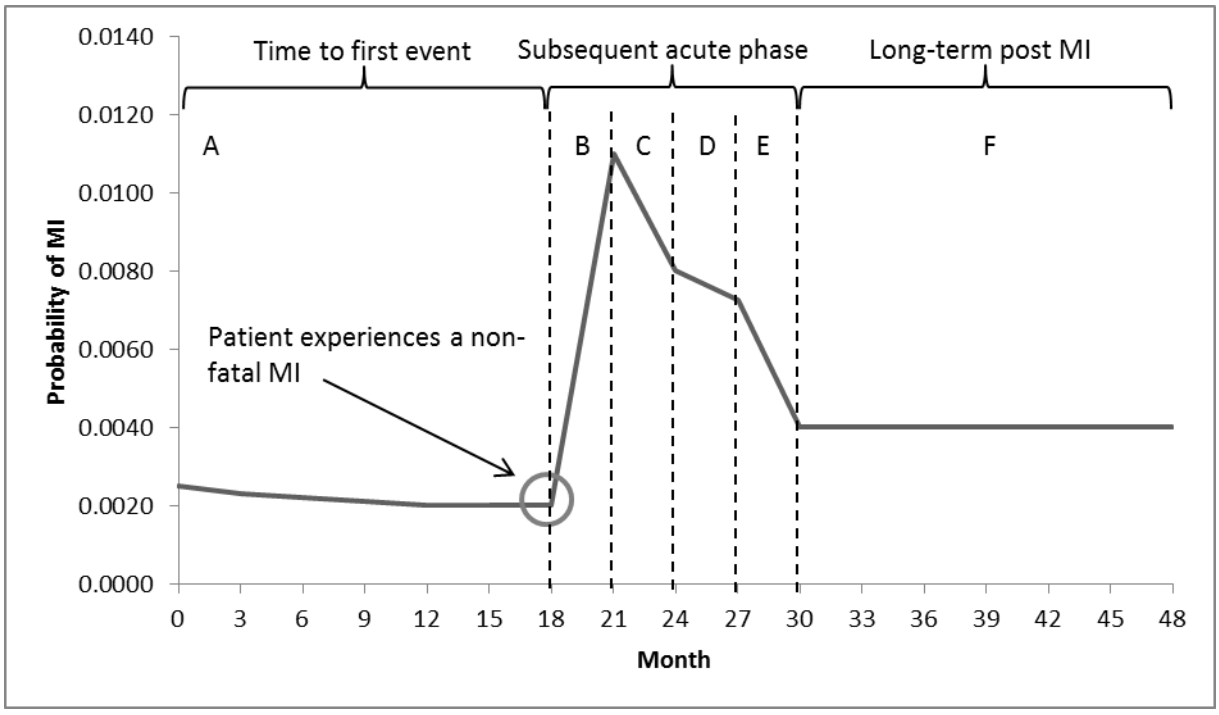
While some patients in PEGASUS-TIMI 54 experienced multiple subsequent events during their acute phase, it becomes problematic and computationally expensive to model these patients into another set of tunnel states. Thus the model implicitly imposes a simplifying assumption for this. To best address this issue, and to ensure that the economic model predicts observed events as closely as possible, survival analyses for subsequent events were estimated allowing for multiple events per patient. This approach removes patients from the 'at-risk' population (for a first

event) at their last observation, which allows for more than one event to be estimated per individual. Patients then move to a new ‘at-risk’ population (for a subsequent event) where the time origin was set to be equal to the time of the first non-fatal event for the patient. For each of the primary events from PEGASUS-TIMI 54, five survival functional forms are estimated. Within the model, these risk equations are only applied for the first 12 months post the patients’ first event.

For the fifth tunnel state (over 12 months post the patients’ first event), an exponential survival function has been applied, where the time origin was set to be 365 days post first non-fatal event (contingent on survival to that date). The exponential survival function assumes a constant hazard, and allows for a pragmatic estimation of long-term events, for those patients experiencing a non-fatal event.

An example for the probability of a non-fatal MI event (by 3-month cycles) is presented in Figure 43. This example illustrates a scenario where a patient experiences a non-fatal MI at month 18 and enters into an acute phase for 12 months, followed by a longer-term post-MI stable phase.

Figure 43: Probability of a non-fatal MI (example profile)



Note: Risks based on the patient profile that most closely represents the overall expected ICER for the full PEGASUS-TIMI 54 population. A = ‘no event’ health state’; B = post first non-fatal MI (0 – 3 months); C = post first non-fatal MI (3 – 6 months); D = post first non-fatal MI (6 – 9 months); E = post first non-fatal MI (9 – 12 months); F = post first non-fatal MI (12+ months)

The PEGASUS-TIMI 54 study protocol indicated that at the time of a patient's first non-fatal event the local investigator could make a decision in accordance with local medical guidelines and standard of care to change treatment. This could be performed in a blinded fashion where patients on placebo + ASA were switched to clopidgrel + ASA and ticagrelor 60 mg BID + low-dose ASA could be switched to ticagrelor 90 mg BID + low-dose ASA. However the investigator could also chose to treat a patient with open-label clopidogrel or another ADP receptor blocker. Of those patients who were randomised to receive ticagrelor and subsequently experienced a non-fatal event, relatively few continued with ticagrelor 90 mg BID + low-dose ASA, while the remainder received an alternative treatment. For those patients who experienced a non-fatal stroke, treatment with ticagrelor was ceased, and best medical practice was administered.

Additional treatment effects were modelled for patients randomised to each of the ticagrelor arms in PEGASUS-TIMI 54, with the exception of patients whose first non-fatal event was a stroke. This allows the economic model to reflect the observed events following the first-event. The economic model incorporates a switch to include or exclude these subsequent treatment effects for the modelling purposes; the base case is to exclude these.

Risk equations for subsequent non-fatal MI events

Preliminary analyses showed that patients whose first event was a non-fatal MI were more likely to experience a subsequent non-fatal MI compared to a non-fatal stroke, and vice versa. Time from first to subsequent events were not analysed by Bonaca et al (6). A treatment effect was incorporated into the analysis to allow the overall modelled non-fatal MI events estimated over the trial period to match as closely as possible to the overall MI events reported in Bonaca et al. (6) This is not used in the base case but is assessed in a scenario analysis. Again neither of the treatment effect variables is statistically significant at a 5% or 10% level, however this isn't unexpected since the PEGASUS-TIMI 54 trial was not powered or designed to be able to estimate a treatment effect for patients entering an acute post non-fatal event phase.

Outcomes from the statistical tests using Schoenfeld residuals (Appendix 16, Table 50) indicate that the proportional hazards assumption holds at the 5% level for the variables included in the risk functions.

Table 68 presents the coefficients and p-values for the survival function that provides the best fit to the observed events (log-logistic).

Table 68: Time to subsequent event (acute phase) – non fatal MI

	Log–logistic	
Variable	**Coef.**	**p-value**
pMI_Tic90	-0.1234	0.7315
pMI_Tic60	-0.3394	0.3425
weight	0.0350	0.0206
bmi	-0.1395	0.0058
smk_his1	-0.5257	0.0814
anpect	0.4770	0.1290
qevtyp2	-0.7776	0.0197
sbpsup	-0.0250	0.0114
dbpsup	0.0473	0.0035
cabg	-0.6892	0.0356
NthAmerica	-0.8491	0.0084
histPAD	-0.7820	0.0442
_cons	10.3937	<0.0001
shape	0.1828	0.0290

Shape variables take the following form: Logistic – ln(gamma). The 'pMI_Tic60' variable was coded 1 for patients whose first event was a non-fatal MI, and was randomised to the ticagrelor 60 mg BID + low-dose ASA treatment arm, otherwise this variable was coded 0.

Appendix 16, Table 51 outlines the coefficients derived from the parametric survival models. The treatment effect variable is not statistically significant at a 5% or 10% level, however this is not unexpected since the PEGASUS-TIMI 54 trial was not powered or designed to be capable of estimating a treatment effect for patients entering an acute post non-fatal event phase. Metrics and a graphical representation for the fit of the parametric models to the observed events are presented in Appendix 16, Table 52 and in Figure 7.

An exponential survival function has been used to model the probability of longer-term stable non-fatal MI. These models estimate the hazard rate starting from 12 months post the first event until the last observation date. Coefficients that inform this model are outlined in Table 69.

Table 69: Time to subsequent event (long term stable phase) – non fatal MI

	Exponential			
Variable	**Coef.**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
pMI_Tic90	0.5930	0.1870	-0.2871	1.4730
pMI_Tic60	0.0838	0.8730	-0.9460	1.1136
dmtype	0.8120	0.0360	0.0541	1.5699
MEDTDDOS_n	-0.0379	0.0600	-0.0773	0.0015
cabg	1.0828	0.0120	0.2405	1.9252
NthAmerica	0.7444	0.0560	-0.0179	1.5066
_cons	-6.3340	<0.0001	-9.6720	-2.9960

Risk equations for subsequent non-fatal stroke events

Treatment effects were not incorporated into the time to subsequent non-fatal stroke risk equations, instead a variable to capture the greater likelihood of a subsequent non-fatal stroke occurring if the first event was also a non-fatal stroke, has been incorporated.

Outcomes from the statistical tests using Schoenfeld residuals (Appendix 16, Table 53) indicate that the proportional hazards assumption holds at the 5% level for the variables included in the risk functions.

Table 70 presents the coeffiecents and p-values for the survival function that provides the best fit to the observed events (Weibull).

Table 70: Time to subsequent event (acute phase) – non-fatal stroke

	Weibull	
Variable	**Coef.**	**p-value**
prevEvent	1.6432	0.0003
age	-0.0372	0.1264
smk_his1	1.5596	0.0568
smk_his2	1.2319	0.1775
cohdhist	0.6390	0.1272
tria	1.2766	0.0138
SthAmerica	0.7490	0.2326
histPAD	0.9746	0.0193
_cons	-7.8999	0.0006
shape*	-0.3010	0.0555

Shape variables take the following form: Weibull – ln(p). The 'prevEvent' was coded 1 if the first event was a non-fatal stroke otherwise this was coded as 0.

Appendix 16, Table 54 outlines the coefficients derived from the parametric survival models. Metrics and a graphical representation for the fit of the parametric models to the observed events are presented in Appendix 16, Table 55 and in Figure 8.

An exponential survival function has been used to model the probability of longer-term stable non-fatal stroke. These models estimate the hazard rate starting from 12 months post the first event until the last observation date. Coefficients that inform this model are outlined in Table 71.

Table 71: Time to subsequent event (long term stable phase) – non-fatal stroke

	Exponential			
Variable	**Coef.**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
prevEvent	2.4285	0.0020	0.8712	3.9858
smk_his2	1.4197	0.0600	-0.0585	2.8979
cabg	2.0910	0.0050	0.6313	3.5507
tria	1.6552	0.0060	0.4693	2.8410
_cons	-12.0598	<0.0001	-13.4536	-10.6661

The 'prevEvent' was coded 1 if the first event was a non-fatal stroke otherwise this was coded as 0.

Risk equations for subsequent fatal CV events

The risk of a subsequent fatal CV event was not influenced by whether the first event was either a non-fatal MI or non-fatal stroke. However a treatment effect was incorporated into the analysis to allow the overall modelled fatal CV events estimated over the trial period to match as closely as possible to the overall CV deaths reported in Bonaca et al. (6) This is not used in the base case but is assessed in a scenario analysis. Again neither of the treatment effect variables is statistically significant at a 5% or 10% level, however this isn't unexpected since the PEGASUS-TIMI 54 trial was not powered or designed to be able to estimate a treatment effect for patients entering an acute post non-fatal event phase.

Outcomes from the statistical tests using Schoenfeld residuals (Appendix 16, Table 56) indicate that the proportional hazards assumption holds at the 5% level for the variables included in the risk functions.

Table 72 presents the coeffiecents and p-values for the survival function that provides the best fit to the observed events (log normal).

Table 72: Time to subsequent event (acute phase) – fatal CV

	Log–normal	
Variable	**Coef.**	**p-value**
pMI_Tic90	0.2025	0.5620
pMI_Tic60	0.3329	0.3700
age	-0.0843	<0.0001
dmtype	-1.5140	<0.0001
MI_HIST	-0.6498	0.0454
smk_his2	-0.6152	0.0960
stentany1	0.7044	0.0393
qevtyp2	0.7976	0.0134
tria	-1.4353	0.0229

chf	-1.1951	0.0001
_cons	15.3756	<0.0001
shape	0.6877	<0.0001

Shape variables take the following form: Log Normal – ln(sigma). The 'pMI_Tic60' variables were coded as 1 for patients whose first event was a non-fatal MI, and was randomised to the ticagrelor 60 mg BID + low-dose ASA treatment arm otherwise these variables were coded as 0.

Appendix 16, Table 57 outlines the coefficients derived from the parametric survival models. Metrics and a graphical representation for the fit of the parametric models to the observed events are presented in Appendix 16, Table 58 and in Figure 9.

An exponential survival function has been used to model the probability of longer-term fatal CV events. These models estimate the hazard rate starting from 12 months post the first event until the last observation date. Coefficients that inform this model are outlined in Table 73.

Table 73: Time to subsequent event (long term stable phase) – fatal CV

	Exponential			
Variable	**Coef.**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
pMI_Tic90	-0.2784	0.5030	-1.2642	0.7075
pMI_Tic60	-1.4561	0.8210	-3.0651	0.1530
age	0.0656	0.0297	0.0074	0.1239
dmtype	1.1836	0.5076	0.1887	2.1785
qevtyp2	-1.3193	0.5717	-2.4399	-0.1988
MEDTDDOS_n	0.0080	0.0034	0.0013	0.0146
tria	2.0922	0.8596	0.4074	3.7769
chf	1.1984	0.4941	0.2300	2.1668
_cons	-14.4348	2.2028	-18.7522	-10.1175

Risk equations for subsequent other fatal events

Time to subsequent 'other fatal' events have also been evaluated using the same approach. As with subsequent 'fatal CV' events, the likelihood of a subsequent 'other fatal' event occurring was not impacted by the type of non-fatal first event that occurred.

Outcomes from the statistical tests using Schoenfeld residuals (Appendix 16, Table 59) indicate that the proportional hazards assumption holds at the 5% level for the variables included in the risk functions.

Table 74 presents the coeffiecents and p-values for the survival function that provides the best fit to the observed events (Weibull).

Table 74: Time to subsequent event (acute phase) – fatal other

	Weibull	
Variable	**Coef.**	**p-value**
pMI_Tic90	-0.4136	0.3002
smk_his1	1.2643	0.0347
smk_his2	1.8924	0.0053
sbpsup	0.0450	<0.0001
dbpsup	-0.0634	0.0011
chf	0.8622	0.0099
NthAmerica	1.0939	0.0018
creatinine~l	-0.7205	0.0305
_cons	-9.0586	<0.0001
shape	-0.5875	0.0001

Shape variables take the following form: Weibull – ln(p)

Appendix 16, Table 60 outlines the coefficients derived from the parametric survival models. Metrics and a graphical representation for the fit of the parametric models to the observed events are presented in Appendix 16, Table 61 and in Figure 10.

An exponential survival function has been used to model the probability of longer-term other fatal events. These models estimate the hazard rate starting from 12 months post the first event until the last observation date. Coefficients that inform this model are outlined in Table 75.

Table 75: Time to subsequent event (long term stable phase) – fatal other

	Exponential			
Variable	**Coef.**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
pMI_Tic90	-17.3358	<0.0001	-18.6198	-16.0519
hyp	-2.5369	0.0230	-4.7281	-0.3457
NthAmerica	2.9332	0.0080	0.7712	5.0951
_cons	-8.8021	<0.0001	-9.9905	-7.6136

Risk equations for TIMI bleed events

All antiplatelet treatments are associated with a higher risk of bleeding events, in the PEGASUS-TIMI 54 study the HR associated with ticagrelor 60 mg BID + low-dose ASA for major TIMI bleeds was 2.32 and that for minor TIMI bleeds was 3.31 (Table 55). These HRs were estimated by Bonaca et al (6) using the safety dataset. For the

economic analysis the same ITT population from the efficacy dataset has been used to estimate risk functions, therefore the HRs used in the economic model will vary slightly from those reported in the clinical paper. However, given that there is only a slight difference between the HRs it was not necessary to use the safety dataset in the creation of these risk equations.The risk of a TIMI bleed event was estimated conditional on the patient remaining on treatment. Therefore, instead of using the last date of follow-up for each patient, the last known date that the patient was on the study drug was applied which was earlier than or the same as the last date of patient follow-up. Exponential hazard functions have been used to estimate the rate of TIMI bleeds as clinically the hazard of bleeds whilst on treatment is likely to be constant (Figure 23).

Risk equations for major TIMI bleeds

Hazard ratios conditional on the patient remaining on treatment (using a Cox proportional hazards model) are summarised in Table 76. Hazard ratios reported by Bonaca et al (6) based on the safety dataset accorded with those based on the efficacy dataset, with and without adjustments for baseline risks.

Table 76: Cox proportional hazard ratios: major TIMI bleeds

Scenario	Dataset used	HR (95% CI)
Bonaca et al	Safety (OT)	2.32 (1.68–3.21)
Economic model (Tx only)	Efficacy (ITT)	2.48 (1.72–3.56)
Economic model (adjusted)	Efficacy (ITT)	2.52 (1.75–3.63)

ITT=Intention-to-treat. OT=On treatment. Tx=Treatment

Coefficients used in the exponential hazard function used to estimate the rate of TIMI major bleeds are outlined in Table 77.

Table 77: Exponential hazard function: major TIMI bleeds

Variable	Coef.	p-value	Lower 95% CI	Upper 95% CI
Tic90	1.0235	<0.0001	0.6576	1.3894
Tic60	0.9355	<0.0001	0.5652	1.3058
sex	0.3507	0.0390	0.0185	0.6830
age	0.0388	<0.0001	0.0217	0.0559
smk_his2	0.4915	0.0030	0.1670	0.8160
sbpsup	0.0138	0.0010	0.0054	0.0222

hypchol	0.3608	0.0430	0.0107	0.7108
spbleed	0.6695	0.1090	-0.1499	1.4890
AsiaAustralia	0.6913	<0.0001	0.3045	1.0782
NthAmerica	0.4590	0.0070	0.1276	0.7904
tClop_7dplus	0.2150	0.1330	-0.0653	0.4954
_cons	-17.2297	<0.0001	-18.8965	-15.5629

Risk equations for minor TIMI bleeds

Hazard ratios for minor TIMI bleeds based on the safety dataset and the efficacy dataset are outlined in Table 78. When adjusting for baseline risks, the HRs from the efficacy dataset accorded more closely with those from the safety dataset.

Table 78: Cox proportional hazard ratios: minor TIMI bleeds

Scenario	Dataset used	HR (95% CI)
Bonaca et al (6)	Safety (OT)	3.31 (1.94–5.63)
Economic model (Tx only)	Efficacy (ITT)	3.03 (1.71–5.36)
Economic model (adjusted)	Efficacy (ITT)	3.17 (1.79–5.62)

ITT=Intention-to-treat. OT=On treatment. Tx=Treatment

Coefficients used in the exponential hazard function used to estimate the rate of TIMI minor bleeds are outlined in Table 79.

Table 79: Exponential hazard function: minor TIMI bleeds

Variable	Coef.	p-value	Lower 95% CI	Upper 95% CI
Tic90	3.8052	1.3364	<0.0001	0.7684
Tic60	3.1932	1.1610	<0.0001	0.5878
age	1.0534	0.0520	<0.0001	0.0273
weight	1.0110	0.0110	0.0750	-0.0011
cadmult	1.6000	0.4700	0.0180	0.0802
qev2rnd	1.0007	0.0007	0.1080	-0.0002
hypchol	2.2316	0.8027	0.0080	0.2059
spbleed	3.3795	1.2177	0.0080	0.3184
creatinine_cl	0.5588	-0.5819	0.0150	-1.0511
_cons	0.0000	-17.2793	<0.0001	-19.6709

Risk equations for dyspnoea (grade 1–2 and 3–4)

In the same manner as TIMI bleeds, an increased risk of dyspnoea is assumed to occur only while the patient remains on active treatment. Patients are removed from the ‘at-risk’ category only when they are known to have permanently stopped active

treatment, or when their last observation date is met. Again, exponential hazard functions have been used to estimate the rate of events as clincially the hazard of dyspnoea whilst on treatment is likely to be constant.

Risk equations for dyspnoea (grade 3–4)

The risk of a serious dyspnoea event while on treatment is estimated to be greater using data from the efficacy dataset compared to the safety dataset (Table 80). As such, the model will overestimate the difference in dysponea events between the treatment arms compared to that observed within the trial, which represents a conservative approach for ticagrelor 60mg BID.

Table 80: Cox proportional hazard ratios: dyspnoea (grade 3–4)

Scenario	Dataset used	HR (95% CI)
Bonaca et al (6)	Safety (OT)	2.70 (1.25–5.84)
Economic model (Tx only)	Efficacy (ITT)	3.79 (1.41–10.20)
Economic model (adjusted)	Efficacy (ITT)	3.90 (1.44–10.51)

ITT=Intention-to-treat. OT=On treatment. Tx=Treatment

Coefficients used in the exponential hazard function used to estimate the rate of dyspnoea (grade 3–4) are outlined in Table 81.

Table 81: Exponential hazard function: dyspnoea (grade 3–4)

Variable	Coef.	p-value	Lower 95% CI	Upper 95% CI
Tic90	3.9557	1.3752	0.0070	0.3829
Tic60	3.9518	1.3742	0.0060	0.3852
age	1.0652	0.0632	0.0030	0.0220
bmi	1.0654	0.0634	0.0140	0.0129
dmtype	2.3686	0.8623	0.0120	0.1899
smk_his1	2.1207	0.7518	0.0250	0.0963
anpect	1.7706	0.5713	0.0720	-0.0507
stroke	20.4112	3.0161	0.0050	0.9174
_cons	0.0000	-21.0550	<0.0001	-24.4954

Risk equations for dyspnoea (grade 1–2)

Bonaca et al (6) did not report a HR for grade 1–2 dyspnoea, instead a HR for the overall rate of dyspnoea was reported (which is not relevant to report in Table 82).

Table 82: Cox proportional hazard ratios: dyspnoea (grade 1–2)

Scenario	Dataset used	HR (95% CI)

Economic model (Tx only)	Efficacy (ITT)	1.68 (1.49–1.89)
Economic model (adjusted)	Efficacy (ITT)	1.87 (1.60–2.19)

ITT=Intention-to-treat. Tx=Treatment

Coefficients used in the exponential hazard function used to estimate the rate of dyspnoea (grade 1–2) are outlined in Table 83.

Table 83: Exponential hazard function: dyspnoea (grade 1–2)

Variable	Coef.	p-value	Lower 95% CI	Upper 95% CI
Tic90	2.2552	0.8133	<0.0001	0.6673
Tic60	1.8516	0.6160	<0.0001	0.4661
age	1.0124	0.0123	<0.0001	0.0057
bmi	1.0211	0.0209	<0.0001	0.0099
dmtype	0.9042	-0.1007	0.1090	-0.2241
smk_his1	1.1244	0.1172	0.0370	0.0071
stentany1	1.4263	0.3551	<0.0001	0.1730
qev2rnd	1.0001	0.0001	0.7100	-0.0002
MEDTDDOS_n	0.9965	-0.0035	0.2200	-0.0092
dbpsup	0.9937	-0.0063	0.0330	-0.0120
cohdhist	1.2001	0.1824	0.0030	0.0641
Asia_Australia	1.3737	0.3175	0.0010	0.1215
NthAmerica	1.8136	0.5953	<0.0001	0.4520
SthAmerica	1.0301	0.0297	0.7760	-0.1742
tADP_30d12m	1.6997	0.5305	<0.0001	0.3322
tADP_12mplus	1.5525	0.4399	<0.0001	0.2132
tClop_7dplus	0.7420	-0.2984	0.0030	-0.4952
_cons	0.0000	-11.2638	<0.0001	-12.2245

Hospitalisation rates

Hospital admissions, for any reason, were recorded for all patients participating in PEGASUS-TIMI 54. Numbers of admissions such as these are count (Poisson) data, and can be represented as rates per unit of patient exposure. The exposure time in PEGASUS-TIMI 54 spans from randomisation until death or until the last observation date (end of follow-up). Regressions were performed to predict the rate of the total 6,048 cardiovascular-related hospitalisations. Analyses have been completed with covariates controlling for baseline risk of hospitalisation, randomisation to treatment arm, and the following health states and events. Before considering the full Poisson regression, we provide a rationale for using this approach in predicting admissions by adjusting only for the treatment arm into which patients were randomised.

Within the efficacy dataset for PEGASUS-TIMI 54 there were 18,404,070 days of patient exposure time. A Poisson regression adjusting only for treatment is shown in Table 84.

Table 84: Poisson regression for hospital admissions, adjusting only for treatment arm

Variable	Coefficient	Std. Error	p-value	Lower 95% CI	Upper 95% CI
Tic90	0.0456	0.0315	0.1480	-0.0162	0.1073
Tic60	0.0222	0.0317	0.4830	-0.0399	0.0844
Constant	-8.0433	0.0225	<0.0001	-8.0874	-7.9993

Exponentiation of the constant and the constant plus treatment arm yields 0.000321, 0.000336 and 0.000328 for low-dose ASA, ticagrelor 90 mg BID + low-dose ASA, and ticagrelor 60 mg BID + low-dose ASA, respectively, which represent the daily rate of hospital admissions for each arm in PEGASUS-TIMI 54. Total patient exposure (in days) by treatment arm was 6,175,992 days for low-dose ASA, 6,117,921 for ticagrelor 90 mg BID + low-dose ASA, and 6,110,157 days for ticagrelor 60 mg BID + low-dose ASA. Combining these rates with the exposure time produces an estimate for the total number of hospital admissions of 1,984 for low-dose ASA, 2,057 for ticagrelor 90 mg BID + low-dose ASA and 2,007 for ticagrelor 60 mg BID + low-dose ASA, respectively, which match the total number of observed hospital admissions in PEGASUS-TIMI 54 (Table 85).

Table 85: Predicted and observed hospital admission, unadjusted Poisson model

Treatment	Rate (daily)	Exposure (days)	Predicted	Observed
Ticagrelor 90 mg BID + low-dose ASA	0.000336	6,117,921	2,057	2,057
Ticagrelor 60 mg BID + low-dose ASA	0.000328	6,110,157	2,007	2,007
Low-dose ASA	0.000321	6,175,992	1,984	1,984
Total		18,404,070	6,048	6,048

The rate of hospital admission varied with baseline characteristics and geographical location. Since PEGASUS-TIMI 54 recruited a heterogeneous population of stable post-MI patients with varying underlying risks, it is probable that particular patients are more likely to be hospitalised, even without the occurrence of a clinical event.

Table 86 shows the Poisson regression accounting for clinical events and health states, in addition to baseline characteristics and geographical location. The base rate for hospital admissions excluding any baseline characteristics is 0.0034 hospitalisations per cycle.

Table 86: Poisson regression for hospitalisation rates, adjusted for clinical events and baseline characteristics

Variable	IRR	Coef.	p-value	Lower 95% CI	Upper 95% CI

Tic90	1.0536	0.0522	0.0580	-0.0017	0.1061
_minorBld	14.6409	2.6838	<0.0001	2.3078	3.0598
_majorBld	5.1947	1.6476	<0.0001	1.3196	1.9756
_SAEdys	7.8955	2.0663	<0.0001	1.5870	2.5456
_AEdys	1.2418	0.2166	0.0260	0.0259	0.4072
_MI	22.2780	3.1036	<0.0001	3.0024	3.2048
_Stroke	13.0710	2.5704	<0.0001	2.2416	2.8992
_PrevMI	2.8215	1.0373	<0.0001	0.8600	1.2145
_PrevStroke	2.8109	1.0335	<0.0001	0.7251	1.3419
_CVdeath	1.5953	0.4671	0.0370	0.0291	0.9050
_OthDeath	6.4297	1.8609	<0.0001	1.6257	2.0962
_PrevSAE	1.2465	0.2203	<0.0001	0.1381	0.3025
age	1.0087	0.0087	<0.0001	0.0039	0.0135
weight	1.0051	0.0051	<0.0001	0.0032	0.0070
dmtype	1.1916	0.1753	<0.0001	0.1160	0.2346
MI_HIST	1.2589	0.2303	<0.0001	0.1640	0.2965
cadmult	1.1004	0.0956	0.0010	0.0387	0.1526
stentany1	1.1209	0.1141	0.0020	0.0420	0.1862
anpect	1.2537	0.2261	<0.0001	0.1680	0.2842
qevtyp2	1.1493	0.1392	<0.0001	0.0838	0.1945
MEDTDDOS_n	1.0018	0.0018	0.0050	0.0005	0.0031
sbpsup	0.9980	-0.0020	0.0480	-0.0040	0.0000
dbpsup	1.0045	0.0045	0.0070	0.0012	0.0078
hyp	1.1405	0.1315	0.0030	0.0450	0.2179
hypchol	1.1402	0.1312	0.0010	0.0572	0.2053
tria	1.2549	0.2270	0.0290	0.0227	0.4314
prcerr	1.3573	0.3055	0.0350	0.0220	0.5890
chf	1.4632	0.3806	<0.0001	0.3183	0.4430
spbleed	1.2839	0.2499	0.0090	0.0628	0.4370
Asia_Australia	1.1160	0.1097	0.0200	0.0176	0.2019
SthAmerica	0.9222	-0.0810	0.0720	-0.1693	0.0072
tADP_12mplus	0.8948	-0.1111	<0.0001	-0.1721	-0.0502
histPAD	1.2999	0.2623	<0.0001	0.1580	0.3667
creatinine_cl	0.8720	-0.1370	<0.0001	-0.2100	-0.0641
_cons	0.0034	-5.6847	<0.0001	-6.1746	-5.1949

IRR=incident rate ratio (exponent of the coefficient); _minorBld=minor TIMI bleed; _majorBLD=major TIMI bleed; _SAEdys=grade 3-4 dyspnoea; _ASdys=grade 1-2 dyspnoea; _MI=non-fatal MI; _Stroke=non-fatal stroke; _PrevMI=post non-fatal MI health state; _PrevStroke=Post non-fatal stroke health state; _CVdeath=cardiovascular death; _OthDeath=death resulting from a non-cardiovascular cause.

The total number of admissions predicted by the model will be lower for the ticagrelor arms (compared to low-dose ASA) due to the lower rate of clinical events. The non-significant coefficient on treatment with ticagrelor 60 mg BID + low-dose ASA demonstrates that treatment assignment, once clinical events, baseline characteristics, and geographical location have been controlled for, has no impact on the rate of hospitalisation (i.e. unexplained factors are unlikely to cause more hospitalisations with ticagrelor 60 mg BID + low-dose ASA).

Table 87 demonstrates the probability (per cycle) that a patient (using average patient characteristics) will be hospitalised in the cycle that an event occurs predicted by the regression model and the probability applied in the economic model. Due to the low hospitalisation rates for MI, stroke and serious adverse events predicted by the regression model, which are unlikely to be represenative of clinical practice within the UK, we have assumed that all patients experiencing a MI, stroke or serious adverse event will be hospitalised.

Table 87: Probabilty (per cycle) of hospital admission by event

Event	Probability (per cycle) of hospital admission, by event, predicted by regression model	Probability (per cycle) of hospital admission, by event, applied in the model
No event	[redacted]%	[redacted]%
First and subsequent event		
Non-fatal MI	[redacted]%	100.0%
Non-fatal stroke	[redacted]%	100.0%
Fatal CV	[redacted]%	[redacted]%
Fatal Other	[redacted]%	[redacted]%
Adverse events		
Bleeding (TIMI-major)	[redacted]%	100.0%
Dyspneoa (Grade 3-4)	[redacted]%	100.0%

See Section 5.7.1 for explanation of the difference between the 'simple' and 'complete' analysis.

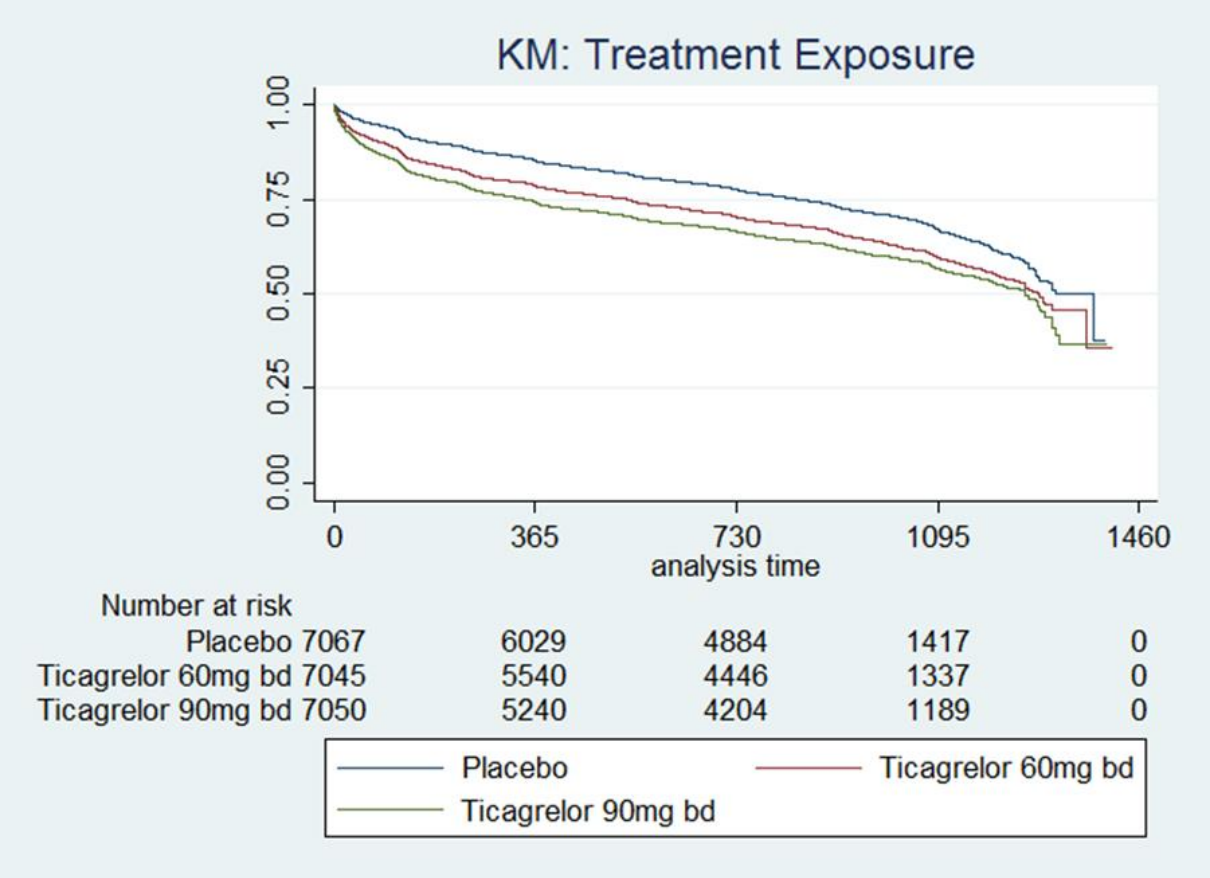
Inpatient costs are estimated in the economic model by estimating the rate of hospitalisation based on patient characteristics, health state occupancy and events that occur prior to and during the model cycle. For example, in any given cycle a number of patients have a fatal CV event. Based on the above table, [redacted]% of these patients would be hospitalised. These patients receive an inpatient cost only. In the case of non-fatal MI, it is assumed that 100% of patients will be hosptialised. Therefore, all patients will receive both the inpatient cost and the outpatient and mainteance costs.

Permanent treatment discontinuation

The total amount of time a patient remains on treatment has been incorporated into the economic model with the estimation of time to permanent treatment discontinuation. In line with the decision problem outlined in section 1.1, patients can only be treated with ticagrelor 60 mg + low-dose ASA for a maximum of three years. On-treatment time is used in the model to estimate the probability of adverse events (TIMI major and minor bleeds, dyspnoea) as well as to attribute drug acquisition costs for ticagrelor. Attributing treatment costs in this manner, assumes that patients were on treatment for the whole time between randomisation until treatment cessation, without any intermediary treatment stops. This assumption is conservative as a number of patients had temporary treatment stops throughout their 'on treatment' period; hence the trial-based treatment cost is likely to be overestimated.

Figure 44 shows the Kaplan–Meier curves for the overall treatment exposure (or time to permanent treatment discontinuation) observed from PEGASUS-TIMI 54. Patients receiving ticagrelor 90 mg BID + low-dose ASA, had the highest rate of permanent discontinuation, followed by patients receiving ticagrelor 60 mg BID + low-dose ASA, a reflection of the AE profile for the two doses.

Figure 44: Time to permanent treatment discontinuation



In total 7,647 patients permanently discontinued treatment during the PEGASUS-TIMI 54 trial. Of these 6,533 (85.4%) were alive at the time of study completion and 944 had died. The remaining 169 patients were either lost to follow-up, withdrew consent or were classified as 'other'. For those completing on study drug after at the study end date, 13,499 were alive and 16 had died. The observed annual rate of treatment discontinuation was approximately 18.2% for ticagrelor 60 mg BID + low-dose ASA and 20.8% for ticagrelor 90 mg BID + low-dose ASA compared to a base trial discontinuation rate for low-dose ASA of 13.6% per annum (Table 88).

Table 88: Estimated daily rate of permanent treatment discontinuation

	Person days	Failures	Annual rate	Daily rate	Lower 95% CI	Upper 95% CI
Placebo + low-dose ASA	5,740,714	2,137	0.1360	0.00037	0.00036	0.00039
Ticagrelor 60 mg BID + low-dose ASA	5,299,880	2,642	0.1821	0.00050	0.00048	0.00052
Ticagrelor 90 mg BID + low-dose ASA	5,027,107	2,868	0.2084	0.00057	0.00055	0.00059
Overall	16,067,701	7,647	0.1738	0.00048	0.00047	0.00049

This equates to an average on-treatment time of 712.8 days for ticagrelor 90 mg BID + low-dose ASA and 752.3 days for ticagrelor 60 mg BID + low-dose ASA (Table 89).

Table 89: Estimated daily rate of permanent treatment discontinuation

	Person days	Patients	Time on treatment		
			Days	Months	Years
Placebo + low-dose ASA	5,740,714	7,067	812.3	26.7	2.2
Ticagrelor 60 mg BID + low-dose ASA	5,299,880	7,045	752.3	24.7	2.1
Ticagrelor 90 mg BID + low-dose ASA	5,027,107	7,050	712.8	23.4	2.0
Overall	16,067,701	21,162	759.3	24.9	2.1

Permanent treatment discontinuation was estimated using a range of survival functions. To account for patient level heterogeneity associated with permanent treatment discontinuation, baseline characteristics were used to control for individual variation, and treatment interaction effects were explored. Interaction effects examined included:

- patients who had a spontaneous bleed requiring hospitalisation (prior to baseline)
- age
- sex

- weight
- time from previous ADP blocker: >12 months prior.

Statistical tests for proportional hazards demonstrated that the interaction of ticagrelor 60 mg BID + low-dose ASA with time from previous ADP blocker treatment required further evaluation to assess whether the proportional hazard assumption held (Appendix 16, Table 62).The log–log plot and Kaplan–Meier-predicted survival charts (Appendix 16, Figure 11) for permanent treatment discontinuation for the interaction between ticagrelor 60 mg BID + low-dose ASA and time from previous ADP blocker, indicated that the proportional hazard assumption held for this term, therefore the interaction term was retained.

Although the AIC and BIC criteria indicate that the Weibull function appears to best represent time to permanent treatment discontinuation (Appendix 16,Table 63), none fitted the first period well. When compared with observed events the Weibull function underestimates the risk during years 2 and 3, but overestimates the risk in subsequent years.

For patients treated with ticagrelor 60 mg BID + low-dose ASA, treatment discontinuation occurred at a higher rate in those patients who had a history of spontaneous bleeding prior to treatment (and who were therefore at increased risk of further treatment-related bleeds). In addition, older patients and those whose previous ADP blocker treatment was more than 12 months prior had a higher discontinuation rate (Appendix 16, Table 64). Across all treatments, discontinuation rate increased with age and weight, and patients with diabetes, a history of more than one MI, and who were current smokers had a higher discontinuation rate.

Further investigation identified a piecewise exponential function that could be used splitting the time periods into the first 91 days, during which the greatest number of treatment discontinuations occurred, and 91–1,260 days (3.5 years) during which the total number of patients at risk became very low. Coefficients for the piecewise exponentials are presented in Table 90.

Table 90: Permanent treatment discontinuation: piecewise exponential

Variable	Model 1: First 91 days	Model 2: After 91 days

	Coef.	p-value	Coef.	p-value
Tic60	-0.9500	0.0610	-0.1135	0.6720
Tic60_spbleed	0.7080	0.0020	0.2244	0.2340
Tic60_age	0.0227	0.0020	0.0045	0.2590
Tic60_tADP12mplus	0.1421	0.1060	0.0712	0.1860
Tic90	-0.9990	0.0880	-0.5402	0.1200
Tic90_age	0.0198	0.0060	0.0097	0.0210
Tic90_weight	0.0090	0.0020	0.0030	0.0990
Tic90_sex	-0.2443	0.0020	-0.1459	0.0110
Tic90_tADP12mplus	0.1790	0.0190	0.0830	0.1260
age	0.0201	0.0010	0.0174	<0.0001
weight	0.0029	0.1390	0.0034	0.0020
dmtype	0.0071	0.8850	0.1449	<0.0001
MI_HIST	0.0428	0.4750	0.1483	<0.0001
smk_his2	0.0695	0.2810	0.1990	<0.0001
sbpsup	0.0029	0.0340	0.0032	<0.0001
tria	0.6480	<0.0001	0.4753	<0.0001
NthAmerica	0.2505	<0.0001	0.2390	<0.0001
histPAD	0.1684	0.0630	0.1374	0.0160
creatinine_cl	-0.2314	<0.0001	-0.2788	<0.0001
_cons	-9.2186	<0.0001	-9.7945	<0.0001

Life tables for the risk of non-cardiovascular death

Although 366 non-cardiovascular deaths occurred in PEGASUS-TIMI 54, modelling the risk of non-cardiovascular death from the trial may be inappropriate, as exclusion of patients with co-morbidities from the trial can lead to an under-estimation of non-disease related mortality rates compared with the general population (Figure 45). Therefore, United Kingdom, National Life Tables (2012-2014) were used to model non-cardiovascular mortality.

Figure 45: Probability of mortality – on trial-based models vs. adjusted life tables

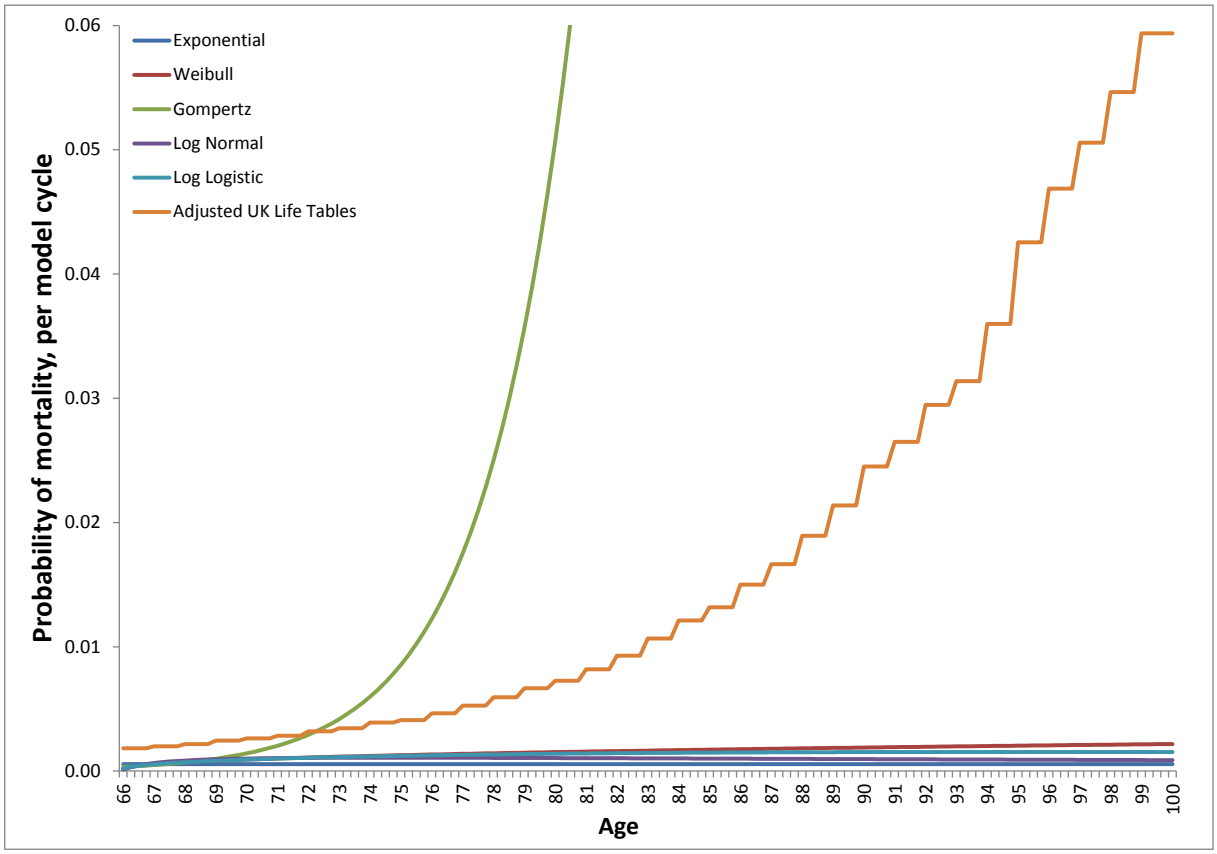


Chart displays the extrapolated probability of an 'other fatal' event, based on an individual 65 years of age at baseline.

As life tables reflect all-cause mortality, including deaths from CV-related causes, CV-specific mortality was excluded from the standard life tables used in the model using a component of contribution for non-CV death compared to all-cause mortality (Table 91). Components of contribution were estimated using the UK Government Actuarial Department's 2004–2006 interim life tables and the Office for National Statistics mortality by cause data. The exclusion of all CV ICD codes (excluding ICD-10, I00–I99) is likely to over-estimate the CV mortality that would have been captured within the PEGASUS-TIMI 54 trial. Expert clinical opinion was used to identify the ICD-10 codes that represent the classifications of CV deaths considered to have been captured within the PEGASUS-TIMI 54 trial: I11, I13, I20-I26, I30-I49, I50-I74, I81-I82 and I85. Excluding these ICD-10 codes allows an all-cause mortality to be calculated. In the UK, cause-specific mortality is available in 5-year age groups, this provides less detailed patterns of increasing mortality risk with increasing age than provided by standard actuarial life tables.

Table 91: Derivation for component of contribution

Age	All-cause mortality		CV ICD-10 codes accounted for in PEGASUS*		Excluding (I00–I99)		Adjusted rate (cause eliminated)		Death rates (life tables)		Component of contribution	
	M	F	M	F	M	F	M	F	M	F	M	F
<1	1,579	1,188	19	24	1,560	1,164	0.016	0.012	0.016	0.012	0.988	0.980
1–4	268	229	12	13	256	216	0.003	0.002	0.003	0.002	0.955	0.943
5–9	151	122	2	7	149	115	0.001	0.001	0.002	0.001	0.987	0.943
10–14	162	133	11	9	151	124	0.002	0.001	0.002	0.001	0.932	0.932
15–19	532	239	26	13	506	226	0.005	0.002	0.005	0.002	0.951	0.946
20–24	897	386	50	23	847	363	0.008	0.004	0.009	0.004	0.944	0.940
25–29	1,161	554	91	43	1,070	511	0.011	0.005	0.012	0.006	0.922	0.922
30–34	1,514	841	158	71	1,356	770	0.014	0.008	0.015	0.008	0.896	0.916
35–39	2,092	1,168	287	121	1,805	1,047	0.018	0.010	0.021	0.012	0.863	0.896
40–44	3,393	2,084	625	259	2,768	1,825	0.028	0.018	0.034	0.021	0.816	0.876
45–49	5,072	3,271	1185	430	3,887	2,841	0.039	0.028	0.051	0.033	0.766	0.869
50–54	6,973	4,786	1831	687	5,142	4,099	0.051	0.041	0.070	0.048	0.737	0.856
55–59	9,667	6,619	2624	999	7,043	5,620	0.07	0.056	0.097	0.066	0.729	0.849
60–64	14,734	9,805	3852	1449	10,882	8,356	0.109	0.084	0.147	0.098	0.739	0.852
65–69	21,687	15,048	5632	2464	16,055	12,584	0.161	0.126	0.217	0.150	0.740	0.836
70–74	26,100	18,934	7315	3836	18,785	15,098	0.188	0.151	0.261	0.189	0.720	0.797
75–79	34,652	28,234	9948	6889	24,704	21,345	0.247	0.213	0.347	0.282	0.713	0.756
80–84	42,705	42,506	12687	11788	30,018	30,718	0.300	0.307	0.427	0.425	0.703	0.723
85–89	40,127	52,899	12079	15629	28,048	37,270	0.280	0.373	0.401	0.529	0.699	0.705
90–94	25,022	48,316	7509	14657	17,513	33,659	0.175	0.337	0.250	0.483	0.700	0.697
95+	7,097	23,843	1967	6381	5,130	17,462	0.051	0.175	0.071	0.238	0.723	0.732

*ICD codes accounted for in PEGASUS-TIMI 54 (and thus excluded): I11, I13, I20-I26, I30-I49, I50–I74, I81–I82, I85.

Calculation of the transition probabilities from the clinical data

The economic model estimates transition probabilities for each of the functional forms for the exponential, Weibull, Gompertz, log–normal and log–logistic. A transition probability for each cycle period (TPt) is estimated using the following relationship with each of the cumulative hazard functions (for proportional hazard models) or the survival functions (for accelerated failure models).

Proportional Hazard Models (i.e. exponential, Poisson, Weibull and Gompertz).

$$TP_t = 1 - exp\{H(t-u) - H(t)\}$$

Exponential (and Poisson): where λ=β0+xjβx, t=time from randomisation and u=time interval (or cycle length).

$$TP_{Exp.} = 1 - exp(\lambda u)$$

Weibull: where λ=β0+xjβx; γ=shape parameter; t=time from randomisation; and u=time interval (or cycle length).

$$TP_{Weib.} = 1 - exp\left(\lambda(t-u)^{exp(\gamma)} - \lambda t^{exp(\gamma)}\right)$$

Gompertz: where λ=β0+xjβx; γ=shape parameter; t=time from randomisation; and u=time interval (or cycle length).

$$TP_{Gomp.} = 1 - exp\left(\frac{\lambda}{\gamma} exp[(t-u)\gamma - 1] - \frac{\lambda}{\gamma} exp(t\gamma - 1)\right)$$

Accelerated Failure Models (i.e. log–normal and log–logistic)

$$TP_t = 1 - \frac{S(t)}{S(t-u)}$$

Log–normal: where λ=β0+xjβx; σ=shape parameter; t=time from randomisation; and u=time interval (or cycle length).

$$TP_{LogNorm.} = 1 - \frac{1 - \phi\left[\frac{ln(t) - \lambda}{\sigma}\right]}{1 - \phi\left[\frac{ln(t-u) - \lambda}{\sigma}\right]}$$

Log–logistic: where λ=β0+xjβx; γ=shape parameter; t=time from randomisation; and u=time interval (or cycle length).

$$TP_{LogLog.} = 1 - exp\left(\frac{\lambda(t-u)^{\frac{1}{\gamma}}}{1+\lambda(t-u)^{\frac{1}{\gamma}}} - \frac{\lambda(t)^{\frac{1}{\gamma}}}{1+\lambda(t)^{\frac{1}{\gamma}}}\right)$$

Changing transition probabilities.

See section 5.3.1

Clinical expert details on assessing the applicability of the clinical parameters:

The individual variables included and the influence of their coefficients in the regression analyses for the full PEGASUS-TIMI 54 population were analysed by two clinical experts. Given that the EMA has suggested that the treatment should be licensed only in a sub-section of the full PEGASUS-TIMI 54 patient population, this gives a clinical indication that the treatment effect for ticagrelor 60 mg BID + low-dose ASA differed between patients that were included in this specified population ('label population') and those who were not included, giving justification for the methodology used to adapt the time-to-first-event risk equations for this 'label population'.

For the label population time-to-first-event risk equations only one variable was added the equations (for first MI – history of CABG was included) and this already was in the risk equation for the subsequent MI event with a similar coefficient. Therefore, we can be confident that all of the parameters in the regression equations are clinically valid.

5.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

Please see section 5.4.8 for full details of how health-related quality-of-life data was collected from the PEGASUS-TIMI-54 trial and applied in the economic model.

Mapping

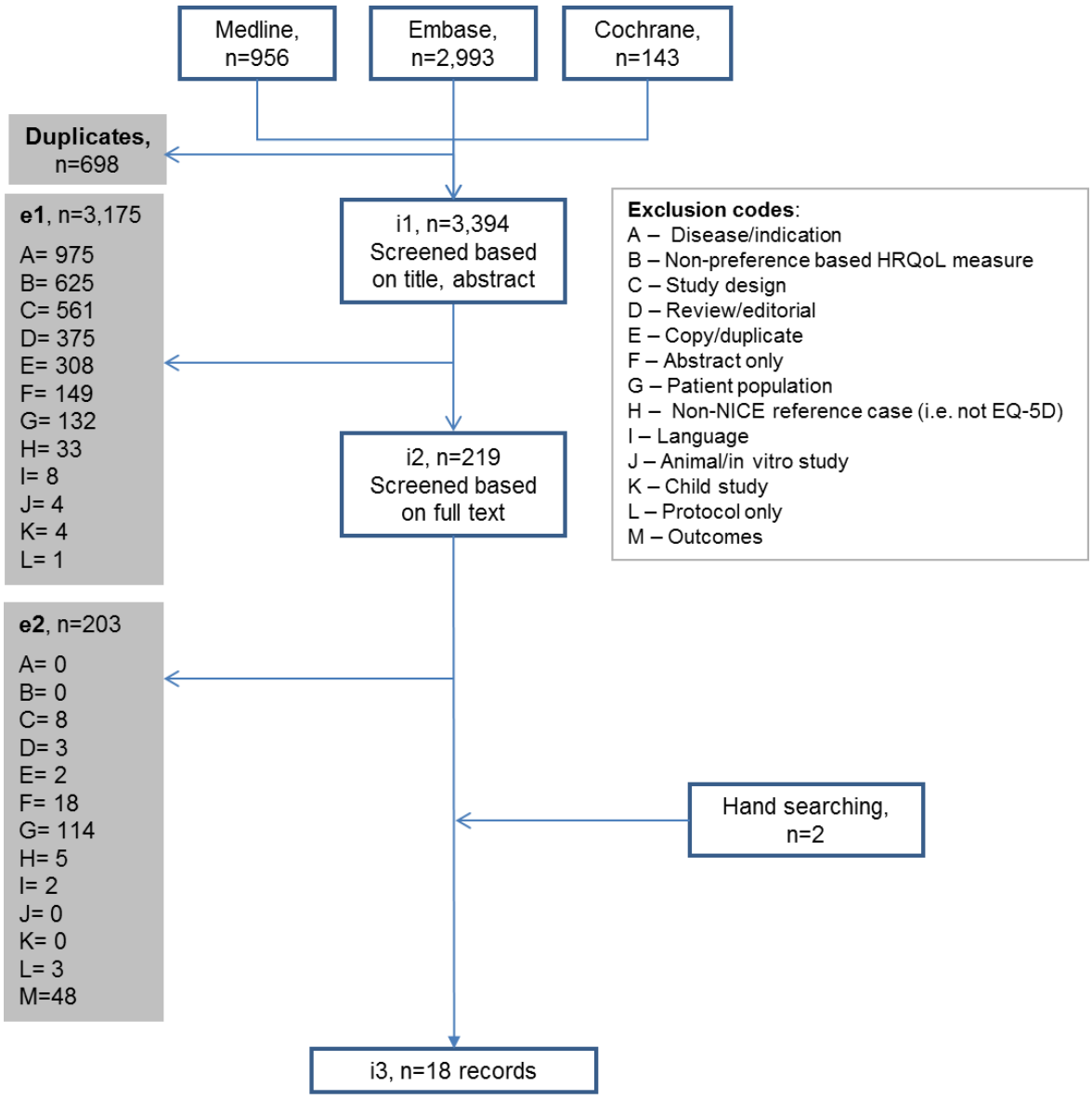
Mapping was not used. The model is based upon EQ-5D data collected in the PEGASUS TIMI-54 trial.

Health-related quality of life studies

A systematic literature review was conducted to identify HRQL and utility studies relevant to the decision problem using the search strategy and eligibility criteria presented inside Appendices 13.3 and 13.5 respectively. In total, 4,092 papers were identified through the electronic database searches. Upon the removal of duplicate papers, 3,394 titles and abstracts were reviewed. Following first pass, 219 publications were ordered for full paper review, 203 of which were excluded. Hand searching yielded an additional two relevant studies for inclusion. This resulted in 18 relevant papers for final inclusion in the updated utility review.

A list of the 18 included studies is provided in Table 23 (Appendix 13.6), and a list of studies excluded on the basis of full publication is provided in Table 24 (Appendix 13.7), along with a rationale for exclusion.

Figure 46. PRISMA flow diagram for the updated utility review



A total of 18 publications were included in the utility SR, of which 15 were full publications, and three were abstracts only (Figure 46). Countries for which the HRQL data were derived included: the UK (n=5) (98-102); Germany (n=3)(103-105); South Korea (n=2)(106, 107); Australia (n=1) (108); the Netherlands (n=1) (109);Poland (n=1) (110); Singapore (n=1) (111); and Sweden (n=1) (112). Three studies were multi-national (113-115).

The included studies considered the following patient populations: patients with acute MI (n=6) (98, 103, 108, 112, 113, 115); patients with ACS (STEMI/NSTEMI/UA) (n=2) (104, 106); patients with NSTEMI (n=1)(99); patients with STEMI (n=1) (110); patients with acute first or recurrent MI (n=1) (105); patients with coronary heart disease (CHD) or peripheral artery disease (PAD) with/without secondary cardiovascular (CV) events (n=1) (109); patients with MI, UA or stroke

(n=1) (100); and patients who have undergone coronary artery bypass surgery (CABG), PCI, acute MI, or myocardial ischaemia (n=1) (113). Four studies considered nationally representative samples from the general population (Singapore (111), Korea (107) and the UK((101, 102)), and reported utilities for the sub-set of patients with MI.

A total of seven studies reported intervention specific utilities (99, 105, 106, 108-110, 115). The interventions considered in these studies included: fractional flow reserve (FFR)-guided vs standard coronary angiography (n=1) (99); trans-radial vs trans-femoral PCI (n=1) (110); traditional vs Care Assessment Platform (CAP)-cardiac rehabilitation (n=1) (108); and case management program vs control (n=1) (105). The remaining three publications reported utilities for populations who had received an intervention, but utilities were not reported according to the intervention received: captopril/valsartan/combination of captopril and valsartan (n=1) (115); PCI (n=1) (106); and various vascular interventions from five clinical trials (n=1) (109).

Utilities were derived directly from patients using the EQ-5D in all included studies according to the pre-specified inclusion criteria and in line with the NICE reference case. No mapping studies were identified. Societal preferences elicited using the time trade off (TTO) method were used to value health states in 12 studies; the country tariffs used included: the UK (n=6) (99, 101, 102, 109, 113, 115); Germany (n=2) (103, 105); Australia (n=1) (108); Singapore (n=1) (111); South Korea (n=1) (107); and Poland (n=1) (110). In six studies it was unclear which societal preferences were used to value health states (98, 100, 104, 106, 112, 114). Therefore a total of six studies were fully aligned with the NICE reference case (99, 101, 102, 109, 113, 115).

Follow up time for utilities ranged from 2 hours (post-intervention) (110) to 3 years (109, 113). Six of the included studies did not report the follow up time of utilities (101-103, 107, 111, 114).

Health states for which utilities were reported included: acute MI at baseline (n=9) (98, 100-103, 111-113, 115) and at 1 month (n=2) (98, 100), 6 months (n=2) (98, 100), 12 months (n=2) (98, 100), 18 months (n=1) (100), and 24 months follow up (n=1) (100); acute MI according to gender (n=2) (98, 114); acute MI according to

occurrence of secondary CV events (n=1) (115); acute MI according to previous coronary artery disease (CAD) (114), PAD (109) or CHD (109); STEMI (n=3) (98, 104, 106); STEMI managed by PCI (n=2) (106, 110); NSTEMI (n=2) (98, 104); NSTEMI or UA (n=1) (106); NSTEMI with FFR-guided or standard coronary angiography at baseline, and 6- and 12-months follow up (n=1) (99); ACS at baseline and 12 months follow up (n=1) (104); acute first or recurrent MI at baseline, and at 3-, 6-, 9-, and 12-months follow up (n=1) (105); MI or ischaemic heart disease (IHD) with or without visual impairment (n=1) (107); MI with traditional or CAP-cardiac rehabilitation (baseline and 6 weeks follow up) (n=1) (108); MI plus stroke (n=1) (103); and acute MI followed by recurrent MI (n=1) (112).

The 18 included studies are summarised in Table 92 and Table 93 and a summary of the studies' relevance to the NICE reference case is presented in Table 94.

Table 92: Summary of HSUVs associated with adult patients with prior MI identified by the utility review update, listed according to study year

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
Dreyer, 2016 (114) Multi-national (Spain and US) (Full publication)	Patients aged 18-55 years with acute MI confirmed by increased cardiac biomarkers within 24 hours of admission, and at least either ischaemic symptoms or electrocardiogram changes; 20% of male patients and 19% of female patients had prior MI, CABG or PCI N=3,501 Median age, 48 years (IQR 43-52) Gender distribution: male, N=1,152 (33%); female, N=2,349 (67%)	NA	NR	Utilities were derived directly from patients using the EQ-5D	Unclear	Male patients with acute MI (20% with prior MI, CABG or PCI), baseline	0.8 [0.2]
						Female patients with acute MI (19% with prior MI, CABG or PCI), baseline	0.7 [0.2]
						Male patients with acute MI and with prior CAD (N=236), baseline	0.73 [0.23]
						Female patients with acute MI and prior CAD (N=436), baseline	0.67 [0.25]
Abdin, 2015 (111) Singapore (Full publication)	A nationally representative sample of residents aged ≥18 years, community dwelling, and able to speak English, Malay or Chinese; results were compared between those with and without chronic	NA	NR	Utilities were derived directly from participants using the EQ-5D	Health states were valued using a Singapore TTO tariff	Overall population (N=5,594), baseline	0.95 (SE 0.002)
						Patients with MI (N=157),	0.81 (SE

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
	physical conditions including MI N=5,594 Mean age of MI patients, NR Gender distribution of MI patients, NR					baseline	0.04)
Alabas, 2015 (98) UK (Abstract)	Patients who have survived an acute MI; results were stratified according to acute MI phenotype (STEMI, n=1,335 [39.9%]; and NSTEMI, n=2,008 [60.1%]) and gender (male, 74.1%; female, 25.9%) N=5,257 Mean age: STEMI, 61.2 years (SD 11.4); NSTEMI, 66.2 years (SD 11.6)	NA	Baseline, 1, 6, and 12 months follow up	Utilities were derived directly from patients using the EQ-5D	NR	Patients with acute MI, baseline	0.76 [0.27]
						Patients with acute MI, 12 month follow up	0.79 [0.26]
						Male patients with acute MI, baseline	0.76 [0.27]
						Female patients with acute MI, baseline	0.69 [0.30]
						Male patients with acute MI, 1 month follow up	0.77 [0.24]
						Female patients with acute MI, 1 month follow up	0.71 [0.27]
						Male patients with acute MI, 6 months follow up	0.81 [0.25]
						Female patients with acute MI, 6	0.73

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
						months follow up	[0.28]
						Male patients with acute MI, 12 months follow up	0.81 [0.25]
						Female patients with acute MI, 12 months follow up	0.74 [0.28]
						Patients with STEMI, baseline	0.77 [0.28]
						Patients with NSTEMI, baseline	0.74 [0.28]
						Patients with STEMI, 1 month follow up	0.79 [0.24]
						Patients with NSTEMI, 1 month follow up	0.74 [0.26]
						Patients with STEMI, 6 months follow up	0.83 [0.24]
						Patients with NSTEMI, 6 months follow up	0.78 [0.26]
						Patients with STEMI, 12 months follow up	0.83 [0.25]
						Patients with	0.78

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
						NSTEMI, 12 months follow up	[0.27]
Goss, 2015 (104) Germany (Abstract)	Patients discharged from hospital after an ACS (STEMI, 44.3%; NSTEMI, 39.5%; UA, 15.2%) into ambulatory cardiology care N=992 Mean age, 62.1 years (SD 11.8) Male, 73.6%	NA	12 months	Utilities were derived directly from patients using the EQ-5D	NR	Patients with ACS, baseline	0.91 [0.18]
						Patients with ACS, 12 months follow up	0.91 [0.18]
						Patients with STEMI, baseline	0.92 [NR]
						Patients with NSTEMI, baseline	0.90 [NR]
						Patients with UA, baseline	0.89 [NR]
Nam, 2015 (99) UK (Full publication)	Patients with recent NSTEMI N=NR Mean age, 62 years Gender distribution, NR	FFR Standard coronary angiography (without FFR)	Baseline, 6 and 12 months	Utilities were derived directly from patients using the EQ-5D-3L	Health states were valued using the UK TTO tariff	Patients with NSTEMI, standard care, baseline	0.80 [0.24]
						Patients with NSTEMI, FFR, baseline	0.78 [0.28]
						Patients with NSTEMI, standard care, 6 months	0.83 [0.24]
						Patients with NSTEMI, FFR, 6 months	0.83 [0.23]

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
						Patients with NSTEMI, standard care, 12 months	0.80 [0.27]
						Patients with NSTEMI, FFR, 12 months	0.83 [0.23]
Park, 2015 (107) South Korea (Full publication)	Individuals aged ≥19 years from the Korean general population who participated in KHNANES (2008-2012); results were reported for patients with various conditions and according to the presence of visual impairment Patients with MI or IHD, N=777 Mean age of MI/IHD patients, NR Gender distribution of MI/IHD patients, NR	NA	NR	Utilities were derived directly from patients using the EQ-5D-3L	Health states were valued using a Korean TTO tariff	Patients with MI or IHD without visual impairment (N=771), baseline	0.860 (SE 0.007)
						Patients with MI or IHD with visual impairment (N=6), baseline	0.850 (SE 0.070)
Seidl, 2015 (105) Germany (Full publication)	Patients aged ≥65 years with an acute first or recurrent MI treated in the Central Hospital of Ausburg; reinfarction occurred in 20.5% of the intervention group and 24.4% of the control group N=329 Mean age: intervention group, 75.2 years (SD 6.0); control group, 75.6 years (SD 5.9)	Case management program Control	Baseline, 3, 6, 9, and 12 months	Utilities were derived directly from patients using the EQ-5D-3L	Health states were valued using the German TTO tariff	Patients with acute first or recurrent MI (20.5% reinfarction), intervention group, baseline	0.74 [0.32]
						Patients with acute first or recurrent MI (24.4%	0.73 [0.31]

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
	Female: intervention group, 37.3%; control group, 38.7%					reinfarction), control group, baseline	
						Patients with acute first or recurrent MI, intervention group, mean change month 3	0.0770 [NR]
						Patients with acute first or recurrent MI, control group, mean change month 3	0.0179 [NR]
						Patients with acute first or recurrent MI, intervention group, mean change month 6	0.0509 [NR]
						Patients with acute first or recurrent MI, control group, mean change month 6	0.0329 [NR]
						Patients with acute first or	0.0111 [NR]

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
						recurrent MI, intervention group, mean change month 9	
						Patients with acute first or recurrent MI, control group, mean change month 9	0.0065 [NR]
						Patients with acute first or recurrent MI, intervention group, mean change month 12	-0.0052 [NR]
						Patients with acute first or recurrent MI, control group, mean change month 12	-0.0121 [NR]
De Smedt, 2014 (113) Multi-national (Europe) (Full	Patients aged 18-80 years, hospitalised for CABG, PCI, acute MI, or myocardial ischaemia N=7,472 Mean age, 63.1 years (SD 9.2)	NA	Between 6 months and 3 years (median, 1.24 years)	Utilities were derived directly from patients using the EQ-5D	Health states were valued using the UK TTO tariff	Overall population (N=7,472), baseline	0.80 (0.69, 1.00)
						Patients with acute MI	0.78 (0.66,

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
publication)	Male, 75%			[SF-6D utilities were also reported but have not been extracted]		(N=NR), baseline	1.00)
						Patients with history of stroke	0.69 (0.25, 0.85)
Henriksson, 2014 (112) Sweden (Full publication)	Patients aged <75 years, diagnosed with acute MI (ICD 10-code I21, I22) admitted to hospital and registered in RIKS-HIA during 2005-2009 and enrolled in SEPHIA; two sub-sets of the population were considered: (i) delay-time population, consisting of patients who had an additional acute MI after the initial event (N=454); (ii) readmission population, consisting of patients who had an additional 1 year follow up after the new MI (N=216) N=18,015 Median age, 65 years (IQR 59-70) Male, 73.6%	NA	12 months	Utilities were derived directly from patients using the EQ-5D	NR	Patients with acute MI, total SEPHIA population (N=18,015), baseline	0.85 (median) (IQR 0.73-1.00)
						Patients with acute MI, delay-time population (new MI registered after initial event; N=454), baseline	0.73 (median) (IQR 0.66-1.00)
						Patients with acute MI, readmission population (new MI registered after initial event + 12 months additional follow up; N=216), baseline	0.76 (median) (IQR 0.69-1.00)

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
Koltowski, 2014 (110) Poland (Full publication)	Patients aged >18 years with an electrocardiographic confirmation of STEMI, and a negative Allen's test result N=103 Mean age, NR Gender distribution, NR	Trans-radial PCI (N=52) Trans-femoral PCI (N=51)	2 hours and 4 days post-PCI	Utilities were derived directly from patients using the EQ-5D-3L	Health states were valued using the Polish TTO tariff	Patients with STEMI who underwent PCI, 2 hours post-PCI	0.46 [0.291]
						Patients with STEMI randomised to radial access, 2 hours post-PCI	0.602 [0.299]
						Patients with STEMI randomised to femoral access, 2 hours post-PCI	0.323 [0.283]
						Patients with STEMI randomised to radial access, 4 days post-PCI	0.779 [NR]
						Patients with STEMI randomised to femoral access, 4 days post-PCI	0.810 [NR]
Lewis, 2014 (115) Multi-national (Argentina,	Patients aged ≥18 years with an acute MI occurring 12 hours to 10 days prior to randomisation in the VALIANT trial; 1,785 patients did not experience a subsequent CV	Captopril Valsartan Combinatio n of both	Baseline, 6, 12, 20 and 24 months (annually	Utilities were derived directly from patients using the	Health states were valued using UK and US	Patients with acute MI without a subsequent CV event (N=1,785),	0.80 [0.23]

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
Australia, Canada, Denmark, France, Germany, Italy, Sweden, UK, US) (Full publication)	event (18.7% had prior MI) and 597 patients experienced a subsequent event and had available EQ-5D data (33.5% had prior MI)† Mean age: patients with CV event + EQ-5D data, 68.6 years (SD 11) Female: patients with CV event + EQ-5D data, 31.5%		there-after)	EQ-5D	TTO tariffs	18.7% prior MI, baseline (UK tariff)	
						Patients with acute MI without subsequent CV event (N=1,785), 18.7% prior MI, baseline (US tariff)	0.83 [0.17]
						Patients with acute MI with a non-fatal CV event post-MI (N=597), 33.5% prior MI, baseline (UK tariff)	0.70 [0.29]
						Patients with acute MI with a non-fatal CV event post-MI (N=597), 33.5% prior MI, baseline (US tariff)	0.76 [0.22]
						Patients with acute MI with a non-fatal	-0.06 (-0.11, -0.01)

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
						recurrent MI (N=214), baseline disutility (UK tariff)	
						Patients with acute MI with a subsequent non-fatal stroke (N=57), baseline disutility (UK tariff)	-0.18 (-0.28, -0.08)
Pockett, 2014 (100) UK (Abstract)	Patients aged ≥18 years from three UK centres one month after admission for MI, UA or stroke N=1,350 Mean age, 68.8 years (SD 12.3) Gender distribution, NR	NA	Baseline, 1, 6, 12, 18, and 24 months	Utilities were derived directly from patients using the EQ-5D	NR	Patients with MI, baseline	0.690 [0.322]
						Patients with MI, 1 month	0.767 [NR]
						Patients with MI, 6 months	0.846 [NR]
						Patients with MI, 12 months	0.877 [NR]
						Patients with MI, 18 months	0.855 [NR]
						Patients with MI, 24 months	0.855 [NR]
Varnfield, 2014 (108) Australia (Full	Post-MI patients referred to cardiac rehabilitation N=120 Mean age: traditional cardiac	Traditional cardiac rehab CAP-	Baseline and 6 weeks	Utilities were derived directly from patients using the	Health states were valued using an Australian	Post-MI patients, traditional cardiac rehabilitation (N=38), baseline	0.80 (IQR 0.7, 1.0)

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
publication)	rehabilitation, 55.7 years (SD 10.4); CAP-cardiac rehabilitation, 55.5 years (SD 9.6) Male: traditional cardiac rehabilitation, 82%; CAP-cardiac rehabilitation, 85%	cardiac rehab		EQ-5D	TTO tariff	(median)	
						Post-MI patients, CAP-cardiac rehabilitation (N=48), baseline (median)	0.83 (IQR 0.8, 1.0)
						Post-MI patients, traditional cardiac rehabilitation (N=23), baseline (median)	0.83 (IQR 0.8, 0.9)
						Post-MI patients, CAP-cardiac rehabilitation (N=38), baseline (median)	0.84 (IQR 0.8, 0.9)
						Post-MI patients, traditional cardiac rehabilitation, 6 weeks (median)	0.82 (IQR 0.7, 0.9)
						Post-MI patients, CAP-cardiac rehabilitation, 6 weeks (median)	0.92 (IQR 0.9, 1.0)
Kim, 2013 (106)	Patients with ACS (STEMI [N=846] or NSTEMI/UA [N=2,516]) who underwent timely PCI; 6.1% of	PCI	Baseline and 30 days post-	Utilities were derived directly from	NR	Patients with NSTEMI/UA (N=2,516),	0.77 [0.27]

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
South Korea (Full publication)	patients had a prior MI N=3,362 Mean age, 63.7 years (SD 11.1) Male, 68.8%		PCI	patients using the EQ-5D		baseline	
						Patients with STEMI (N=846), baseline	0.78 [0.29]
						Patients with NSTEMI/UA (N=2,516), 30 days post-PCI	0.86 [0.21]
						Patients with STEMI (N=846), 30 days post-PCI	0.89 [0.17]
Stafford, 2012 (101) UK (Full publication)	Adult participants in the HSE 2003 and 2006; patients with MI, 2.3% N=26,104 Mean age, NR Male, 50.2%	NA	NR	Utilities were derived directly from patients using the EQ-5D	Health states were valued using the UK TTO tariff	Patients with MI, baseline	0.636 (0.602, 0.669)
						Patients without MI, baseline	0.868 (0.865, 0.871)
						Patients with MI, mean difference in utility	-0.139 (SE 0.013)
						Patients with stroke, baseline	0.680 (0.619, 0.741)
						Patients without stroke, baseline	0.867 (0.864, 0.870)
						Patients with	-0.160

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
						stroke, mean difference in utility	(SE 0.015)
Van Stel, 2012 (109) Netherlands (Full publication)	Patients enrolled in five clinical trials: three trial recruited patients with CHD (Benestent II, ARTS, and Octopus) and two trials recruited patients with PAD (BOA and DIST)‡ N=3,972 (PAD, 1,379; CHD, 2,593); 126 MIs occurred post-intervention in the trials Mean age, NR Gender distribution, NR	Various vascular interventions as detailed by the five clinical trials	Baseline and post-intervention (12-36 months)	Utilities were derived directly from patients using the EQ-5D	Health states were valued using the UK TTO tariff	Patients with PAD and subsequent MI, baseline	0.63 (0.42, 0.84)
						Patients with CHD and subsequent MI, baseline	0.77 (0.67, 0.87)
Bach, 2011 (103) Germany (Full publication)	Patients who have experienced MI (N=2,181 [3.9%]), stroke (N=783 [1.4%]), both events (N=145 [0.3%]), or neither of these events (N=52,409 [94.4%]) N=55,518 Mean age: patients with MI, 67.4 years (SD 10.2); patients with stroke, 68.2 years (SD 10.8); patients with both, 70.3 years (SD 8.4) Female, 59.2%	NA	NR	Utilities were derived directly from patients using the EQ-5D-3L	Health states were valued using a German TTO tariff	Patients with stroke or MI, baseline	0.74
						Patients with MI, baseline	0.66
						Patients with stroke, baseline	0.62
						Patients with both MI and stroke, baseline	0.57
Sullivan, 2011 (102)	Adult individuals aged ≥18 years from the MEPS 2000-2003 sample	NA	NR	Utilities were derived	Health states were	MEPS entire sample, baseline	0.828 (0.825,

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
UK (Full publication)	(N=79,522); sub-set of patients had acute MI according to the CCC classification (N=496) Mean age: MEPS entire sample, 42.8 years; patients with acute MI, 63.1 years Gender distribution for patients with acute MI, NR			directly from participants using the EQ-5D	valued using the UK TTO tariff		0.821) (SE 0.0015)
						Patients with acute MI, CCC disease classification, baseline	0.605 (0.561, 0.648) (SE 0.022)
						Patients with acute MI, CCC disease classification, baseline disutility	-0.0557 (SE 0.0112)
						Patients with acute MI, ICD 9 classification, baseline	0.605 (0.561, 0.648) (SE 0.022)
						Patients with acute MI, ICD 9 classification, baseline disutility	-0.0626 (SE 0.0132)
						Patients with old MI, ICD 9 classification, baseline	0.671 (0.581, 0.761) (SE 0.046)
						Patients with old MI, ICD 9	-0.0368 (SE

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation	Health states	Utility score (95% CI) [SD]
						classification, baseline disutility	0.0257)
						Patients with acute cerebrovascular disease, CCC classification, baseline disutility	-0.1009 (SE 0.0123)

ACS: acute coronary syndrome; CABG: coronary artery bypass graft; CAP: Care Assessment Platform; CCC: Clinical Classification Categories; CHD: coronary heart disease; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FFR: fractional flow reserve; HRQL: health-related quality of life; HSE: Health Survey for England; HSUV: health state utility value; ICD: International Classification of Disease; IHD: ischaemic heart disease; IQR: interquartile range; KHNANES: Korean National Health and Nutrition Examination Survey; MEPS: Medical Expenditure Panel Survey; MI: myocardial infarction; NA: not applicable; NICE: National Institute for Health and Care Excellence; NR: not reported; NSTEMI: non-ST segment elevation myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; RIKS-HIA: The Register of Information and Knowledge about Swedish Heart Intensive Care Administrations; SD: standard deviation; SE: standard error; SEPHIA: Secondary Prevention after Heart Intensive Care Admission; STEMI: ST segment elevation myocardial infarction; TTO: time trade off; UA: unstable angina; UK: United Kingdom; US: United States.

† The distribution of subsequent CV events was as follows (overall, N=597): (i) heart failure hospitalisation, N=309; (ii) recurrent MI, N=214; (iii) stroke, N=57; (iv) resuscitated sudden death, N=17.

‡ Cardiovascular events (including death, MI, cerebrovascular accident, amputation, infrainguinal-vein-graft occlusion, extracranial bleeding, and re-interventions) occurring after the vascular intervention under study in the five clinical trials were considered to be secondary events.

Table 93. Discussion of HSUVs described in Table 92

Study, Country	Discussion (summary of relevance to NICE reference case and quality assessment)
Dreyer, 2016 (114) Multi-national (Spain and US) (Full publication)	It is unclear if this study meets the requirements of the NICE reference case; although the preferred EQ-5D instrument was used to derive utilities directly from patients, it is unclear if societal preferences were used to value health states. Only ~20% of the study population were reported to have experienced a prior MI (or CABG or PCI). However, the population consisted of patients who had survived an acute MI, and the reported utilities could therefore be used as baseline estimates of HRQL for a population of patients who have experienced a prior MI. It is possible that only healthier patients agreed to participate in this study and this may have impacted the observed results. It is unclear if the results are generalisable to a UK setting as the study was conducted in the US/Spain and the societal tariff used to value health states is unknown. Due to the observational study design, any differences in health status observed between genders may be due to residual confounding.
Abdin, 2015 (111) Singapore (Full publication)	This study does meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D instrument, however, health states were valued using TTO societal preferences from Singapore rather than the UK. Although the study population consisted of a nationally representative sample from the general population in Singapore, the utility of MI was reported, and this could be used as a baseline utility value in the economic model. The study was conducted in Singapore and societal preferences from Singapore were used to value health states; it is therefore unclear how generalisable the results are to a UK setting. The small sample size of patients with MI may reduce the precision of the mean EQ-5D estimate (indicated by higher mean SE). The survey only considered community-dwelling individuals and did not capture data for those who were institutionalised at the time of the study (e.g. nursing homes, hospitals); these individuals may have considerably different HRQL.
Alabas, 2015 (98) UK (Abstract)	It is unclear if this study meets the requirements of the NICE reference case; although utilities were derived directly from patients using the preferred EQ-5D instrument, it is unclear if societal preferences were used to value health states. The study population consisted of patients who had survived an acute MI, and the reported utilities could therefore be used as baseline estimates of HRQL for a population of patients who have experienced a prior MI. The study was conducted in the UK, and although it is unclear which societal preferences were used to value health

	states, it is likely that the results are representative of a UK setting. The study was reported as an abstract only, therefore limited information was reported regarding the patient recruitment process and the methodology used to derive utilities.
Goss, 2015 (104) Germany (Abstract)	It is unclear if this study meets the requirements of the NICE reference case; although utilities were derived directly from patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states. Although the study population consisted of patients with ACS, utilities associated with STEMI and NSTEMI were reported and could be used as a baseline utility values in the economic model. It is unclear how generalisable the results from this study are to a UK setting as the study was conducted in Germany and it unclear which societal preferences were used to value health states. The study was reported as an abstract only, therefore limited information was reported regarding the patient recruitment process and the methodology used to derive utilities. Additional limitations which may restrict the usefulness of the study for economic evaluation: Absence of measures of uncertainty for some reported utilities.
Nam, 2015 (99) UK (Full publication)	The utilities reported in this study meet the requirements of the NICE reference case; they were derived directly from patients using the preferred EQ-5D, and health states were valued using UK societal preferences elicited using the TTO technique (assumed from reference to Dolan 1997) The study population consisted of only patients with NSTEMI. The study was conducted in the UK and health states were valued using UK preferences, therefore the results may be considered representative of a UK setting.

Park, 2015 (107) South Korea (Full publication)	This study does not meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, however, Korean rather than UK societal preferences were used to value health states. It is unclear how representative the utilities are of a population of adults with prior MI as the utilities reported are associated with MI or IHD. Additionally, KHNANES did not include institutionalised individuals in which chronic health problems may be prevalent and participants without EQ-5D results were also excluded; the results may not therefore be generalisable to institutionalised/hospitalised individuals. A representative Korean sample of patients was used to describe utilities and Korean preferences were used to value health states; it is unclear if results are generalisable beyond this population to a UK setting.
Seidl, 2015 (105) Germany (Full publication)	This study does not meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, however, German rather than UK societal preferences were used to value health states. The study population consisted of patients with first acute or recurrent MI, and the reported utilities could therefore be used as baseline estimates of HRQL for a population of patients who have experienced a prior MI. The study population was restricted, however, to patients over the age of 65 years, and results may not be generalisable to other age groups in the same setting. The single centre study design also restricts generalisation of the results beyond the study population or to different healthcare structures. In addition, the study was conducted in Germany, and German societal preferences were used to value health states; it is therefore unclear how representative the results are of a UK setting. Additional limitations which may restrict the usefulness of the study for economic evaluation: Absence of measures of uncertainty for reported changes in utilities.
De Smedt, 2014 (113) Multi-national (Europe) (Full publication)	This study meets the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, and health states were valued using UK societal preferences. Although the study population was broader than that of interest for the review and consisted of patients with coronary heart disease, the utility of MI was reported, and this could be used as a baseline utility value in the economic model. Although the study was conducted across a number of European countries, as UK societal preferences were used to value health states, the results are likely to be representative of a UK setting.
Henriksson, 2014 (112) Sweden (Full publication)	It is unclear if this study meets the requirements of the NICE reference case; although utilities are derived directly from patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states. The study population may be considered comparable to a population of adults with prior MI; utilities associated with acute MI and subsequent MI after the initial event were reported. It may not be possible, however, to generalise the findings to patients aged >75 years. The study was conducted in Sweden and it is not clear which societal preferences were used to value health states; it is

	therefore unclear if results are generalisable to a UK setting. Additional limitations which may restrict the usefulness of the study for economic evaluation: Absence of measures of uncertainty for reported utilities.
Koltowski, 2014 (110) Poland (Full publication)	This study does not meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, however, Polish rather than UK societal preferences were used to value health states. The utilities reported may be considered appropriate for use in economic evaluation in the absence of higher quality evidence. The study population consisted of patients with STEMI, and the reported utilities could therefore be used as baseline estimates of HRQL for a population of patients who have experienced a prior MI. The study was conducted in Poland and health states were valued using Polish societal preferences; it is therefore unclear how generalisable the results are to a UK setting. Additional limitations which may restrict the usefulness of the study for economic evaluation: Absence of measures of uncertainty for some reported utilities Short time scale of follow up.
Lewis, 2014 (115) Multi-national (Argentina, Australia, Canada, Denmark, France, Germany, Italy, Sweden, UK, US) (Full publication)	This study meets the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D and UK TTO societal preferences were used to value health states (assumed from reference to Dolan 1997). The US based tariff was also used to value health states. The study population may be considered comparable to a population of adult patients with prior MI; utilities associated with acute MI and subsequent CV events were reported, as well as the disutility of recurrent MI and stroke. Data from patients who died within 1 year after CV events were excluded from this analysis, and as these patients may represent a sicker population than survivors this may have impacted the HRQL results observed. Although the study was conducted across a number of countries, UK societal preferences were used to value health states and so the results are likely to be representative of a UK setting.
Pockett, 2014 (100) UK (Abstract)	It is unclear if this study meets the requirements of the NICE reference case; although utilities are derived directly from patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states. The study population included patients with MI, and the associated utilities could therefore be used as baseline estimates of HRQL for a population of patients who have experienced a prior MI. Although it is unclear which societal preferences were used to value health states, the study was conducted in the UK and so the results may be considered representative of a UK setting. The study was reported as an abstract only, therefore limited information was reported regarding the patient recruitment process and the methodology used to derive utilities.

	Additional limitations which may restrict the usefulness of the study for economic evaluation: Absence of measures of uncertainty for reported utilities.
Varnfield, 2014 (108) Australia (Full publication)	This study does not meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, however, Australian rather than UK societal preferences were used to value health states. The study population consisted of post-MI patients; as it unclear if patients had experienced a prior MI the utilities reported may be used as baseline estimates of HRQL in adult patients with a prior MI. However, the study only focused on patients referred for cardiac rehabilitation, and did not address all patients potentially eligible for this management. The study was conducted in Australia and Australian preferences were used to value health states; it is therefore unclear how generalisable the results are to a UK setting. Additional limitations which may restrict the usefulness of the study for economic evaluation: Absence of measures of uncertainty for reported utilities Small study sample size.
Kim, 2013 (116) South Korea (Full publication)	It is unclear if this study meets the requirements of the NICE reference case; although utilities were derived directly from patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states. Only 6.1% of the study population were reported to have experienced a prior MI. However, utilities associated with STEMI and NSTEMI/UA were reported which could be used as baseline estimates of HRQL for a population of patients who have experienced a prior MI. As ACS is a rapidly progressive disease, the 30 day HRQL results should be interpreted as a complex of the results of treatment and clinical factors. In addition, the short follow up time may mean that results are not reflective of the true impact of treatment on HRQL. It is unclear if the results are generalisable to a UK setting as the study was conducted in South Korea and it is unclear which societal preferences were used to value health states.
Stafford, 2012 (101) UK (Full publication)	Utilities reported in this study meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D and UK societal preferences were used to value health states elicited using the TTO method (assumed from reference to Dolan 1996). Although the study population consisted of adults who took part in the HSE 2003 and 2006, the utility associated with a MI was reported which could be used as a baseline estimate for HRQL for a population of patients who have experienced a prior MI. The study was conducted in the UK and health states were valued using UK societal preferences so the results may be considered representative of a UK setting.
Van Stel, 2012 (109)	This study meets the requirements of the NICE reference case; utilities were derived directly from patients using the

Netherlands (Full publication)	preferred EQ-5D and health states were valued using UK societal preferences elicited using the TTO method (assumed from reference to Dolan 1997). It is unclear if patients recruited in the five clinical trials had experienced a prior MI, however, utilities associated with MI in patients with CHD or PAD are reported which may be useful as baseline estimates for the economic model. Although the study was conducted in the Netherlands, UK societal preferences were used to value health states and results may therefore be considered representative of a UK setting.
Bach, 2011 (103) Germany (Full publication)	This study does not meet the requirements of the NICE reference case; the preferred EQ-5D instrument was used to derive utilities directly from patients, however, German rather than UK societal preferences were used to value health states. This may be considered appropriate in the absence of higher quality evidence. The study reports utilities for patients with MI and both MI and stroke, and so may be considered comparable to the population of interest. The study was conducted in Germany, and German societal preferences were used to value health states; it is therefore unclear how representative the results from this study are of a UK setting. Additional limitations which may restrict the usefulness of the study for economic evaluation: Absence of measures of uncertainty for reported utilities Small sample size of patients with both MI and stroke.
Sullivan, 2011 (102) UK (Full publication)	Utilities reported in this study meet the requirements of the NICE reference case as they were derived directly from patients using the preferred EQ-5D, and health states were valued using UK societal preferences elicited using the TTO method (assumed from reference to Dolan 1997). Although the study population consisted of a sample from the general population in the US, the disutility associated to acute, old MI and acute cerebrovascular disease was reported and could be used in the economic model. The results from this study may be considered to be generalisable to a UK setting, as although a US general population sample was used to derive EQ-5D scores, the UK TTO tariff was used to value health states.

ACS: acute coronary syndrome; CABG: coronary artery bypass graft; CAP: Care Assessment Platform; CCC: Clinical Classification Categories; CHD: coronary heart disease; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FFR: fractional flow reserve; HRQL: health-related quality of life; HSE: Health Survey for England; HSUV: health state utility value; ICD: International Classification of Disease; IHD: ischaemic heart disease; IQR: interquartile range; KHNANES: Korean National Health and Nutrition Examination Survey; MEPS: Medical Expenditure Panel Survey; MI: myocardial infarction; NA: not applicable; NICE: National Institute for Health and Care Excellence; NR: not reported; NSTEMI: non-ST segment elevation myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; RIKS-HIA: The Register of Information and Knowledge about Swedish Heart Intensive Care Administrations; SD: standard deviation; SE: standard error; SEPHIA: Secondary Prevention after Heart Intensive Care Admission; STEMI: ST segment elevation myocardial infarction; TTO: time trade off; UA: unstable angina; UK: United Kingdom; US: United States.

† The distribution of subsequent CV events was as follows (overall, N=597): (i) heart failure hospitalisation, N=309; (ii) recurrent MI, N=214; (iii) stroke, N=57; (iv) resuscitated sudden death, N=17.

‡ Cardiovascular events (including death, MI, cerebrovascular accident, amputation, infrainguinal-vein-graft occlusion, extracranial bleeding, and re-interventions) occurring after the vascular intervention under study in the five clinical trials were considered to be secondary events.

Table 94. Relevance of identified HSUVs to NICE reference case

Study	Is EQ-5D used?	Do patients describe the health states?	Are appropriate societal preferences used?	Is the TTO/SG method used?	Is the study consistent with NICE body reference case?
Dreyer, 2016 (114)	Yes	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case; although utilities are derived directly from patients using the preferred EQ-5D instrument, it is unclear if societal preferences were used to value health states
Abdin, 2015 (111)	Yes	Yes	Yes – Singapore tariff	Yes - TTO	This study may meet the requirements of the NICE reference case; the preferred EQ-5D was used to derive utilities from patients, however, health states were valued using societal preference from Singapore, rather than the UK
Alabas, 2015 (98)	Yes	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case; although utilities were derived directly from patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states
Goss, 2015 (104)	Yes	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case; although utilities were derived directly from patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states
Nam, 2015 (99)	Yes	Yes	Yes – UK tariff	Yes – TTO (assumed from	This study meets the requirements of the NICE reference case; utilities were derived directly from

Study	Is EQ-5D used?	Do patients describe the health states?	Are appropriate societal preferences used?	Is the TTO/SG method used?	Is the study consistent with NICE body reference case?
				reference to Dolan 1997)	patients using the preferred EQ-5D instrument, and health states were valued using UK TTO societal preferences
Park, 2015 (107)	Yes	Yes	Yes – Korean tariff	Yes – TTO	This study may meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, however, Korean rather than UK societal preferences were used to value health states
Seidl, 2015 (105)	Yes	Yes	Yes – German tariff	Yes – TTO	This study may meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, however, German TTO rather than UK societal preferences were used to value health states
De Smedt, 2014 (113)	Yes	Yes	Yes – UK tariff	Yes – TTO	This study meets the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D instrument, and health states were valued using UK TTO societal preferences
Henriksson, 2014 (112)	Yes	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case; although utilities were derived directly from patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states
Koltowski, 2014 (110)	Yes	Yes	Yes – Polish tariff	Yes – TTO (assumed from reference to Golicki 2010)	This study may meet the requirements of the NICE reference case; patients described health states using the preferred EQ-5D, however, Polish rather than UK societal preferences were used to value health states

Study	Is EQ-5D used?	Do patients describe the health states?	Are appropriate societal preferences used?	Is the TTO/SG method used?	Is the study consistent with NICE body reference case?
Lewis, 2014 (115)	Yes	Yes	Yes – UK and US tariffs	Yes – TTO (assumed from reference to Dolan 1997)	This study meets the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, and health states were valued using UK societal preferences elicited using the TTO method (the US tariff was also used to value health states)
Pockett, 2014 (100)	Yes	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case; although utilities were derived directly by patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states
Varnfield, 2014 (108)	Yes	Yes	Yes – Australian tariff	Yes – TTO	This study may meet the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D, however, Australian rather than UK societal preferences were used to value health states
Kim, 2013 (106)	Yes	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case; although utilities were derived directly from patients using the preferred EQ-5D, it is unclear if societal preferences were used to value health states
Stafford, 2012 (101)	Yes	Yes	Yes- UK tariff	Yes – TTO (assumed from reference to Dolan 1996)	This study meets the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D and health states were valued using UK TTO societal preferences
Van Stel, 2012 (117)	Yes	Yes	Yes – UK tariff	Yes – TTO (assumed from reference to	This study meets the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D and health states

Study	Is EQ-5D used?	Do patients describe the health states?	Are appropriate societal preferences used?	Is the TTO/SG method used?	Is the study consistent with NICE body reference case?
				Dolan 1997)	were valued using UK TTO societal preferences
Bach, 2011 (103)	Yes	Yes	Yes – German tariff	Yes – TTO (assumed from reference to Greiner 2003)	This study may meet the requirements of the NICE reference case; the preferred EQ-5D was used to derive utilities from patients, however, health states were valued using German rather than UK societal preferences
Sullivan, 2011 (102)	Yes	Yes	Yes – UK tariff	Yes – TTO (assumed from reference to Dolan 1997)	This study meets the requirements of the NICE reference case; utilities were derived directly from patients using the preferred EQ-5D and health states were valued using UK TTO preferences

EQ-5D: European Quality of Life-5 Dimensions; NICE: National Institute for Health and Care Excellence; SG: standard gamble; TTO: time trade off; UK: United Kingdom.

In order to ensure that all relevant evidence are reviewed and collected, the NICE website was also searched aiming to explore the utility values used in other oral antiplatelet completed manufacture's submissions. Utility values of the following submissions were extracted and presented inside Table 95:

- NICE (2009). TA182: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention (118).
- NICE (2010). TA210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (119).
- NICE (2011). TA236: Ticagrelor for the treatment of acute coronary syndromes (120).
- NICE (2014). TA317: Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (121).
- NICE (2015). TA335: Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (122).

Table 95. Utility values used in past NICE submissions.

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Source
MI				
TA335(122, 123)	Utility	MI	• Utility (1st cycle): 0.779 • Utility (2nd cycle): 0.821 • Utility (3rd cycle): 0.821	Literature
	Utility	MI+MI	• Utility (1st cycle): 0.607 • Utility (2nd cycle): 0.674 • Utility (3rd cycle): 0.674	
	Utility	MI+IS	• Utility (1st cycle): 0.548 • Utility (2nd cycle): 0.614 • Utility (3rd cycle): 0.650	
	Utility	MI+HS/ICH	• Utility (1st cycle): 0.548 • Utility (2nd cycle): 0.614 • Utility (3rd cycle): 0.650	
	Utility	MI	0.78 (0.25, 1)	ATLAS 2 trial
TA317 (97, 121)	Event utility	Non-fatal MI	-0.037 (-0.147, 0.073)	Literature
TA236(120)	Utility	Non-fatal MI	• Ticagrelor: 0.786 (0.759, 0.814) • Clopidogrel: 0.774 (0.747, 0.802) • MM: 0.779 (0.760, 0.799)	PLATO HECON substudy
	Utility	Non-fatal MI	0.650 (0.620, 0.681)	Literature
	Utility	Post MI	MM: 0.821 (0.802, 0.841)	
	Utility	Post MI	0.685 (0.653, 0.717)	PLATO HECON substudy
TA210(119, 124)	Long term utility	After MI	• Patients with previous stroke: 0.61 • Patients with previous MI: 0.87 • Patients with previous PAD: 0.61 • Patients with MVD: 0.61	Literature
	Short term utility decrements	MI	• Patients with previous stroke: -0.058 • Patients with previous MI: -0.082	

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Source
			• Patients with previous PAD: -0.076 • Patients with MVD: -0.058	
TA182(97, 118)	Utility decrement compared to general population	MI	0.0524 (±0.0001)	
Stroke				
TA335(122, 123)	Utility	IS	• Utility (1st cycle): 0.703 • Utility (2nd cycle): 0.748 • Utility (3rd cycle): 0.792	Literature
	Utility	HS/ICH	• Utility (1st cycle): 0.703 • Utility (2nd cycle): 0.748 • Utility (3rd cycle): 0.792	
	Utility	IS+IS	• Utility (1st cycle): 0.494 • Utility (2nd cycle): 0.559 • Utility (3rd cycle): 0.627	
	Utility	IS+HS/ICH	• Utility (1st cycle): 0.494 • Utility (2nd cycle): 0.559 • Utility (3rd cycle): 0.627	
	Utility	HS/ICH+HS/ICH	• Utility (1st cycle): 0.494 • Utility (2nd cycle): 0.559 • Utility (3rd cycle): 0.627	
	Utility	Stroke	0.67 (0, 1)	ATLAS 2 trial
TA317 (97, 121)	Event utility	Non-fatal non disabling stroke	0 (0, -0.200)	Set to zero due to controversial values in the literature
	Event utility	Non-fatal disabling stroke	0 (0, -0.200)	Set to zero due to controversial values in the literature
	Utility in health state	Non-disabling stroke	• Male: 0.838 (0.821, 0.855) • Female: 0.769 (0.751, 0.786)	NR

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Source
	Utility in health state	Disabling stroke	• Male: 0.487 (0.463, 0.512) • Female: 0.418 (0.392, 0.443)	NR
TA236(120)	Utility	Non-fatal stroke	• Ticagrelor: 0.709 (0.588, 0.831) • Clopidogrel: 0.695 (0.632, 0.758) • MM: 0.703 (0.629, 0.778)	PLATO HECON substudy
	Utility	Post stroke	MM: 0.703 (0.629, 0.778)	PLATO HECON substudy
	Utility	Non-fatal stroke	0.595 (0.484, 0.707)	Literature
	Utility	Post stroke	0.595 (0.484, 0.707)	
TA210(119, 124)	Long term utility	After stroke	• Patients with previous stroke: 0.61 • Patients with previous MI: 0.61 • Patients with previous PAD: 0.61 • Patients with MVD: 0.61	Literature
	Long term utility	After Stroke and MI	• Patients with previous stroke: 0.61 • Patients with previous MI: 0.61 • Patients with previous PAD: 0.61 • Patients with MVD: 0.61	
	Short term utility decrements	Stroke	• Patients with previous stroke: -0.174 • Patients with previous MI: -0.248 • Patients with previous PAD: -0.228 • Patients with MVD: -0.174	
TA182(97, 118)	Utility decrement compared to general population	Stroke	0.0524 (±0.0001)	Literature
TIMI major bleed				
TA335(122, 123)	Utility	TIMI Major Bleed (excluding ICH)	0.77 (0.19, 1.00)	ATLAS 2 trial
TA210(119, 124)	Short term utility decrements	Major bleed	• Patients with previous stroke: -0.3 • Patients with previous MI: -0.3	Literature

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Source
			• Patients with previous PAD: -0.3 • Patients with MVD: -0.3	
TA182(97, 118)	Utility decrement compared to general population	Major bleed	0.007	Assumption
TIMI minor bleed				
TA335(122, 123)	Utility	TIMI Minor Bleed	0.84 (0.31, 1)	ATLAS 2 trial
	Utility	TIMI Bleed requiring medical attention	0.87 (0.47, 1)	ATLAS 2 trial
TA210(119, 124)	Short term utility decrements	Minor bleed	• Patients with previous stroke: -0.001 • Patients with previous MI: -0.001 • Patients with previous PAD: -0.001 • Patients with MVD: -0.001	Literature
CV-related death				
TA335(122, 123)	Utility	Fatal MI	• Utility (1st cycle): 0 • Utility (2nd cycle): 0 • Utility (3rd cycle): 0	Literature
	Utility	Fatal IS	• Utility (1st cycle): 0 • Utility (2nd cycle): 0 • Utility (3rd cycle): 0	
	Utility	Fatal HS/ICH	• Utility (1st cycle): 0 • Utility (2nd cycle): 0 • Utility (3rd cycle): 0	
	Utility	Other CV death	• Utility (1st cycle): 0 • Utility (2nd cycle): 0 • Utility (3rd cycle): 0	
TA317 (97, 121)	Event utility	Fatal MI	-0.100 (0, -0.200)	Notional value
	Event utility	Fatal stroke	-0.100 (0, -0.200)	
	Event utility	Other Vascular death	-0.100 (0, -0.200)	

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Source
Non-CV related death				
TA335(122, 123)		Non-CV death	• Utility (1st cycle): 0 • Utility (2nd cycle): 0 • Utility (3rd cycle): 0	Literature
TA317 (97, 121)		Non-vascular death	-0.100 (0, -0.200)	Notional value
Long term No event				
TA335(122, 123)	Utility	No further ACS event	• Utility (1st cycle): 0.842 • Utility (2nd cycle): NA • Utility (3rd cycle): NA	Literature
TA317 (97, 121)	Event utility	Event free/MI only	0.874 (0.869-0.880)	NR
TA236(120)	Utility	No further event	• Ticagrelor: 0.840 (0.834, 0.846) • Clopidogrel: 0.844 (0.838, 0.850) • MM: 0.842 (0.838, 0.846)	PLATO HECON substudy
		No further event	0.711 (0.693, 0.730)	Literature
TA210(119, 124)	Long term utility	No event	• Patients with previous stroke: 0.61 • Patients with previous MI: 0.87 • Patients with previous PAD: 0.80 • Patients with MVD: 0.61	Literature

Differences between values obtained in the literature search and those reported in the trial

Table 96: Comparison of the utility values taken from literature and those collected in PEGASUS-TIMI 54 trial

Health state/ Event	Value from trial	Value form literature	Difference	Literature reference
Non-fatal MI	-0.0474	-0.0626	+0.0152	Sullivan et al 2011
		-0.0524	+0.0050	TA182
		-0.0820	+0.0346	TA210
		-0.0630	+0.0156	TA236
		-0.0370	-0.0104	TA317
		-0.0630	+0.0156	TA335
Non-fatal stroke	-0.0934	-0.0524	-0.0410	TA182
		-0.2480	+0.1546	TA210
		-0.1390	+0.0456	TA236
		-0.1390	+0.0456	TA335
Post non-fatal MI	-0.0342	-0.1800	+0.1458	Lewis et al 2014
		-0.1390	+0.1048	Stafford et al 2011
		-0.0368	+0.0026	Sullivan et al 2011
		0	-0.0342	TA210
		-0.0210	-0.0132	TA236
		0	-0.0342	TA317
		-0.0210	-0.0132	TA335
Post non-fatal stroke	-0.0665	-0.0600	-0.0065	Lewis et al 2014
		-0.1600	+0.0935	Stafford et al 2011
		-0.1009	+0.0344	Sullivan et al 2011
		-0.1390	+0.0725	TA236
		-0.2600	+0.1935	TA317
		-0.0500	-0.0165	TA335
Dyspnoea (Grade 3-4)	-0.0481	N/A	N/A	N/A
Dyspnoea (Grade 1-2)	-0.0154	N/A	N/A	N/A
TIMI minor bleed	-0.0129	-0.0010	-0.0119	TA210
		-0.0420	+0.0291	TA335
TIMI major bleed	-0.0466	-0.0070	-0.0396	TA182
		-0.3000	-0.0166	TA210

		-0.0920	+0.0454	TA335

Based on the findings of the SLR for HRQL it was decided that the utility values from TA335 (122) and Sullivan et al. 2011 (102) were most appropriate for use within sensitivity analyses, on account of TA335 providing disutility values for the broadest number of endpoints and Sullivan providing differentiated disabilities for the acute and longer term time periods following MI.

Adverse reactions

Bleeding is an important safety issue for all antiplatelet medications. A TIMI major bleeding event will require in-patient hospitalisation and is likely to have a high impact on HRQL, though this is likely to be short-term in nature (3-months HRQL impact assumed in the cost-effectiveness model). EQ-5D data collected in the PEGASUS TIMI 54 trial suggests that the impact of a TIMI major bleed on HRQL is similar in magnitude to the impact of the acute phase of a myocardial infarction (first 3 months following MI). As expected, TIMI minor bleeding events are less severe than TIMI major bleeds and based on the collected EQ-5D data are assumed to impact HRQL for 30 days.

Dyspnoea was another observed adverse reaction in the PEGASUS-TIMI 54 study. Dyspnoea is a feeling of breathlessness which refers to the sensation of shortness of breath or difficulty breathing. As a symptom it can be both distressing and frightening for patients however, dyspnoea cases observed in the study were usually rated as mild or moderate in severity. The impact of dyspnoea on HRQL is likely to be transient and minor.

Health-related quality-of-life data used in cost-effectiveness analysis

The impact on patients' HRQL of non-fatal CV events comprises an acute phase and a chronic phase. Acute symptoms of a MI include central chest pain, which may spread to the arms, neck or jaw, feeling sick or sweat or short of breath. Patients suffering a ST-segment elevation MI are recommended to receive percutaneous coronary intervention. Patients suffering a non-ST-segment elevation MI are recommended to have early coronary angiography and revascularisation. Symptoms, treatment and hospitalisation all impact on HRQL. However, this is likely

to be a short-term decrement (3 months assumed in the model) and a patient's HRQL is likely to improve thereafter. Longer-term impacts, modelled as the post-MI health state in the economic model, can include reduced fitness/ capacity to maintain activities of daily living and anxiety about future events. Repeated events can have a cumulative impact on patients overall health and quality of life.

Symptoms of acute stroke include trouble with speaking and understanding, confusion, paralysis or numbness of the face, arm or leg, trouble with vision, headache and trouble walking. Symptoms and hospitalisation impact HRQL, with patients often being hospitalised for a significant number of days. The acute utility impact is applied for 3 months assumed in the economic model. The long term impact of non-fatal stroke on quality of life is dependent on the severity of the stroke. In PEGASUS-TIMI 54, 22.9% of non-fatal stroke events were disabling, which bring a debilitating impact and results in long term impact on quality of life, ability to perform usual activities and the need for long term care. Patients with non-disabling often recover much and sometimes all of the function lost at the time of the acute event however, typically this is only achieved after long term rehabilitation designed to facilitate restoration of, or adaptation to, the loss of physiological or psychological function, so as to enhance functional activities and participation in society.

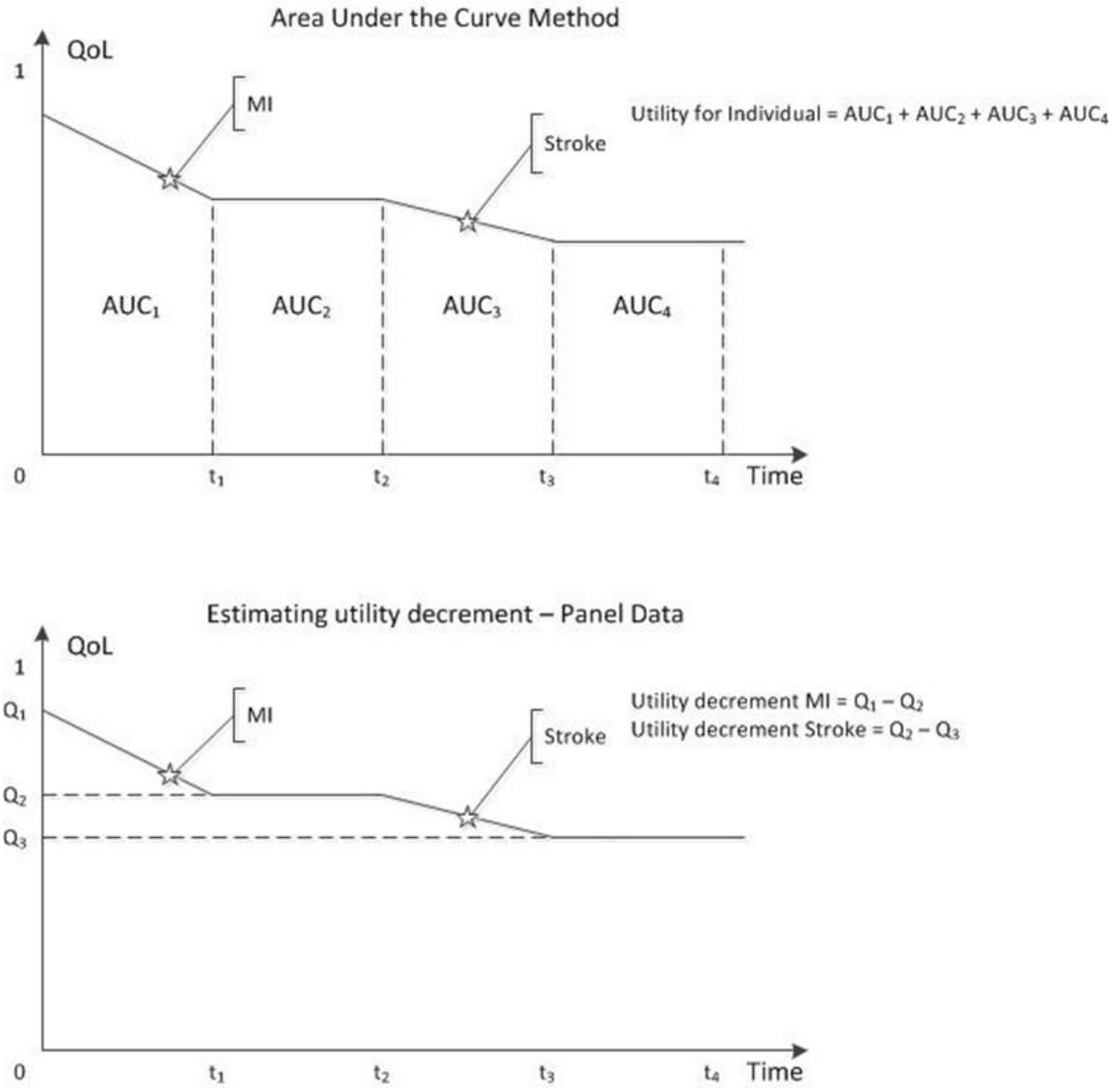
How HRQL changes over the course of the disease or condition.

The EQ-5D-3L health status questionnaire was used to collect HRQL data for patients in the PEGASUS-TIMI 54 study. These data were collected at baseline, at 8 months, 12 months, 18 months and subsequently every 6 months until the end of follow-up.

The UK TTO valuations have been used as a default for the EQ-5D-3L questionnaire, converting questionnaire responses to utilities which are applied in the economic model. Utility decrements (controlling for baseline characteristics) are estimated for the health states of living patients in the model. Panel data methods have been used to estimate utility decrements for the following events: non-fatal MI; post non-fatal MI; non-fatal stroke; post non-fatal stroke; TIMI major bleeds; TIMI minor bleeds; dyspnoea (grade 3–4); dyspnoea (grade 1–2).

The panel data method differs from an area-under-the-curve (AUC) approach, since a decrement in utility is estimated rather than the overall observed utility for an individual. This is illustrated in Figure 47, where the panel data approach for utility decrement estimation is focused on the magnitude of the drop in utility following an event. With these values estimated, a utility decrement can be applied in the economic model, when an event occurs.

Figure 47: Comparison of utility estimation methods



Response rates for the EQ-5D for each of the pre-determined collection dates are outlined in Table 97. Overall the response rate for the EQ-5D questionnaire was

high. For those participants who did not complete a questionnaire, the following observations can be made:

- Those who were cognitively incapable or refused constituted a small proportion of those who did not respond at the predetermined visits.
- For those who didn't complete the questionnaire at each pre-determined visit, the major reason provided for non-completion was 'interview held over phone'.

Table 97: EQ-5D questionnaire response rate

Approx month	Completed EQ5D questionnaire				Total
	Yes (n, %)	No (n, %)	Cognitively incapable	Refused	
0	20,573 (97.4)	558 (2.6)	5	18	21,131
8	19,097 (91.9)	1,685 (8.1)	23	352	20,782
12	17,815 (88.0)	2,418 (12.0)	15	312	20,233
18	17,147 (87.4)	2,477 (12.6)	15	289	19,624
24	15,941 (86.3)	2,527 (13.7)	14	283	18,468
30	13,755 (86.6)	2,132 (13.4)	13	209	15,887
36	9,779 (85.9)	1,609 (14.1)	13	150	11,388
42	4,162 (81.6)	937 (18.4)	5	76	5,099
48	464 (63.1)	271 (36.9)	0	30	735
54	12 (50.0)	12 (50.0)	0	0	24
Total	118,745 (89.0)	14,626 (11.0)	103	1,719	133,371

Since HRQL trial data were collected at set intervals during the course of the PEGASUS-TIMI 54 study, as opposed to following events, it was necessary to apply a window of time to determine whether an event occurred within a cycle.

Since the model uses 3-month cycles, a window of 91 days prior to EQ-5D data collection has been applied. Making this distinction is particularly important for estimating a long-term decrement associated with MI and stroke. Variables that use the cycle duration of 91 days as a window are denoted with 'cd91' in Table 98. Where transient events such as bleeds and dyspnoea are not associated with a statistically significant utility decrement with a 91-day window, a shorter 30-day window was applied (this is denoted with 'cd30' in Table 98).

Table 98: Utility decrements using UK TTO tariff on the trial based EQ-5D responses

Variable	Coef.	p-value	Lower 95% CI	Upper 95% CI
cd30_minorBld	-0.0393	0.1000	-0.0861	0.0075
cd91_majorBld	-0.0466	<0.0001	-0.0649	-0.0283
SAEdys	-0.0253	0.1160	-0.0569	0.0063
cd91_AEdys	-0.0154	<0.0001	-0.0233	-0.0075
cd91_MI	-0.0474	<0.0001	-0.0590	-0.0358
cd91_prevMI	-0.0342	<0.0001	-0.0416	-0.0267
cd91_Stroke	-0.0934	<0.0001	-0.1130	-0.0737
cd91_prevStroke	-0.0665	<0.0001	-0.0803	-0.0526
sex	0.0627	<0.0001	0.0576	0.0677
age	-0.0018	<0.0001	-0.0021	-0.0015
bmi	-0.0040	<0.0001	-0.0044	-0.0035
dmtype	-0.0141	<0.0001	-0.0186	-0.0096
MI_HIST	-0.0163	<0.0001	-0.0218	-0.0108
smk_his1	-0.0059	0.0150	-0.0106	-0.0011
smk_his2	-0.0338	<0.0001	-0.0402	-0.0275
anpect	0.0400	<0.0001	0.0344	0.0457
pci	-0.0346	<0.0001	-0.0392	-0.0300
qevtyp2	0.0052	0.0150	0.0010	0.0094
MEDTDDOS_n	-0.0001	0.0200	-0.0003	0.0000
dbpsup	-0.0003	0.0020	-0.0006	-0.0001
hyp	0.0048	0.0620	-0.0002	0.0098
hypchol	-0.0180	<0.0001	-0.0231	-0.0128
cohdhist	-0.0070	0.0020	-0.0116	-0.0025
stroke	-0.0553	<0.0001	-0.0851	-0.0254
tria	-0.0489	<0.0001	-0.0673	-0.0305
chf	-0.0521	<0.0001	-0.0576	-0.0467
spbleed	-0.0227	0.0120	-0.0404	-0.0050
Asia_Australia	0.0600	<0.0001	0.0526	0.0674
NthAmerica	-0.0052	0.0730	-0.0109	0.0005
histPAD	-0.0444	<0.0001	-0.0534	-0.0355
creatinine_cl	0.0189	<0.0001	0.0130	0.0247
_cons	1.0692	<0.0001	1.0356	1.1029
sigma_u	0.1394			
sigma_e	0.1174			
rho	0.5851			

A value of 1 represents perfect health for 1 year. minorBld=TIMI minor bleed, majorBld=TIMI major bleed; SAEdys=grade 3–4 dyspnoea; AEdys=grade 1–2 dyspnoea

Due to the low numbers of events observed in PEGASUS-TIMI 54 for grade 3–4 dyspnoea it was not possible to estimate a utility decrement using either a 91-day or a 30-day window. However, a utility decrement could be estimated using the full-time interval between EQ-5D questionnaire collection points, which on average was 174 days. Practically, this duration is longer than the modelled cycle length, hence the disutility associated with grade 3–4 dyspnoea is factored up by 1.9 (173.57 /

91.3215). The utility decrements applied for events and health states in the model for each cycle are summarised in Table 99.

Table 99: QALY decrements applied in the economic model

	Duration of utility decrement	QALY decrement (cycle length adjusted utility decrement)
Events (transient event)		
Non-fatal MI	91 days (x1)	-0.0118
Non-fatal stroke	91 days (x1)	-0.0233
TIMI major bleed	91 days (x1)	-0.0117
TIMI minor bleed	30 days (x0.33)	-0.0032
Dyspnoea (grade 3–4)	174 days (x1.9)	-0.0120
Dyspnoea (grade 1–2)	91 days (x1)	-0.0038
Health states (permanent state)		
Post non-fatal MI	91 days (x1)	-0.0085
Post non-fatal stroke	91 days (x1)	-0.0166

Coefficients in Table 98 represent change in utility. QALY change (decrement) calculated here by adjusting for cycle length.

The baseline HRQL used in the cost-effectiveness analysis

Baseline utilities were estimated using coefficients associated with the individuals' characteristics. The model calculates a baseline utility, excluding the coefficient associated with age. The age coefficient is added into an age-dependent utility matrix, to reflect patients' overall utility and to account for a decline in base utility associated with aging. Since a linear random effect panel data analysis has been used to estimate utility decrements associated with characteristics and events, it is technically possible for an individual's utility to be >1. To avoid this, the model imposes a cap to the individual's base utility. Average utility at baseline (UK TTO) is outlined in Table 100.

Table 100: Average utility at baseline (first visit)

	N	Model baseline average (UK TTO)
Ticagrelor 90 mg BID + low-dose ASA	6,855	0.8505
Ticagrelor 60 mg BID + low-dose ASA	6,841	0.8505
Low-dose ASA	6,873	0.8493
Total	20,569	0.8501

After adjusting the baseline utility from PEGASUS-TIMI 54 for age, patients 60 years of age had a utility of 0.84276 whilst patients 80 years of age had a utility of 0.80703. These are considerably higher than those estimated for the UK general population (125) of 0.78 and 0.81 for patients aged 60 years, and 0.75 and 0.71 for male and female patients aged 80 years, respectively (see Table 101). It was assumed that the patient population under consideration within the model was unlikely to have a higher baseline utility than that of the UK general population. Therefore, in the base case the baseline utility was assumed to be the same as that of the UK general population, which decreases over time with a linear reduction within each age banding. A sensitivity analysis examined the impact of using the PEGASUS-TIMI 54 values.

Table 101: Utility by age in the UK general population (Kind et al 1999)

Age Group	Male utilities	SE	Female utilities	SE
<25	0.94	0.011	0.94	0.009
25–34	0.93	0.009	0.93	0.007
35–44	0.91	0.011	0.91	0.007
45–54	0.84	0.018	0.85	0.014
55–64	0.78	0.020	0.81	0.015
64–75	0.78	0.019	0.78	0.016
>75	0.75	0.027	0.71	0.019

To determine patients' overall utility, a base utility score is combined with the utility decrements. Disutilities for events and health states were taken from PEGASUS-TIMI 54 (see section 5.4.8).

Adjustment of the health state utility values

All adjustments are detailed in sections 5.4.8 and 5.4.9.

Health effects found in clinical trials that were excluded

A small excess of gout was observed in PEGASUS-TIMI 54 for ticagrelor 60mg BID vs. placebo (0.46% ARI; HR 1.48; 95% CI 1.10 to 2.00; p=0.01). Gout is not modelled as an adverse event within the economic model. Further explanation in this regard is provided at section 5.11.1.

Summary of the utility values chosen for the model

A summary of utility values used in the cost-effectiveness analysis are detailed in Table 102.

Table 102: Summary of utility values for cost-effectiveness analysis

State	Utility	Justification
Baseline	UK population norm (age and gender specific)	Baseline utility in PEGASUS-TIMI 54 is considerably higher than UK general population
Non-fatal MI	-0.0474	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Non-fatal stroke	-0.0934	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Post MI	-0.0342	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Post stroke	-0.0665	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Dyspnoea (Grade 3-4)	-0.0481	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Dyspnoea (Grade 1-2)	-0.0154	Taken from PEGASUS-TIMI 54 in line with NICE reference case
TIMI minor bleed	-0.0129	Taken from PEGASUS-TIMI 54 in line with NICE reference case
TIMI major bleed	-0.0466	Taken from PEGASUS-TIMI 54 in line with NICE reference case

Details of clinical expert assessment of the utility values

Please see section 5.3.4.

5.5 Cost and healthcare resource use identification, measurement and valuation

Table 103 details the acute inpatient, acute outpatient and maintenance, long term outpatient and maintenance, and adverse event costs used within the cost-effectiveness model.

Table 103: List of resource use and associated costs in the economic model

Resource use	Value
Inpatient	
Non-fatal MI	£4,476.18
Non-fatal stroke	£4,925.76
Fatal events (CAD and non-CAD)	£2,497.83

'No event'	£2,497.83
Outpatient and maintenance	
Post non-fatal MI (0-3 months)	£639.45
Post non-fatal MI (3-6 months)	£639.45
Post non-fatal MI (6-9 months)	£319.73
Post non-fatal MI (9-12 months)	£319.73
Post non-fatal MI (12+ months, every cycle)	£160.31
Post non-fatal stroke (0-3 months)	£1,343.39
Post non-fatal stroke (3-6 months)	£1,119.49
Post non-fatal stroke (6-9 months)	£877.57
Post non-fatal stroke (9-12 months)	£689.71
Post non-fatal stroke (12+ months, every cycle)	£689.71
'No event' (every cycle)	£160.31
Adverse events	
Grade 3-4 Dyspnoea	£732.98
Major TIMI bleed	£2,206.87
Minor TIMI bleed	£122.48

Resource identification, measurement and valuation studies

Alongside the economic literature search, two separate literature reviews were facilitated in Pubmed aiming to obtain articles reporting cost data for pre-specified health states incorporated in the economic analysis of this decision problem. To ensure that all health states of interest are captured, one search focused on MI/ACS studies/evidence aiming to capture resource use data on the following:

• Cost of MI event health state

• Cost of CV related death health state

• Cost of non-CV related death health state

• Cost of TIMI major and minor bleeding event

• Cost of dyspnoea

Data for the health state of stroke were also essential for informing the model for which a separate search was facilitated. The relevant search strategy for both searches is presented inside Appendix 14 (Table 25). As demonstrated in Figure 48 and Figure 49, the MI/ACS and stroke searches yield 233 and 425 articles

respectively that were screened according to pre-specified criteria (Appendix 14; Table 26 and Table 27 for MI/ACS and stroke correspondingly). Once screened, included articles from both searches were grouped and data were extracted for each field of interest. All Pubmed records were exported in Endnote X7 and Excel 2013 in order to be abstract, full text screened and data extracted. Articles included twice as relevant from both reviews were only data extracted once.

Figure 48. PRISMA flow diagram for MI/ACS studies screened in resource use review

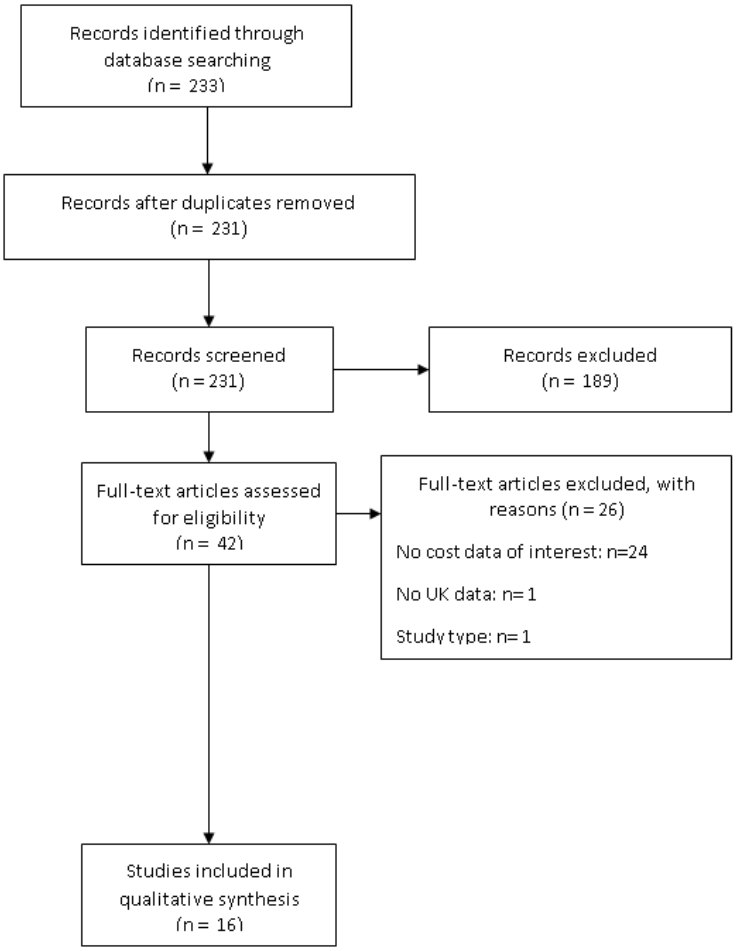
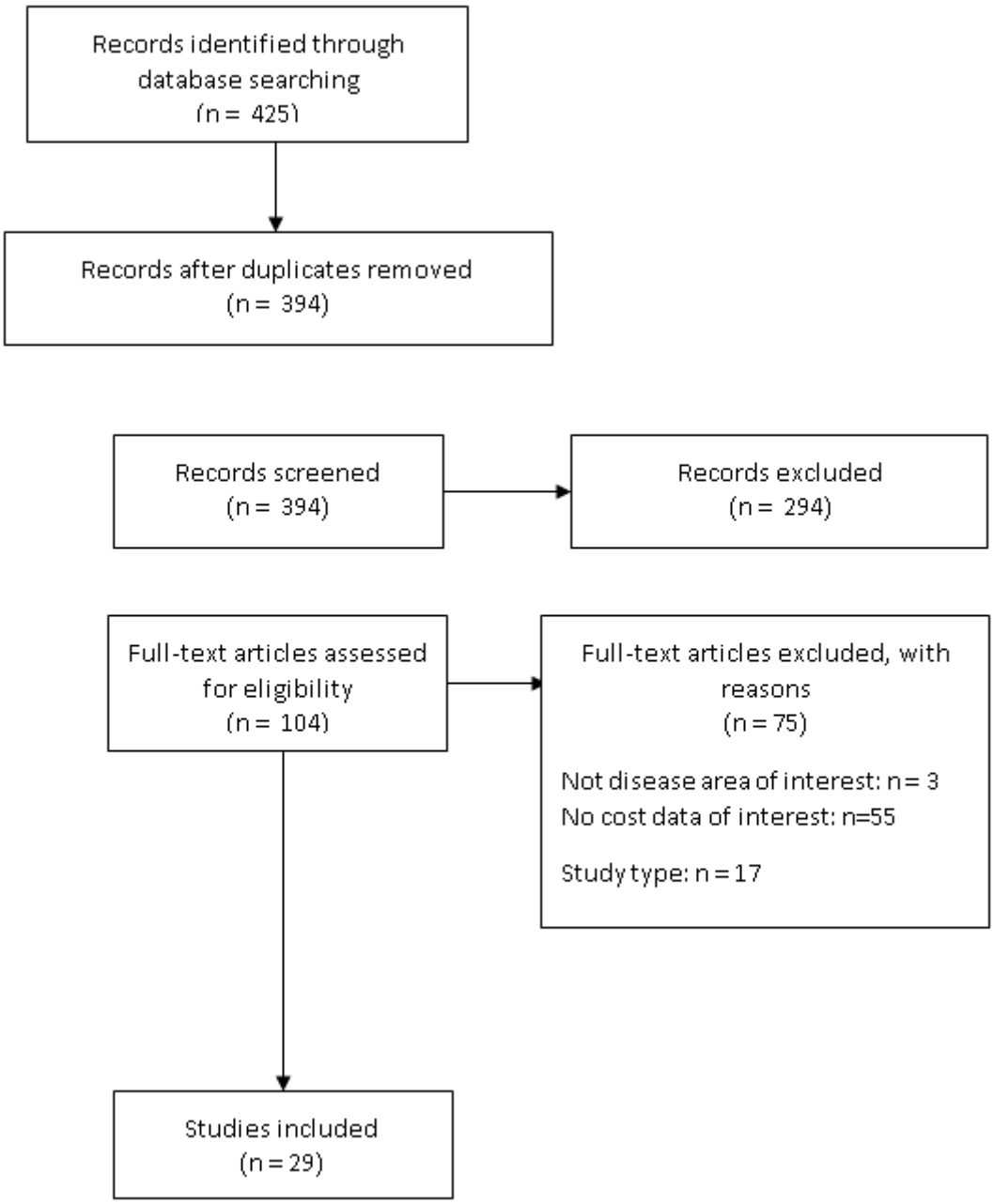


Figure 49. PRISMA flow diagram for stroke studies screened in resource use review


Records identified through database searching (n = 425)
Records after duplicates removed (n = 394)
Records screened (n = 394)
Records excluded (n = 294)
Full-text articles assessed for eligibility (n = 104)
Full-text articles excluded, with reasons (n = 75)
Not disease area of interest: n = 3
No cost data of interest: n=55
Study type: n = 17
Studies included (n = 29)

In total, 45 articles were included from both searches at full text review (MI review: n=16, Figure 48; Stroke review: n=19, Figure 49) out of which seven studies (99, 126-131) were common and are counted as a single data record in the results. This led to a total of 38 appropriate studies (Appendix 14; Table 28) results of which are presented in the following tables of Appendix 14:

- Resource use data for the state of MI, Table 29. Data were collected for both acute and subsequent care where appropriate.

- Resource use data for the state of stroke, Table 30. Stroke costs relevant to index event but also costs associated with care after the index event and rehabilitation were also extracted when provided.

- Resource use data for the state of TIMI bleeding, Table 31. Only costs associated with TIMI major bleeding, when defined as such, were collected in accordance with the modelling approach for this health state category.

- Resource use data for the state of death (CV and non-CV related), Table 32. CV related death cost data either as individual CV events or as a total were collected along with cost of death data that were not associated to a CV event.

- Long term cost of not having an event, Table 33. This cost group was only relevant to studies presenting data for ACS patients and referred to the state of not experiencing an event.

Although dyspnoea was amongst the cost groups of interest, no resource use data were detected for this state.

For completeness, the NICE website was also searched to identify any relevant, completed HTA submissions of other oral antiplatelet treatments. The results of this search identified the following potentially relevant HTA submissions:

- NICE (2009). TA182: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention (118).

- NICE (2010). TA210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (119).
- NICE (2011). TA236:Ticagrelor for the treatment of acute coronary syndromes (120).
- NICE (2014). TA317: Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (121).
- NICE (2015). TA335: Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (122).

Information obtained from this search were also data extracted in an identical manner to the literature review studies. Results are presented in Table 104 below.

Table 104. NICE submissions relevant to the decision problem

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Outcome Source as Provided by Article
MI				
TA335(122, 123)	ACS event	MI	• Acute care (1st 3 months): £3,586 • Follow: on care (2nd 3 months): £1,980 • Cost (3rd and 4th 3 months): £1,440 • Cost (later 3 months): £540	(94, 132)
TA317 (97, 121)	Cost of event	Non-fatal MI	£6165.21 (SE: £314.55; £5,548.69-£6,781.73*)	(119)
TA236(120)	Health state cost	MI	• Ticagrelor: £16,643 • Clopidogrel: £16,362	NR
TA210(119, 124)	Event cost	Non-fatal MI (Rankin 0-2)β	£5,761.88	(133)
		Non-fatal MI (Rankin 3-5)α	£5,761.88	
		Non-fatal MI, annual continuing care cost	£577.60	
TA182(97, 118)	Cost per episode	Non-fatal MI	• Clopidogrel: £1,492 • Pasugrel: £1,492	NHS reference costs 2006-2007
Stroke				
TA335(122, 123)	ACS event	IS	• Acute care (1st 3months): £7,756 • Follow: on care (2nd 3 months): £3,060 • Cost (3rd and 4th 3 months): £4,200	(94, 132)

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Outcome Source as Provided by Article
			• Cost (later 3 months): £1,560	
		HS/ICH	• Acute care (1st 3months): £12,778 • Follow: on care (2nd 3 months): £3,060 • Cost (3rd and 4th 3 months): £4,200 • Cost (later 3 months): £1,560	
TA317 (97, 121)	Cost of event	Non-fatal non-disabling stroke	£6,858.64 (SE: £349.93; £6,172.77-£7,544.50*)	(119)
		Non-fatal disabling stroke	£14,602.70 (SE: £754.04; £13,142.43-£16,062.97*)	
		Non-disabling stroke – long term	£1,804.06 (SE: £92.04; £1,623.66-£1,984.47*)	
		Disabling stroke – long term	£5,537.72 (SE: £282.54; £4,983.95-£6,091.50*)	
TA236(120)	Health state cost	Non-fatal Stroke	• Ticagrelor: £15,394 • Clopidogrel: £17,483	(134)
TA210(119, 124)	Event cost	Non-fatal IS (Rankin 0-2)β	£6,409.94	(134)
		Non-fatal IS (Rankin 3-5)α	£13,674.38	
		Non-fatal haemorrhagic stroke / ICH (Rankin 0-2)β	£6,409.94	
		Non-fatal haemorrhagic stroke / ICH	£13,647.38	

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Outcome Source as Provided by Article
		(Rankin 3-5)[α]		
		Non-fatal non-disabling stroke, annual continuing care cost	£1,686.04	
		Non-fatal disabling stroke, annual continuing care cost	£5,175.44	
TA182(97, 118)	Cost per episode	Non-fatal Stroke	• Clopidogrel: £1,932 • Pasugrel: £1,822	NHS reference costs 2006-2007
TIMI major bleed				
TA335(122, 123)	ACS event	Major Bleed	£670.00	National Reference Costs 2012-2013
TA210(119, 124)	Event cost	Major bleeding event	£2,010.35	(135)
TA182(97, 118)	Cost per episode	Major bleed	• Clopidogrel: £1,155 • Pasugrel: £1,155	NHS reference costs 2006-2007
TIMI minor bleed				
TA335(122, 123)	ACS event	Minor Bleed	£68.00	National Reference Costs 2012-2013
TA210(119, 124)	Event cost	Minor bleeding event	£111.57	(135)
TA182(97, 118)	Cost per episode	Minor bleed	• Clopidogrel: £1,382 • Prasugrel: £1,604	NHS reference costs 2006-2007
CV-related death				

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Outcome Source as Provided by Article
TA335(122, 123)	ACS event	Fatal MI	£1,500.00	(94, 132)
		Fatal IS	£4,500.00	
		Fatal HS/ICH	£4,500.00	
		Other CV Death	£3,000.00	
TA317 (97, 121)	Cost of event	Other Vascular death	£2407.50 (SE: £122.83; £2,166.75-£2,648.25)	(119)
		Fatal MI	£2373.68 (SE:£121.11; £2,136.31-£2,611.05*)	
		Fatal Stroke	£9381.43 (SE: £478.64; £8,443.29-£10,319.57*)	
TA210(119, 124)	Event cost	Fatal MI (Rankin 0-2)[β]	£2,218.39	(133)
		Fatal MI (Rankin 3-5)[α]	£2,218.39	
		Other vascular death (Rankin 0-2)[β]	£2,225.00	NR
		Other vascular death (Rankin 3-5)[α]	£2,225.00	NR
		Fatal IS (Rankin 0-2)[β]	£8,767.69	(134)
		Fatal IS (Rankin 3-5)[α]	£8,767.69	
		Fatal haemorrhagic stroke / ICH	£8,767.69	

Author, year	Type of outcome	Definition of outcome as provided by article	Outcome	Outcome Source as Provided by Article
		(Rankin 0-2)[β]		
		Fatal haemorrhagic stroke / ICH (Rankin 3-5)[α]	£8,767.69	
Non-CV related death				
TA335(122, 123)	ACS event	Non CV Death	£300.00	(94, 132)
TA317 (97, 121)	Cost of event	Non-vascular death	£2407.50 (SE: £122.83; £2,166.75-£2,648.25*)	(119)
TA210(119, 124)	Event cost	Other non-vascular death (Rankin 0-2)[β]	£2,225.00	NR
		Other non-vascular death (Rankin 3-5)[α]	£2,225.00	
Long term cost of not having an event				
TA335(122, 123)	ACS event	No Further ACS Event	£0.00	NR
TA317 (97, 121)	Cost of event	Event free/MI only	£618.03 (SE: £31.53; £556.23-£679.84*)	(119)
TA236 (120)	Health state cost	No event	• Ticagrelor: £8,544 • Clopidogrel: £8,633	NR
TA210(119, 124)	Event cost	No Key events, annual continuing care cost	£0.00	NR

ACS: Acute coronary syndrome; CV: Cardiovascular; HS: Haemorrhagic stroke; HS/ICH: Haemorrhagic stroke/ Intracranial haemorrhage; ICH: Intracranial haemorrhage; IS: Ischaemic stroke; MI: Myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction

*95% Confidence interval, α Disabled, β Non-disabled.

From submissions listed inside Table 104, the ERG cost data suggested in the review of TA317(121) were considered as appropriate to inform the decision problem of this submission and were inflated to 2015 values and adopted for the base case scenario. However, TA317(121) did not provide data for all health states of interest therefore such information was supplemented from the ERG review of TA210 and the NHS reference costs 2014/2015 (Table 106). Health state cost data used for the TA335(122) manufacturer submission and presented in Table 104 above were incorporated into a scenario analysis, presented at section 5.8 below.

Costing of the clinical management of atherothrombotic events in the NHS

While NHS reference or healthcare resource group (HRG) costs could have been used to populate events that occur within the cost-effectiveness model a comparison against previous technology appraisals, in similar patients and indications, found that NHS reference and HRG costs appear to underestimate the total cost of events. For example, the weighted average cost of EB10A-E; 'Actual or suspected myocardial infarction' is £1,468.51, whilst in TA317(97) the cost for a non-fatal MI event is £6,165.21. This is because EB10A-E does not capture the cost of procedures associated to the MI being treated, such as PCI or CABG. Costs from Evidence Review Group (ERG) developed models associated to previous NICE technology appraisals for oral antiplatelets were used where possible and inflated to 2015 values. NHS reference costs were used to calculate the cost of an inpatient event for grade 3–4 dyspnoea (weighted average of DZ19 'Other Respiratory Diseases') owing to a lack of published values.

Approximation of healthcare costs by clinicians

Not applicable. Costs sourced from ERG models developed for previous NICE appraisals and NHS reference costs.

Intervention and comparators' costs and resource use

Summary of the cost and associated healthcare resource use of each treatment

As detailed at section 2.3, the cost of ticagrelor 60mg is £54.60 for 28 days supply, which equates to £1.95 a day. We have used the generic medicine cost for aspirin of £0.03 per day (136).

Table 105: Unit costs associated with the technology in the economic model

Technology	Daily dose	Cost per day	Cost per cycle*
ASA	75 mg	£0.03	£2.64
Ticagrelor 60mg	120 mg	£1.95	£178.06

*The cycle length is 3 months, or 91.3125 days.

Health-state unit costs and resource use

Summary of health state unit costs

The model includes costings for four broad categories:

- acute inpatient costs
- acute outpatient and maintenance costs (within 12 months from event)
- long-term outpatient and maintenance costs (over 12 months from event)
- adverse events.

Unit costs were obtained from the ERG assessment report of TA317 (97) where possible and inflated to 2015 values (132). Where TA317 was unable to provide unit costs, costs were supplemented by the ERG assessment report TA210 (124) and NHS reference costs (137). Table 106 details all the costs taken from these sources, inflated to 2015 values. Both ERG models used a one year cycle length and therefore the 'event' costs sourced from the ERG assessment reports represent the cost applied for the year following occurrence of the event.

Table 106: Unit costs for events and health states

Event	Source	Original value	2015 value

Non-fatal MI	ERG TA317(97)	£6,165.21	£6,394.54
Non-fatal non-disabling stroke	ERG TA317(97)	£6,858.64	£7,115.99
Non-fatal disabling stroke	ERG TA317(97)	£14,602.70	£15,150.62
Other vascular death	ERG TA317(97)	£2,407.50	£2,497.83
Non vascular death	ERG TA317(97)	£2,407.50	£2,497.83
Grade 3-4 dyspnoea	NHS Reference Cost(137)		£732.98
Major TIMI bleed	TA210 ERG model (124)	£2,010.35	£2,206.87
Minor TIMI bleed	TA210 ERG model (124)	£111.57	£122.48
Annual cost in health state			
Event free/ post non-faatal MI	ERG TA317(97)	£618.03	£641.22
Post non-fatal non-disabling stroke	ERG TA317(97)	£1,804.06	£1,871.75
Post non-fatal disabling stroke	ERG TA317(97)	£5,537.72	£5,745.51

Given the considerable difference, both clinically and economically, between a disabling and non-disabling stroke, a weighted average cost for non-fatal stroke was generated using the Rankin score of patients with strokes from PEGASUS-TIMI 54 and the costs for non-fatal stroke (disabling and non-disabling) from TA317 (see Table 107). This approach has been necessary as the risk equation within the model did not differentiate between non-disabling and disabling stroke. Within the PEGASUS-TIMI 54 trial, 77.1% of patients had a stroke with a Rankin score of 0–2 (non-disabling), whilst 22.9% of patients had a stroke with a Rankin score of 3–5 (disabling). This information was used to caculate the annual weighted cost, as presented at Table 107.

Table 107: Non-fatal stroke cost (annual cost)

Year of Event	Cost	Events (%)
Non-fatal non-disabling stroke	£7,115.99	77.1
Non-fatal disabling stroke	£15,150.62	22.9
Non-fatal stroke (weighted average)	**£8,955.92**	

Inpatient costs

The cost-effectiveness model includes acute inpatient costs for non-fatal MI, non-fatal stroke, fatal events (CVD and non-CVD) and hospitalisations due to non-CVD events ('no events'). Inpatient costs are applied in the model in the cycle in which the event occurs, conditional upon the event resulting in a hospitalisation. Due to the potential range of 'no event' inpatient costs, we have assumed that the inpatient cost of 'no event' would be the same as the cost of fatal events (Table 108).

Table 108: Inpatient costs for non-CVD events and fatal events

Event	Cost
Non-CVD events ('no events')	£2,497.83
Fatal events (CVD and non-CVD)	£2,497.83

As already noted there is a considerable difference between the inpatient cost from the NHS reference costs and the event costs for non-fatal MI and non-fatal stroke from TA317.(97) In order not to overstate the initial acute inpatient costs, we have assumed that the costs from TA317 are representative of the cost for the first 12 months from the event. We have assumed that 70% of the cost of the non-fatal MI is accrued as an inpatient whilst 55% of the cost of a non-fatal stroke (both disabling and non-disabling) is accrued as an inpatient (Table 109). The remainder is accrued as an outpatient and maintenance cost.

Table 109: Inpatient costs for non-fatal MI and non-fatal stroke

	Percentage of annual non-fatal MI cost	Non-fatal MI cost	Percentage of annual non-fatal stroke cost	Non-fatal stroke cost
Inpatient cost	70%	£4,476.18	55%	£4,925.76

Outpatient and maintenance costs

The cost-effectiveness model includes acute outpatient and maintenance costs for non-fatal MI and non-fatal stroke with long-term outpatient and maintenance costs for non-fatal MI, non-fatal stroke and 'no events'.

The remainder of the acute cost for non-fatal MI and non-fatal stroke costs, not accrued as inpatient cost, is accrued as an outpatient and maintenance cost (30% and 45%, respectively), in order to arrive at the same cost in the year following event as applied in the ERG models (after inflation and for the same mix of disabling and non-disabling strokes). Given that higher costs are often experienced closest to the event we have assumed that the acute outpatient and maintenance costs will decrease over the first 12 months. The proportion of the remaining costs accrued in each quarter of the first year from the event is tapered to the long-term outpatient and maintenance cost. These are detailed in Table 110.

Table 110: Acute outpatient and maintenance costs applied to tunnel states

Cycle	Proportion of annual non-fatal MI cost value	Non-fatal MI cost	Proportion of annual non-fatal stroke cost value	Non-fatal stroke cost
0–3 months	10%	£639.45	15%	£1,343.39
3–6 months	10%	£639.45	12.5%	£1,119.49
6–9 months	5%	£319.73	9.8%[#]	£877.57
9–12 months	5%	£319.73	7.7%*	£689.71

*same as long term cost, [#]residual of annual cost from TA317.

Additionally, we have included the cost of generic clopidogrel (£5.57 per cycle)(136) for the first 12 months following a non-fatal MI.

Long-term outpatient and maintenance costs were obtained from TA317 and adjusted to reflect the cycle length in the model (3 months) and inflation (Table 111). We have assumed that the long-term 'no event' cost is the same as the long-term non-fatal MI cost as all patients have at least one MI in their history (the qualifying MI for the trial). A 'no event' patient in the model is a patient with no events beyond the qualifying MI. The long term maintenance cost is expected to be the same, irrespective of the number of MIs in a patient's history.

Table 111: Long-term outpatient and maintenance costs

Health state	Cost
Post non-fatal MI	£160.31
Post non-fatal stroke	£689.71
'No event'	£160.31

Initiation of ticagrelor 60mg BID

For base case it was assumed that the decision on whether or not ticagrelor 60mg BID should be prescribed for history of MI will be taken by the cardiologist at the time the patient is discharged from hospital for the qualifying MI (via the letter of discharge recommendations to the GP). As such no incremental healthcare visit associated to the initiation of ticagrelor 60mg BID is assumed for base case. Other scenarios are explored under sensitivity analysis

Adverse reaction unit costs and resource use

Summary of costs for each adverse reaction listed in section 4.12

Within PEGASUS-TIMI 54 (6) there was a significant increase in dyspnoea and TIMI bleeding (both p<0.001) for ticagrelor 60 mg BID + low-dose ASA. Both have been included in the cost-effectiveness model. The cost for grade 3–4 dyspnoea was calculated by taking a weighted average of DZ19 ‘Other Respiratory Disorders’ from NHS reference costs 2014/15. The cost for major and minor TIMI bleeds was taken from TA210 (124). These are detailed in Table 112 and are applied in the model in the cycle in which the event occurs. It was assumed that there was no outpatient or maintenance cost for dyspnoea grade 1-2.

Table 112: Adverse event costs

Adverse event	Cost
Grade 3–4 dyspnoea	£732.98
Major TIMI bleed	£2,206.87
Minor TIMI bleed	£122.48

Miscellaneous unit costs and resource use

Additional costs and healthcare resource use

Not applicable

5.6 Summary of base-case de novo analysis inputs and assumptions

Variables included in the cost-effectiveness analysis

A summary of the key variables included in the model are provided in Table 113.

Table 113: Summary of variables applied in the economic model

Risk equations		
Variable	**Distribution**	**Reference to section in submission**
First event		
Non-fatal MI	Log-logistic	Section 5.3.1 & Appendix 16
Non-fatal stroke	Log-logistic	Section 5.3.1 & Appendix 16
Fatal CV	Log-logistic	Section 5.3.1 & Appendix 16
Other fatal event	Log-logistic	Section 5.3.1 & Appendix 16
Subsequent event		
Non-fatal MI	Log-logistic	Section 5.3.1 & Appendix 16
Non-fatal stroke	Weibull	Section 5.3.1 & Appendix 16
Fatal CV events	Log-normal	Section 5.3.1 & Appendix 16
Other fatal events	Weibull	Section 5.3.1 & Appendix 16
Adverse event		
TIMI Major bleeds	Exponential	Section 5.3.1 & Appendix 16
Dyspnoea grade 3-4	Exponential	Section 5.3.1 & Appendix 16
Others		
Discontinuation	Piecewise exponential	Section 5.3.1 & Appendix 16
Costs		
Variable	**Value**	**Reference to section in submission**
Unit costs		
ASA (daily)	£0.03	Section 5.5.5
Ticagrlelor 60 mg BID (daily)	£1.95	
Inpatient		
Non-fatal MI	£4,476.18	Section 5.5.6
Non-fatal stroke	£4,925.76	Section 5.5.6
Fatal events (CAD and non-CAD)	£2,497.83	Section 5.5.6
'No event'	£2,497.83	Section 5.5.6
Outpatient and maintenance		
Post non-fatal MI (0-3 months)	£639.45	Section 5.5.6
Post non-fatal MI (3-6 months)	£639.45	Section 5.5.6
Post non-fatal MI (6-9 months)	£319.73	Section 5.5.6
Post non-fatal MI (9-12 months)	£319.73	Section 5.5.6
Post non-fatal MI (12+ months, every cycle)	£160.31	Section 5.5.6
Post non-fatal stroke (0-3 months)	£1,343.39	Section 5.5.6
Post non-fatal stroke (3-6 months)	£1,119.49	Section 5.5.6
Post non-fatal stroke (6-9 months)	£877.57	Section 5.5.6
Post non-fatal stroke (9-12 months)	£689.71	Section 5.5.6

Post non-fatal stroke (12+ months, every cycle)	£689.71	Section 5.5.6
'No event' (every cycle)	£160.31	Section 5.5.6
Adverse events		
Grade 3-4 Dyspnoea	£732.98	Section 5.5.7
Major TIMI bleed	£2,206.87	Section 5.5.7
Minor TIMI bleed	£122.48	Section 5.5.7
Disutilities		
Variable	**Value**	**Reference to section in submission**
Non-fatal MI	-0.0474	Section 5.4.8
Non-fatal stroke	-0.0934	Section 5.4.8
Post MI	-0.0342	Section 5.4.8
Post stroke	-0.0665	Section 5.4.8
Dyspnoea (Grade 3-4)	-0.0481	Section 5.4.8
Dyspnoea (Grade 1-2)	-0.0154	Section 5.4.8
Minor bleed	-0.0129	Section 5.4.8
Major bleed	-0.0466	Section 5.4.8

Comparison of the base case analysis with the NICE reference case

Base case analysis reflects the NICE reference case.

Assumptions

- We have assumed that it is appropriate to extrapolate the risk equations beyond the time frame of the clinical trial. This is a generally accepted assumption within economic modelling and we have undertaken a deterministic sensitivity analysis to assess the impact of choosing different functional forms. No extrapolation of treatment effect is made beyond the trial.

- Assumed that risk equations other than the time to first event are not impacted upon by whether the patient is included or is not included within the label population. There is no clinical rationale for there to be any difference between these risk equations for the label and the full PEGASUS-TIMI 54 trial population. If there is a difference, this should be accounted for by the patients underlying baseline characteristics.

- It was appropriate to impute missing data in order to assist with the statistical analysis.

- Risk of adverse events (dyspnoea and bleeding) is assumed only to occur whilst patients remain on active treatment

- Although patients can have multiple subsequent events, the risk of further subsequent events is constant and is independent of the number of subsequent events the patient has had.

- Although permanent treatment discontinuation is taken into account we have assumed that all patients will remain 100% adherent to treatment until permanent treatment discontinuation occurs, for the purposes of drug costing. This represents a conservative approach for ticagrelor 60mg BID.

- Subsequent events have the same inpatient costs as first events.

- Due to the potential range of 'no event' inpatient costs, we have assumed that the inpatient cost of 'no event' would be the same as the cost of fatal events.

- It is assumed that all patients experiencing a non-fatal MI, non-fatal stroke or severe adverse event will be hospitalised.

- Costs from TA317 are representative of the cost for the first 12 months from the event. We have assumed that 70% of the cost of the non-fatal MI is accrued as an inpatient whilst 55% of the cost of a non-fatal stroke (both disabling and non-disabling) is accrued as an inpatient. The remainder is accrued as an outpatient and maintenance cost, in order to arrive at the same cost in the year following event as applied in the ERG models (after inflation and for the same mix of disabling and non-disabling strokes).

- Given that higher costs are often experienced closest to the event we have assumed that the acute outpatient and maintenance costs will decrease over the first 12 months

- We have assumed that the long-term 'no event' cost is the same as the long-term non-fatal MI cost as all patients have at least one MI in their history (the

qualifying MI for the trial). A ‘no event’ patient in the model is a patient with no events beyond the qualifying MI. The long term maintenance cost is expected to be the same, irrespective of the number of MIs in a patient’s history.

- There is no outpatient and maintenance cost for dyspnoea grade 1-2.
- For base case it was assumed that the decision on whether or not ticagrelor 60mg BID should be prescribed for history of MI will be taken by the cardiologist at the time the patient is discharged from hospital for the qualifying MI (via the letter of discharge recommendations to the GP). As such no incremental healthcare visit associated to the initiation of ticagrelor 60mg BID is assumed for base case. Other scenarios are explored under sensitivity analysis.
- It was assumed that the patient population under consideration within the model were unlikely to have a higher baseline utility than that of the UK general population.

5.7 Base case results

The economic model allows deterministic analyses to be completed in two ways.

- Complete analysis: estimates the parametric functions for each patient individually using their specific characteristics and estimates the expected value across all patients – E[g(·)]
- Simple analysis: attributes the expected value (calculated across all patients) for each patient baseline characteristic into the parametric functions used in the economic model – g(E[·])

Since Markov models with discounting are non-linear by nature:

$$E[g(\cdot)] \neq g(E[\cdot])$$

the results of the simple analysis will not match those of the complete analysis.

The ‘simple analysis’ and ‘complete analysis’ are both included in the model for pragmatic purposes. The complete analysis runs each individual included within the ‘label’ population (N = 10,779) through the model one at a time, generating and

storing results. After all patients have been run through the model, the average of the results is taken to estimate results for the cohort that has been selected in the model (via the filters for patient baseline characteristics). The ‘simple’ analysis takes the average baseline charactertistics of all the selected patients and runs this through the model on a cohort basis, as would normally be expected within a markov model.

Due to the computational requirements of the ‘complete’ analysis, the ‘simple analysis’ is included to generate quick analyses of results to test alternative assumptions and parameters. This will provide an indication of the directional effect for model adjustments as well as the relative magnitude for a change. The computational requirements of the ‘complete’ analysis have resulted in a different methodology being required for the PSA and DSA (see section 5.8).

Given the above all results are provided using the complete analysis, unless explictly stated otherwise, to take into account the non-linearity of the model. Simple analysis results have been used to supplement these results where necessary. For example, it is not possible to generate a Markov trace from within the complete analysis, so this has been generated from the simple analysis.

Base-case incremental cost effectiveness analysis results

The base case considers patients with MI <2 years ago.

Ticagrelor 60 mg BID + low-dose ASA accumulates total (discounted) costs of £14,443 and 9.2742 QALYs. Low-dose ASA accumulates total (discounted) costs of £13,019 and 9.2034 QALYs. This equates to ticagrelor 60 mg BID + low-dose ASA producing an additional 0.0708 QALYs at an incremental cost of £1,424 when compared to low-dose ASA. This generates a base-case ICER of £20,098. Table 114 below presents the base-case incremental cost-effectiveness results in detail.

Table 114: Base-case results (complete analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) per inc QALY
Low-dose ASA	£13,019	12.2453	9.2034	-	-	-	-
Ticagrelor 60 mg BID + low-dose ASA	£14,443	12.3363	9.2742	£1,434	0.0909	0.0708	£20,098*

*The corresponding 'simple analysis' overestimates the ICER for this population by 21% (ICER of £24,378).

Clinical outcomes from the model

Please see section 5.10.1.

Proportion of the cohort in the health state over time (Markov trace)

Markov traces (from the simple analysis) for the proportion of the cohort in each health state, for low-dose ASA and ticagrelor 60 mg BID + low-dose ASA are provided in Figure 50 and Figure 51.

Figure 50: Low-dose ASA Markov trace (simple analysis)

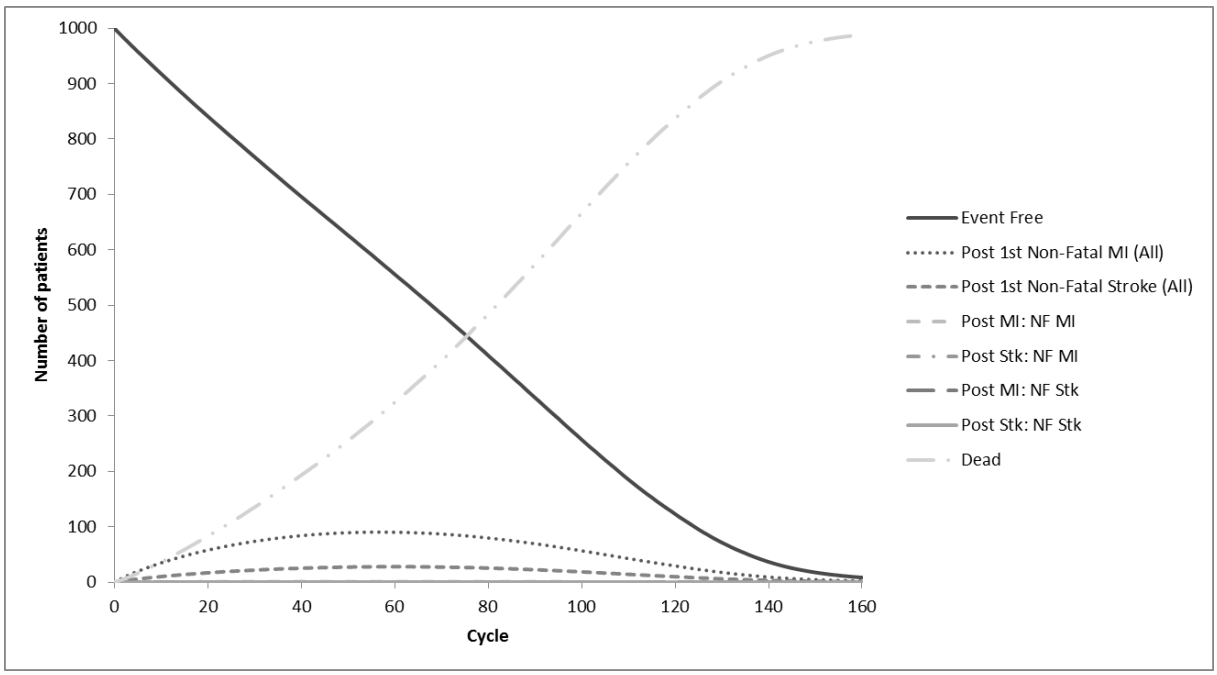
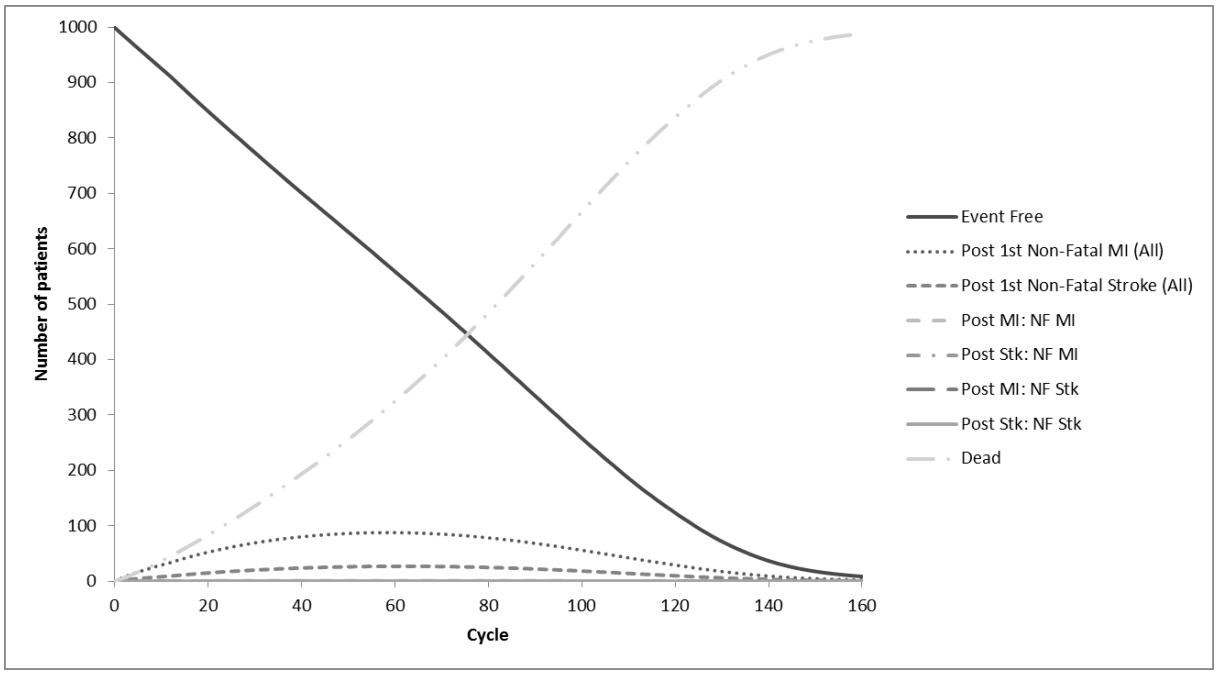


Figure 51: Ticagrelor 60 mg BID + low-dose ASA Markov trace (simple analysis)



Provide details of how the model assumes QALYs accrued over time

See Section 5.7.6

Disaggregated results of the base case incremental cost effectiveness analysis

Disaggregated QALYs by health state and disaggregated costs by cost category are detailed in Table 115 and Table 116, respectively. Figure 52 and Figure 53 (generated using the 'simple' analysis) detail the accumulation of QALYs and costs over the time horizon of the cost-effectiveness model.

Three conclusions can be drawn here:

1. Ticagrelor 60 mg BID + low-dose ASA accumulates more QALYs than low-dose ASA, owing to patients spending more time in the 'no event' state.

2. 94.37% of the incremental cost is due to the cost of the ticagrelor 60 mg BID + low-dose ASA, which occurs in the first 36 months of treatment.

3. The statistically significant increase in TIMI bleeds (major and minor) and grade 3–4 dyspnoea associated with ticagrelor 60 mg BID + low-dose ASA has a negligible impact on both QALYs and costs.

Table 115: Summary of QALY gain by health state (complete analysis)

Health state	QALY intervention (ticagrelor 60 mg BID + LD ASA)	QALY comparator (Low-dose ASA)	Increment	Absolute increment	Absolute increment (%)
No event	8.4136	8.2962	0.1174	0.1174	71.59
First event					
Post non-fatal MI	0.0218	0.0228	-0.0010	0.0010	0.60
Post non-fatal stroke	0.0065	0.0068	-0.0004	0.0004	0.23
Subsequent events					
No event	0.8193	0.8635	-0.0442	0.0442	26.95
Post non-fatal MI	0.0110	0.0116	-0.0006	0.0006	0.36
Post non-fatal stroke	0.0034	0.0036	-0.0002	0.0002	0.12
Adverse events					
Dyspnoea	-0.0009	-0.0008	-0.0001	0.0001	0.08
TIMI Bleeds	-0.0005	-0.0004	-0.0001	0.0001	0.07
Total	9.2742	9.2034	0.0708	0.1640	100.00
QALY=quality-adjusted life year, HS1=health state 1, HS2=health state 2 Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 116: Summary of costs by cost category (complete analysis)

Health state	Cost intervention (ticagrelor 60 mg BID + LD ASA)	Cost comparator (Low-dose ASA)	Increment	Absolute increment	Absolute increment (%)
Drug acquisition	£1,571	£132	£1,439	£1,439	94.37
Outpatient costs	£8,683	£8,672	£12	£12	0.78

Inpatient: MI events	£790	£826	-£36	£36	2.37
Inpatient: stroke events	£227	£240	-£13	£13	0.83
Inpatient: Fatal events	£143	£143	£0	£0	0.03
Inpatient: other/ No Event	£2,928	£2,930	-£2	£2	0.12
Dyspnoea	£9	£6	£3	£3	0.22
TIMI Bleeds	£91	£71	£19	£19	1.28
Total	£14,443	£13,019	£1,424	£1,524	100.00

HS1, health state 1; HS2, health state 2

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Figure 52: Accrual of QALYs over time horizon (Simple analysis)

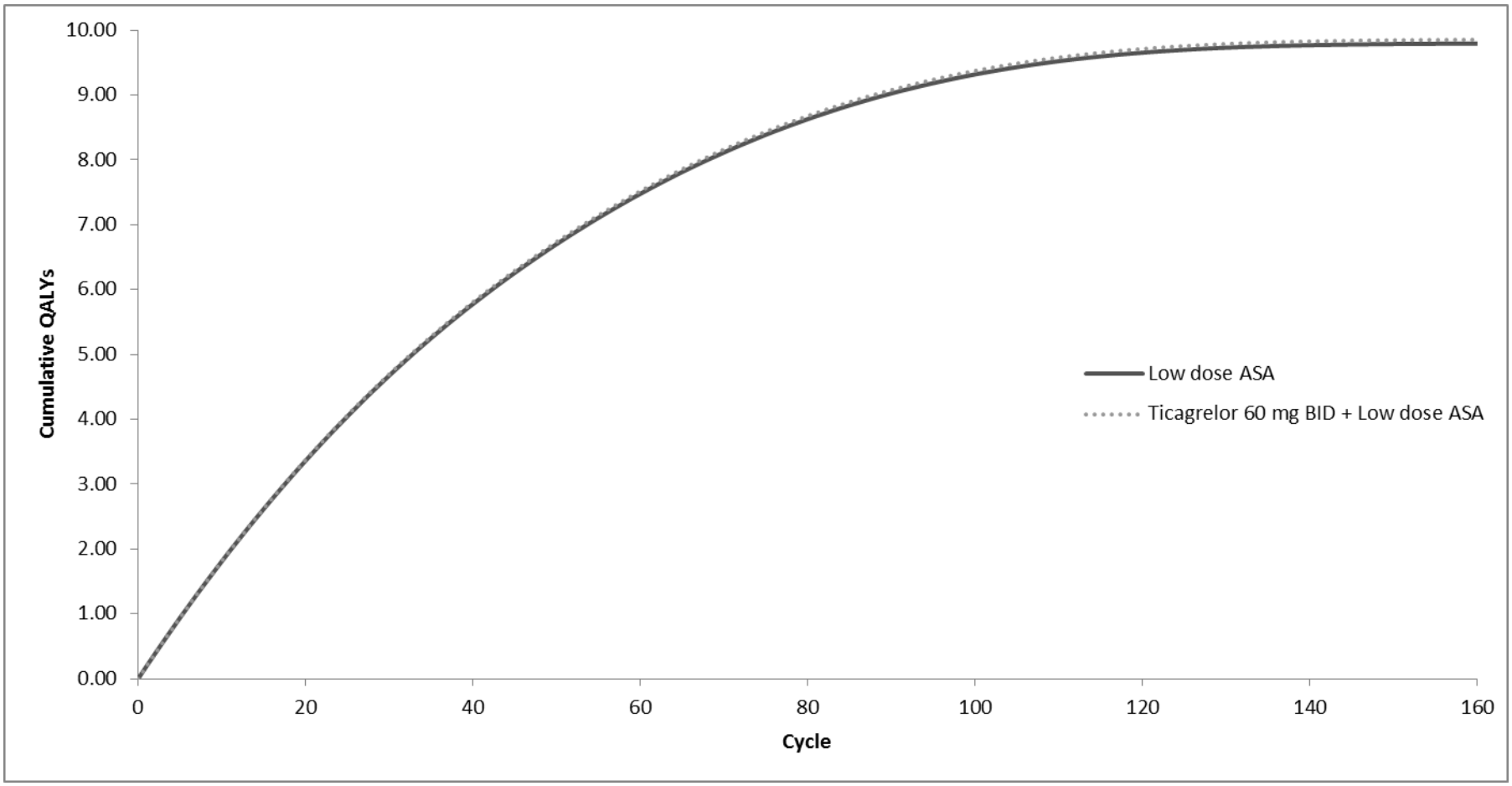
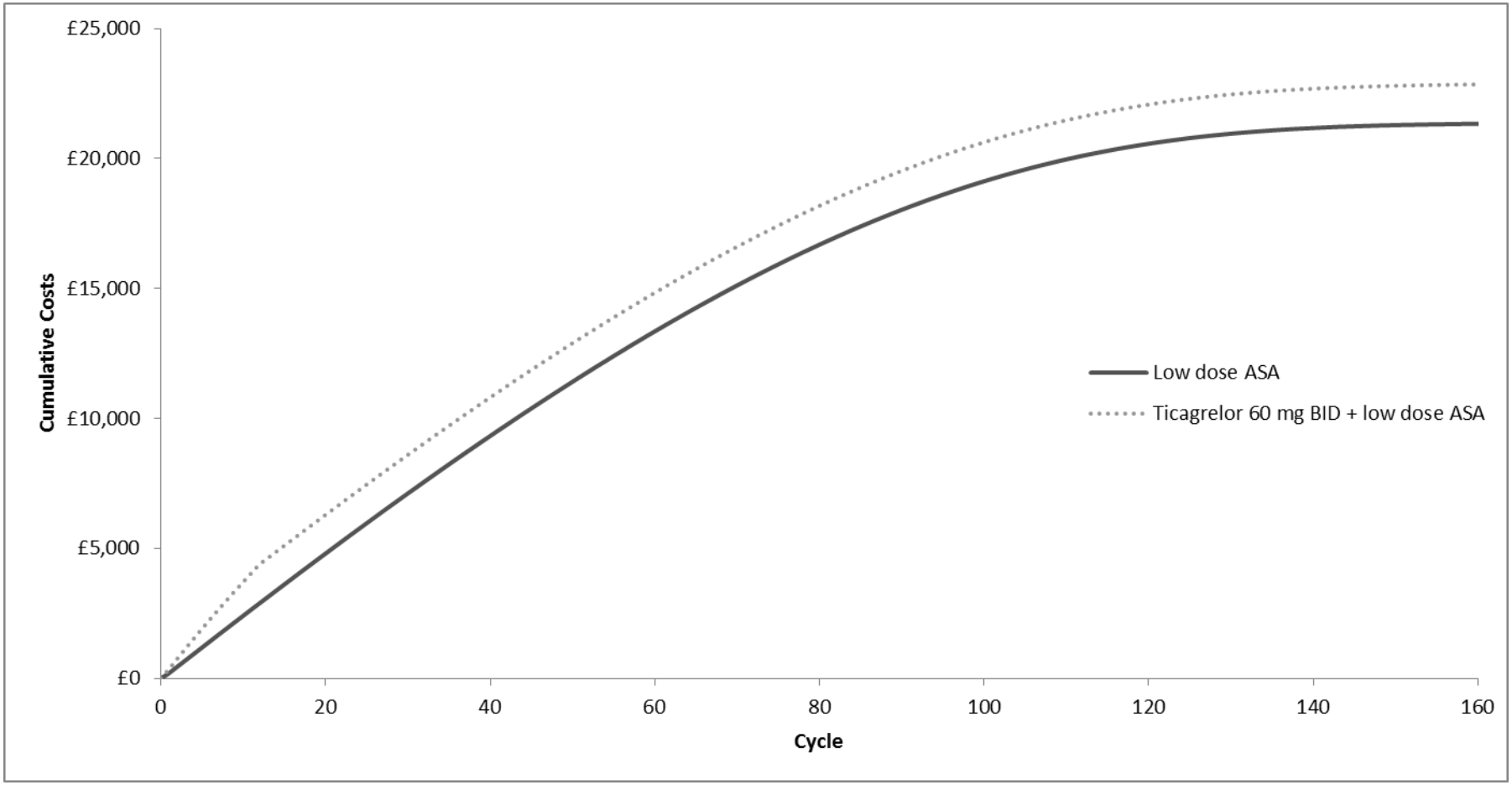


Figure 53: Accrual of costs over time horizon (simple analysis)



5.8 Sensitivity analyses

Due to the computational requirements in undertaking an individual patient level sensitivity analysis a traditional deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were deemed infeasible.

In this model, both the DSA and PSA are performed for a single individual patient profile, overcoming the issue of performing sensitivity analysis using averages for dichotomous parameters (i.e. a patient who is 76% male, 32% diabetic, with 76% hypertension). The specific patient profile is chosen by selecting the patient with the ICER that most closely respresents that of the 'complete' analysis (i.e. the cohort as a whole). During the development phase of the model, an additional approach was proposed whereby the model would also perform sensitivity analysis based on the patient profile where composite risk (CV death, non-fatal MI, non-fatal stroke) most closely reflected that of the cohort as a whole. However, this approach was found to lead to unstable probablistic ICERs which were out of keeping with the 'complete' analysis, owing to the fact that the components of composite risk do not impact QALYs and costs equally. For example, a patient may have 'typical' composite risk made up of a higher than average risk for CV death and non-fatal stroke and a very low risk of non-fatal MI. This scenario would lead to the model yielding a probablistic ICER much lower than the ICER from the deterministic 'complete' analysis. Consequently for the final design of the model, it was decided to proceed using only the patient profile with the ICER that most closely respresents that of the 'complete' analysis.

Given that the sensitivity analyses relate to parameter values rather than to covariates, we would not expect the use of the average characteristics (in place of the representative patient) to change the impact on the results in any meaningful way. Therefore, the impact of the sensitivity analyses on the representative patient selection should reflect the impact for the average patient.

The PSA results evaluate the uncertainty around the incremental costs and incremental effects for one patient profile, not for the average cohort. Results of the PSA should not be compared to the deterministic results of the entire cohort (complete analysis), since the patient profile may be considerably different from the

average results of the cohort. Instead the PSA should be compared against the deterministic results for the specific individual. Analysis is presented in this regard.

Similarly, the DSA performs the analysis on an individual patient profile, which is the same profile as the PSA (for a given population). Therefore, the base-case ICER will not be equal to the ICER generated for the cohort. Furthermore, performing a manual sensitivity analysis within the model will not generate the same results, since the model observes the mean ICER in the cohort, whereas the DSA considers an individual patient profile. However, the same principle applies for the DSA as the PSA in that the impact of the sensitivity analyses on the representative patient selection should reflect the impact for the average patient.

Probabilistic sensitivity analysis

The PSA considers all of the risk equations within the model to be probabilistic, using a variance co-variance Cholesky decomposition matrix (rather than the selection of distributions and standard errors), in addition to other point estimates used within the model.

The PSA makes the following parameters probabilistic:

- event-based risk equations
- time to first event
- time to subsequent event
- dyspnoea
- TIMI bleeds
- background mortality (from standardised mortality rates from life tables)
- utility
- utility decrements from the PEGASUS-TIMI 54 trial
- baseline utility (UK population norms)
- risk of hospitalisation (post-event)
- treatment discontinuation

Other than the scenario analysis, costs are not considered in the sensitivity analyses. In the PSA, while the resource use (hospitalisations, events, etc) is probabilistic none of the costs are as they are not considered to be uncertain.

Results

The average basecase baseline characteristics and individual patient baseline charactertistics chosen to undertake the average ICER PSA and DSA are presented in Table 117. This demonstrates that although the patient has been chosen based upon having the ICER closest to that of the cohort, the characteristics may have a very different composition.

Table 117: Baseline characteristics (average vs individual chosen for PSA and DSA)

Baseline characteristics	Cohort average (MI <2 years ago)	Individual (Average ICER)
Mean age (years)	65.3	69
Male (%)	75.8	No
Mean weight (kg)	81.6	57
Mean BMI (kg/m^2)	28.3	22.1
Diabetes (%)	31.6	No
≥1 prior MI (%)	16.2	No
Multi-vessel CAD (%)	59.9	Yes
Non-smoker (%)	35.1	No
Previous smoker (%)	48.1	No
Current smoker (%)	16.8	No
Previous stent (%)	83.8	Yes
Angina history (%)	30.3	No
Time from prior MI (days)	505.4	375
NSTEMI (%)	40.8	Yes
ASA dose (mg)	90.3	81
Supine SBP (mmHg)	132.6	140
Supine DBP (mmHg)	77.8	71
Hypercholesterolemia (%)	76.1	Yes
Hypertension (%)	77.3	Yes
Family history of CHD (%)	29.6	No
Prior CABG (%)	4.9	No
Prior stroke (%)	0.5	No
Prior TIA (%)	1.2	No
Prior revascularisation (%)	0.4	No
CHF (%)	19.5	No

Spontaneous bleed requiring hospitalisation (%)	1.5	No
Europe and South Africa (%)	59.8	No
Asia and Australia (%)	11.3	No
North America (%)	17.9	Yes
South America (%)	11.0	No
ADP blocker: <30 days	41.5	Yes
ADP blocker: 30 days to <12 months	40.9	No
ADP blocker: >12 months	8.2	No
Clopidogrel: >7 days	55.2	No
History of PAD (%)	5.5	No
Creatinine clearance (≥60 mL/min)	79.2	-

The base-case PSA results are presented in Table 118. The individual patient scatter plot is presented in Figure 54. The CEAC is presented in Figure 55.

Table 118: Base-case PSA results (MI <2 years ago)

	PSA performed on an individual patient (avg. ICER)
Incremental costs	£1,289
95% CI around costs	£1,249 to £1,323
Incremental QALYs	0.0669
95% CI around QALYs	0.537 to 0.0806
Change in costs (%)	-3.16 to 2.59
Change in QALYs (%)	-19.15 to 21.45
ICER	£19,275*

*deterministic ICER for individual patient £19,436

Ticagrelor 60 mg BID + low-dose ASA has a 64.6% probability of being cost-effective at £20,000 per QALY gained, increasing to 100% at £30,000 per QALY gained.

Figure 54: Base-case PSA scatterplot (MI <2 years ago)

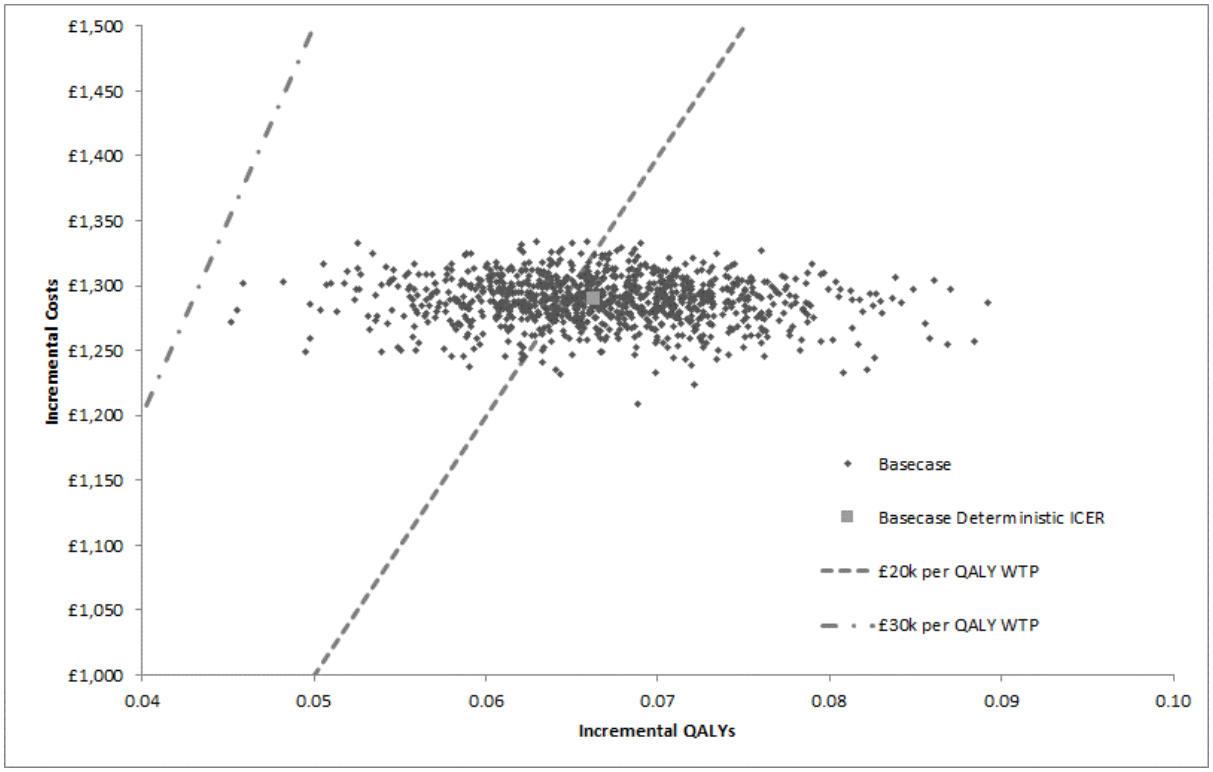
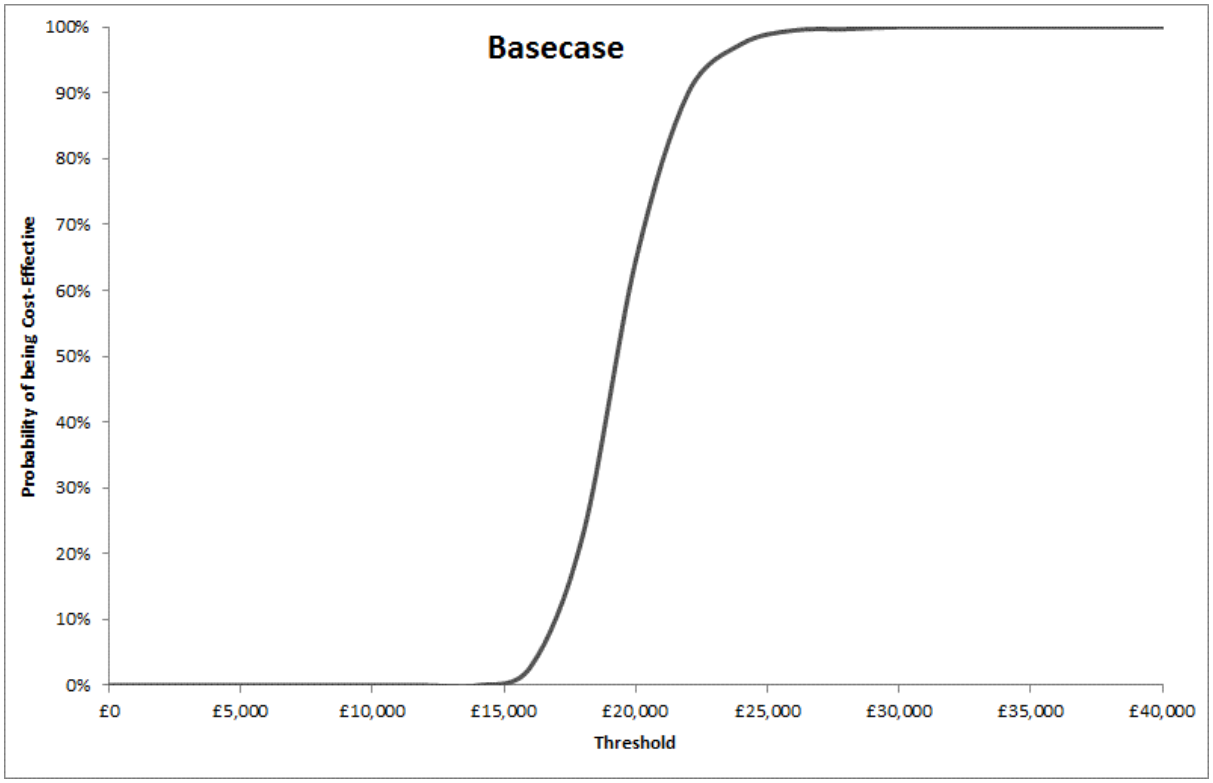


Figure 55: Base-case PSA CEAC (MI <2 years ago)



The probabilistic and deterministic ICERs for each individual patient used in the PSA are similar (Table 118). The ICER for the PSA of £19,275 is similar to that of the

base case deterministic analysis of £20,098 (whereby the ICER is calculated across all patients in the cohort) however as described previously the two should not be directly compared.

Deterministic sensitivity analysis

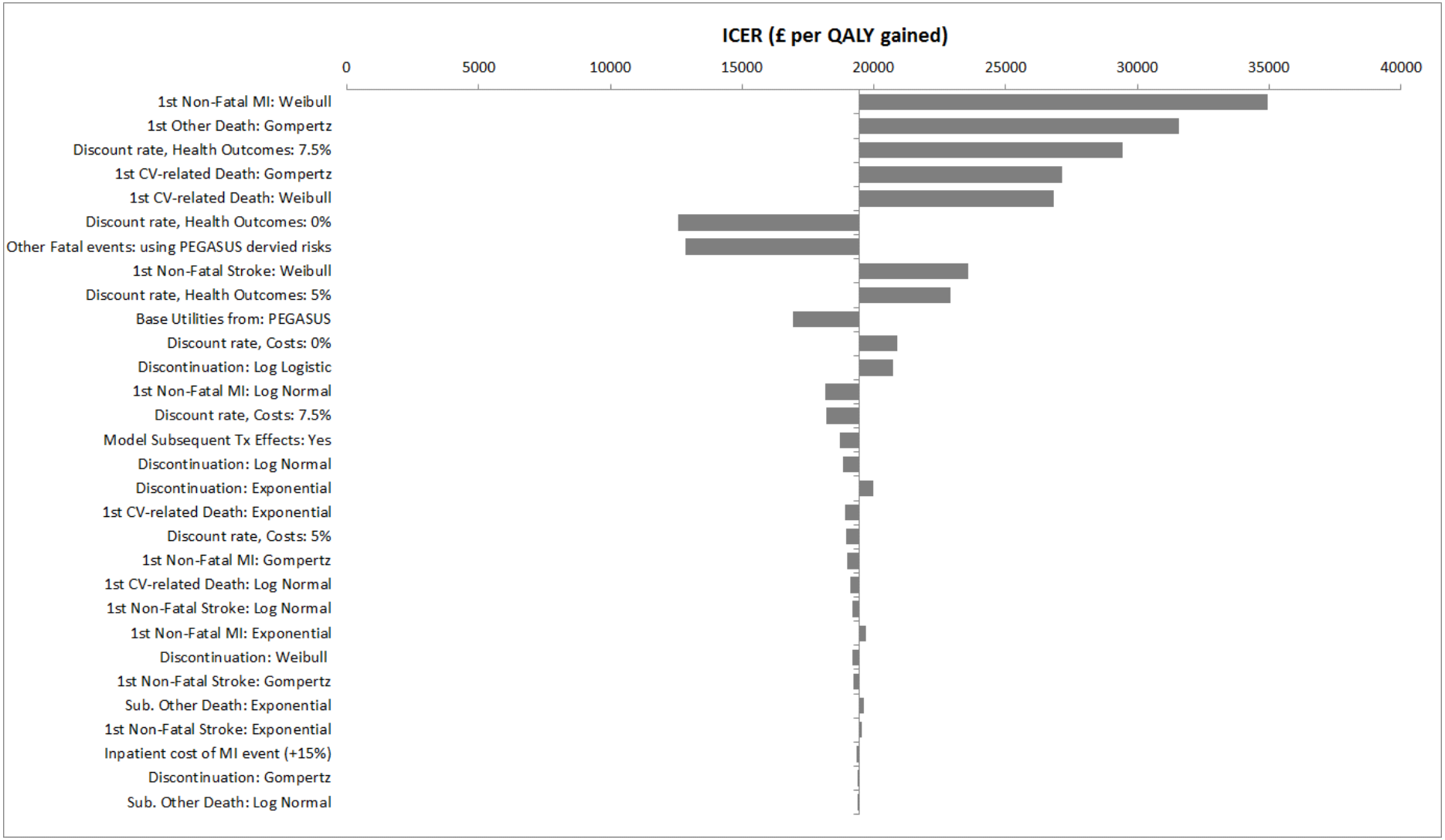
The assumptions in the model are tested through a series of deterministic analyses through which the impact of alternative assumptions is evaluated.

- Time to first event risk equations: including non-fatal MI, non-fatal stroke, CV death, and other death. In the base case each of these four equations (for first events) uses a log–logistic distribution. A scenario analysis is undertaken for each first event for each of the following alternative distributions (exponential, Gompertz, Weibull, log–normal).
- Time to subsequent event risk equations: considering the four alternative distributions not used for base case, for each of the four subsequent events.
- Treatment discontinuation: in the base case, treatment discontinuation is modelled using a piecewise exponential distribution. In the scenario analysis alternative distributions are considered (exponential, Gompertz, Weibull, log–normal and log–logistic).
- Discount rates: discount rate for costs and health outcomes are varied individually, from 3.5% (base case) to 0%, 5% or 7.5%.
- Utility: changes the baseline utility values from population norms (base case) to PEGASUS-derived values.
- Model subsequent treatment effects: in the base case the assumption is made that there is no treatment effect on the risk of subsequent events. This sensitivity analysis changes that to allow for a treatment effect during time to subsequent events.
- Other fatal events: this uses PEGASUS-derived values for risk of other mortality in place of the base-case approach (using standardised life tables for the UK).

- TIMI bleeds: considers risk for TIMI major bleeds only (ignores risk of TIMI minor bleed).
- Acute costs: inpatient cost for MI event, stroke event or TIMI major bleed event is increased and decreased by 15%, individually.

The results for the individual patient profile that yields the ICER closest to that of the cohort as a whole is presented in Figure 56.

Figure 56: DSA for base-case (MI <2 years ago)



Amongst the most sensitive parameters in the DSA analysis (are the distributions chosen to extrapolate the risk equations beyond the length of the trial, especially the use of the Weibull and Gompertz functions. Clinically, patients are at highest risk shortly after an event, which then diminishes over time. Using the Weibull or Gompertz function is counter to this clinical rationale as the risk continues to increase over time for these distributions. As the majority of incremental costs are accrued initially while the incremental QALYs are accrued over the entire time horizon, a shorter life expectancy decreases the incremental QALYs relative to incremental costs and leads to an increaed ICER. The model is somewhat sensitive to the choice of discount rate applied to health outcomes. The use of a high discount rate (7.5%) increases the ICER to just short of the threshold for cost-effectiveness. A 3.5% discount rate is chosen for base case, in line with the NICE reference case.

The final price **t**or ticagrelor 60mg has been confirmed and therefore this parameter is not included in the DSA.

Structural uncertainty

Seven scenario analyses were undertaken:

A. inclusion of an initiation cost

B. using costs and utilities from the rivaroxaban technology appraisal

C. using utilities derived from the systematic review of HRQL

D. using PEGASUS-TIMI 54 trial mortality

E. including subsequent treatment effects

F. a two-way analysis assessing the ‘no event’ maintenance cost

G. a one-way analysis assessing the impact of starting age.

Results of structural sensitivity analysis

A. Initiation cost

There is potential for the means by which ticagrelor 60mg BID is initiated to vary across the NHS locally. The impact of different scenarios on the initiation of

ticagrelor 60mg BID, whether by GP, cardiologist, a mixture or no incremental healthcare visit, were assessed to determine the financial impact on the NHS.

Table 119: Initiation cost scenario analyses (complete analysis)

Scenario	Initiation by GP (%)		Initiation by cardiologist (%)		Incremental costs	ICER*
	ASA	Tica 60mg BID + ASA	ASA	Tica 60mg BID + ASA		
1	15	15	0	0	£1,424	£20,098
2	15	100	0	0	£1,461	£20,619
3	15	15	0	85	£1,527	£21,554
4	0	0	0	100	£1,545	£21,810

*incremental QALY in all analyses remained 0.0708

As shown in Table 119, even if all patients were initiated to ticagrelor 60mg BID did so via a cardiologist, with no initation cost associated to the comparator, the ICER would still be within the cost-effectiveness threshold defined by NICE.

B. Rivaroxaban technology appraisal

To assess the assumptions made on the costs and utilities used within the base case, we applied costs and utilities used within the recent rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome technology appraisal (TA335) (122) supplemented by the base-case model values where values were not available from the submission.

Three different scenarios were undertaken:

- using TA335 costs with base-case utilities
- using base-case costs with TA335 utilities only
- using TA335 costs and TA335 utilities.

Table 120 and Table 121 list the costs (inflated to 2015 values) and utilities from the rivaroxaban submission used in this analysis.

Table 120: List of resource use and associated costs in the scenario analysis

Resource use	Value
Inpatient	

Non-fatal MI	£1,637.82
Non-fatal stroke	£5,963.97
Fatal events (CAD and non-CAD)	£1,683.43
'No event'	£1,637.82#
Outpatient and maintenance	
Post non-fatal MI (0-3 months)	£2,020.11
Post non-fatal MI (3-6 months)	£2,020.11
Post non-fatal MI (6-9 months)	£1,469.17
Post non-fatal MI (9-12 months)	£1,469.17
Post non-fatal MI (12+ months, every cycle)	£550.94
Post non-fatal stroke (0-3 months)	£3,121.99
Post non-fatal stroke (3-6 months)	£3,121.99
Post non-fatal stroke (6-9 months)	£4,285.09
Post non-fatal stroke (9-12 months)	£4,285.09
Post non-fatal stroke (12+ months, every cycle)	£1,591.61
'No event' (every cycle)	£550.94
Adverse events	
Grade 3-4 Dyspnoea	£732.98*
Major TIMI bleed	£683.35
Minor TIMI bleed	£69.16

*unchanged from base-case analysis; #assumed same as MI inpatient cost

Table 121: QALY decrements applied in the economic model

State	**QALY decrement (cycle length adjusted utility decrement)**
Baseline	UK population norm for age and sex*
Non-fatal MI	-0.0158
Non-fatal stroke	-0.0348
Post MI	-0.0053
Post stroke	-0.0125
Dyspnoea (grade 3–4)	-0.0120*
Dyspnoea (grade 1–2)	-0.0038*
Minor bleed	-0.0105
Major bleed	-0.0230

*unchanged from base-case analysis

It should be noted that due to the methodology used to calculate the utility in the post event tunnel states in the model, it has been necessary, in this sensitivity analysis, to apply the acute utility decrements (derived from the rivaroxaban analysis) for a shorter period of time than in the original analysis. The tunnel states each represent 3 months duration and the initial utility decrement following an event has been

applied for this three month period only. Following the initial decrement a long-term decrement is applied. For MI, the initial decrement, applied for 6 months in the rivaroxaban analysis, is applied for 3 months followed by the long term decrement. For stroke, the initial decrement, applied for 6 months in the rivaroxaban analysis, is applied for 3 months followed by the long term decrement. The intermediate decrement used in the rivaroxaban analysis (for months 6-12) is not applied. See Table 122 for details. The no event baseline in the rivaroxaban analysis is 0.842. The likely impact is that the acute utility decrement is underestimated in the current model compared to the rivaroxaban analysis, which would represent a conservative approach from the perspective of ticagrelor 60mg BID + low dose ASA, owing to the model predicting fewer MI and stroke events for this arm than for low dose ASA.

Table 122: Rivaroxaban utilities applied in the scenario analysis

	Non-fatal MI (sensitivity analysis)	Non-fatal MI (rivaroxaban analysis)	Non-fatal stroke (sensitivity analysis)	Non-fatal stroke (rivaroxaban analysis)
0-3 Months	0.779	0.779	0.703	0.703
3-6 Months	0.821	0.779	0.792	0.703
6-9 Months	0.821	0.821	0.792	0.748
9-12 Months	0.821	0.821	0.792	0.748
>12 Months	0.821	0.821	0.792	0.792

As demonstrated in Table 123, using the costs from rivaroxaban appraisal increased the base case ICER to £21,240 and if the utilities are used or the combination of both costs and utilities, the ICER is £20,366 and £21,524 respectively.

Table 123: Rivaroxaban TA cost and utilities scenario analyses (complete analysis)

Scenario	Costs	Utilities	Incremental costs	Incremental QALYs	ICER
1	X	-	£1,505	0.0708	£21,240
2	-	X	£1,424	0.0699	£20,366
3	X	X	£1,505	0.0699	£21,524

All of these ICERs are within the range deemed acceptable by NICE, illustrating that ticagrelor 60 mg BID + low-dose ASA is cost-effective with a different set of assumptions for costs and utilities.

C. HRQL systematic review data

In order to further test the sensitivity of the model to utilities, data identified from the systematic review of HRQL data, utility data from Sullivan et al (102) was used within the model.

Sullivan et al produced a catalogue of EQ-5D scores for the United Kingdom by applying UK community based preferences to EQ-5D questionnaires responses from the US Medical Expenditure Based Panel Survey. Regressions were undertaken to estimate the disutility of each condition (as defined by ICD-9 or CCC codes). The relevant codes relating to non-fatal MI for our analysis are 'ICD-9 410 – Acute Myocardial Infarction' and 'ICD-9 412 – Old Myocardial Infarction'. For non-fatal stroke only 'CCC 109 – Acute Cerebrovascular Disease' is reported, however, given how this has been calculated within the paper, it is more applicable to the long term post-non fatal stroke state. No other codes were applicable to our analysis. The disutilities for these conditions are listed in Table 124.

Table 124: HRQL systematic review data scenario analyses

Code	Disutility
ICD-9 410 – Acute Myocardial Infarction	-0.0626
ICD-9 412 – Old Myocardial Infarction	-0.0368
CCC 109 – Acute Cerebrovascular Disease (appears 'long term')	-0.1009

We have applied the disutility for acute myocardial infarction to the non-fatal MI state and the disutility for old myocardial infarction to the post non-fatal MI state. Owing to the absence of a disutility suitable to apply to the non-fatal stroke state the disutility for acute cerebrovascular disease has been applied to both the post non-fatal stroke and non-fatal stroke states.

Using this set of disutilities, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0716 QALYs at an incremental cost of £1,424, generating an ICER of £19,889 (Table 125). This demonstrates that even though the disutility for these

events was increased (and approximately doubled for the chronic states compared to the base case) the impact on the ICER was minimal.

Table 125: HRQL systematic review data scenario analyses (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,424	0.0716	£19,889

D. PEGASUS-TIMI 54 trial mortality

In the base case we use UK life tables to estimate non-cardiovascular mortality. However, 366 non-cardiovascular deaths occurred in PEGASUS-TIMI 54. Due to the exclusion of patients with co-morbidities within the trial it was assumed that using just this data would underestimate mortality. To explore this assumption we undertook an analysis where mortality was based on that observed in PEGASUS-TIMI 54 alone.

As demonstrated in Table 126, using this approach decreases the ICER to £14,544.

Table 126: PEGASUS-TIMI 54 trial mortality scenario analyses (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,466	0.1008	£14,544

However, the ‘simple analysis’ (chosen in order to view the markov trace) shows that in this case over 35% of patients are still alive at 100 years of age (in both arms). This demonstrates that the base-case assumption, to undertake an analysis using the UK life tables, was appropriate.

E. Subsequent events treatment effects

As detailed in section 5.3, with the exception of patients whose first non-fatal event was a stroke, subsequent events were modelled for patients randomised to each of the arms in PEGASUS-TIMI 54. In the base case we excluded any treatment effect on subsequent events. However, we have included these in this scenario analysis.

In this analysis (Table 127) ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0767 QALY at an incremental cost of £1,443, generating an ICER of £18,817. This demonstrates that our initial assumption was the more conservative.

Table 127: Subsequent events treatment effects scenario analyses (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,443	0.0767	£18,817

F. 'No event' maintenance cost

In the base case we have assumed that the maintenance cost for 'no event' is likely to be the same as a patient with a non-fatal MI. This is because the patient with 'no event' will have already had an MI and the likelihood of long-term maintenance being different for a patient with either one or two MIs is low. However, in order to assess this assumption, we undertook a two-way analysis (using the 'simple' analysis methodology) varying the outpatient and maintenance cost for 'no event' and non-fatal MI between £0 and £500 per quarter. Results can be seen at Table 128. Results demonstrate that in all scenarios ticagrelor 60 mg BID + low-dose ASA is cost-effective at a threshold of £30,000 per QALY gained. It should also be noted that this analysis was undertaken using the 'simple analysis' which overstates the ICER by approximately 21% (as stated in Section 5.7). Assuming this overstatement would apply to all the analyses here, if this analysis had been undertaken using the 'complete analysis' the ICERs would have ranged from £17,677 to £23,567.

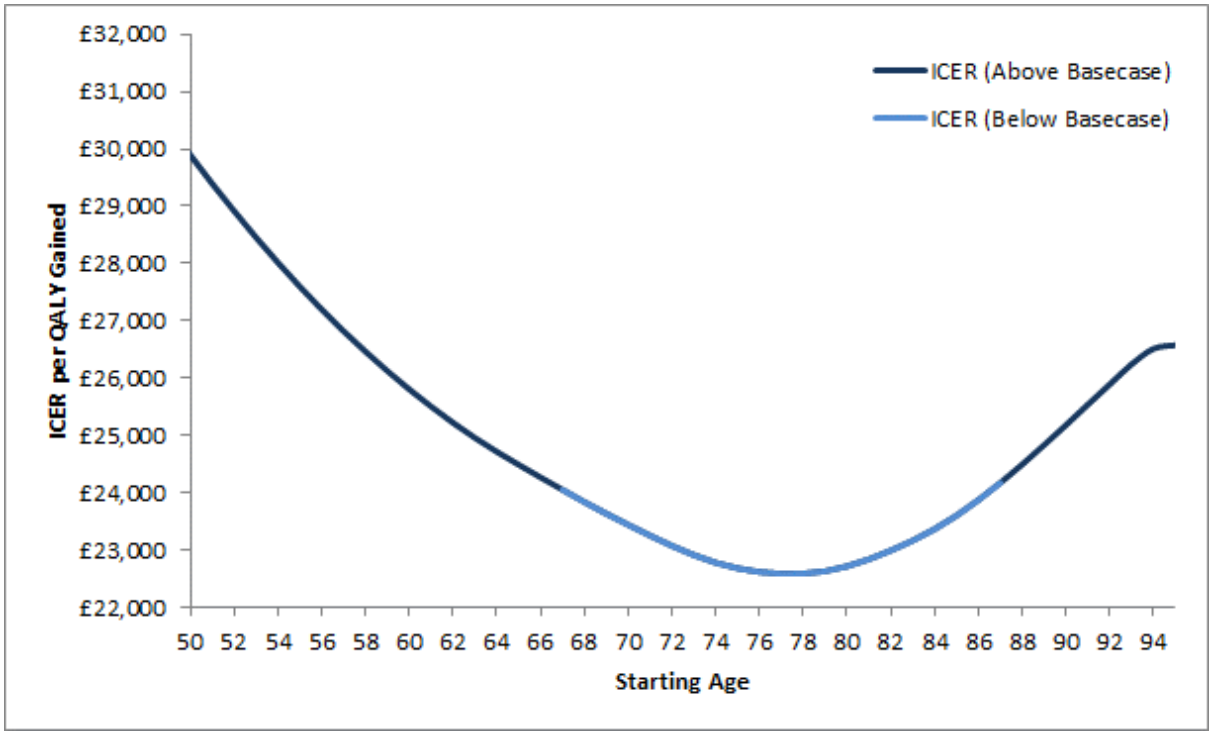
Table 128: No event and non-fatal MI outpatient and maintenance cost scenario analysis (simple analysis)

		Outpatient and maintenance cost per patient: no event					
		£0	**£100**	**£200**	**£300**	**£400**	**£500**
Outpatient and maintenance cost per patient: non-fatal MI (Stable phase, 12+ months)	**£0**	£23,242	£24,311	£25,380	£26,448	£27,517	£28,586
	£100	£22,882	£23,951	£25,019	£26,088	£27,157	£28,226
	£200	£22,522	£23,591	£24,659	£25,728	£26,797	£27,866
	£300	£22,162	£23,231	£24,299	£25,368	£26,437	£27,506
	£400	£21,802	£22,870	£23,939	£25,008	£26,077	£27,146
	£500	£21,442	£22,510	£23,579	£24,648	£25,717	£26,785

G. Impact of starting age

The mean age of patients with MI <2 years ago entering the PEGASUS-TIMI 54 trial was 65.3 years. The 'real world' patient in England may be some years older. The mean age of patients within the observational study as presented at section 4.11 was 77.0. Therefore, using the 'simple analysis' methodology, we assessed the impact on starting age on the ICER.

Table 129: Impact of starting age on ICER (simple analysis)



* This analysis considers patients of 50 years or older (as per the inclusion criteria specified in the PEGASUS TIMI-54 trial). There was one patient included in the analysis aged 49 years, and this starting age generated an ICER of £30,412, using the 'simple analysis'.

As demonstrated, based on the 'simple analysis', patients older than 50 years generate an ICER that would be deemed cost effective using NICE thresholds. Those aged between 67 and 87 years had an ICER below that of the base-case ICER, generated with an average cohort age of 65.3 years. The ICER for a patient with starting age 77.0 years is approximately £2,000 less than that of the base case. As noted previously, as this analysis was undertaken using the 'simple analysis'; the ICER is likely overstated by approximately 21% (refer to Section 5.7).

Summary of sensitivity analyses results

5.8.10 Describe the main findings of the sensitivity analyses, highlighting the key drivers of the cost-effectiveness results.

The model is most sensitve to the choice of distributions used to extrapolate the risk equations for first event beyond the length of the trial and the discount rate applied to health outcomes. Regarding first event risk equations, the use of the Weibull and Gompertz functions increases the ICER considerably. However, given that these are counter to clinical understanding that risk declines following the initial MI, this is not of concern. A discount rate of 7.5% applied to health outcomes may increase the ICER to just less than the threshold for cost-effectiveness, however this is not in line with the NICE reference case. The substantial range of scenario analyses demonstrated that for patients aged 50 years and older the ICER remains below £30,000 per QALY gained, irrespective of the setting for initation or source for utilities and costs information.

5.9 Subgroup analysis

The choice of subgroups for de novo economic analysis, their definition and related commentary can be found within Table 130 below.

Table 130: Specification of subgroups

Subgroup	Definition	Comments
Continuation therapy	MI <2 years ago AND ADP < 30 days	Feedback from cardiologists indicates that ticagrelor 60mg BID will be used as "continuation therapy", after the initial one-year treatment with an ADP receptor inhibitor. Consequently we include analysis focussing on those patients with MI <2 years ago with recent ADP inhibitor therapy (ADP < 30 days). Whilst each of the two groups in question were pre-specified, combining via an 'AND' renders this a post-hoc analysis.
Diabetes (yes)	MI <2 years ago AND Diabetes	As requested in the scope. Baseline risk of CV events would be expected to vary according to presence/absence of diabetes. Analysis focussed on the subset of patients

		with MI <2 years ago, so as to represent a subgroup of the base case. Whilst each of the two groups in question were pre-specified, combining via an 'AND' renders this a post-hoc analysis.
Diabetes (no)	MI <2 years ago AND No diabetes	As per Diabetes (yes)
History of PCI (yes)	MI <2 years ago AND History of PCI	Scope requests 'prior revascularisation', which is not a pre-specified subgroup. History of PCI is pre-specified. Baseline risk of CV events would be expected to vary according to whether the patient has a history of PCI. Analysis focussed on the subset of patients with MI <2 years ago, so as to represent a subgroup of the base case. Whilst each of the two groups in question were pre-specified, combining via an 'AND' renders this a post-hoc analysis.
History of PCI (no)	MI <2 years ago AND No history of PCI	Similar to that for History of PCI (yes)

Baseline characteristics for subgroups

Baseline characteristics for subgroups are presented at section 4.5 ("continuation therapy" subgroup presented in Appendix 4).

Statistical analysis for subgroups

Clinical analyses for subgroups are presented at section 4.8 ("continuation therapy" subgroup presented in Appendix 4).

Within the economic model, subgroups are considered via filters placed on patient characteristics. In practice this means that the same risk equations are applied to subgroups as are applied for the base case population (and the full label population) but baseline risk is allowed to vary according to the characteristics of patients in the subgroup. The model simply filters for the specified patients and thereafter aggregates costs and QALYs across over the selected subgroup and recalculates the ICER. As such there is no need to re-run the complete analysis for each subgroup. This methodology means that heterogeneity within the subgroup has been explored and accounted for.

Results

A. Continuation therapy

Within clinical practice it is expected that the majority of patients who start ticagrelor 60 mg BID + low-dose ASA will do so immediately after the cessation of their previous ADP inhibitor treatment. As such, we have analysed those patients within the base-case population who withdrew from their previous ADP inhibitor treatment less than 30 days before randomisation (N=3,602) as these patients are likely to be most representative of clinical practice.

Ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0677 QALYs at an incremental cost of £1,415, generating an ICER of £20,890 (Table 131).

Table 131: Continuation therapy (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£13,352	9.3779			
Ticagrelor 60 mg BID + low-dose ASA	£14,767	9.4456	£1,415	0.0677	£20,890

Results for the PSA are shown in Table 132, Figure 57 and Figure 58.

Table 132: Continuation therapy PSA results

	PSA performed on an individual patient (avg. ICER)
Incremental costs	£1,589
95% CI around costs	£1,550 to £1,622
Incremental QALYs	0.0740
95% CI around QALYs	0.0563 to 0.0913
Change in costs (%)	-2.29 to 2.06
Change in QALYs (%)	-23.43 to 24.20
ICER	£21,476*

*deterministic ICER for individual patient £21,615

Ticagrelor 60 mg BID + low-dose ASA has a 25.6% probability of being cost-effective at £20,000 per QALY gained, increasing to 99.3% at £30,000 per QALY gained.

Figure 57: Continuation therapy PSA scatterplot

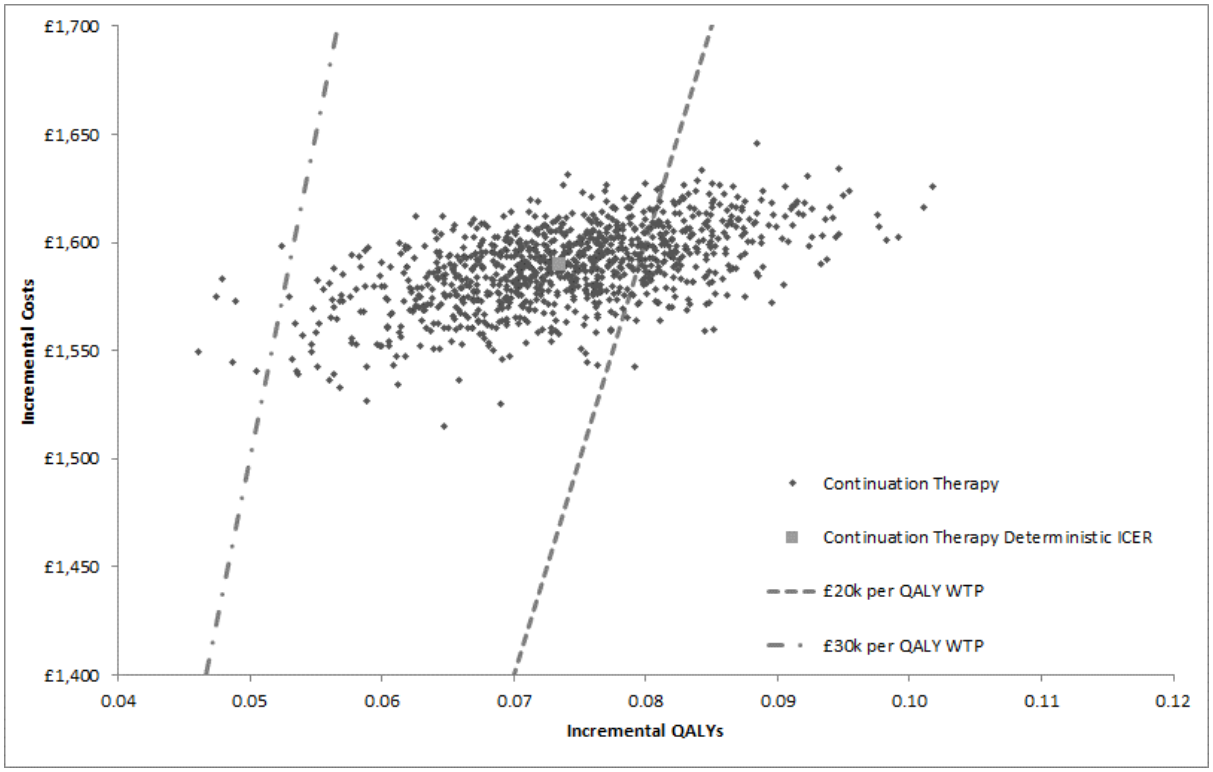
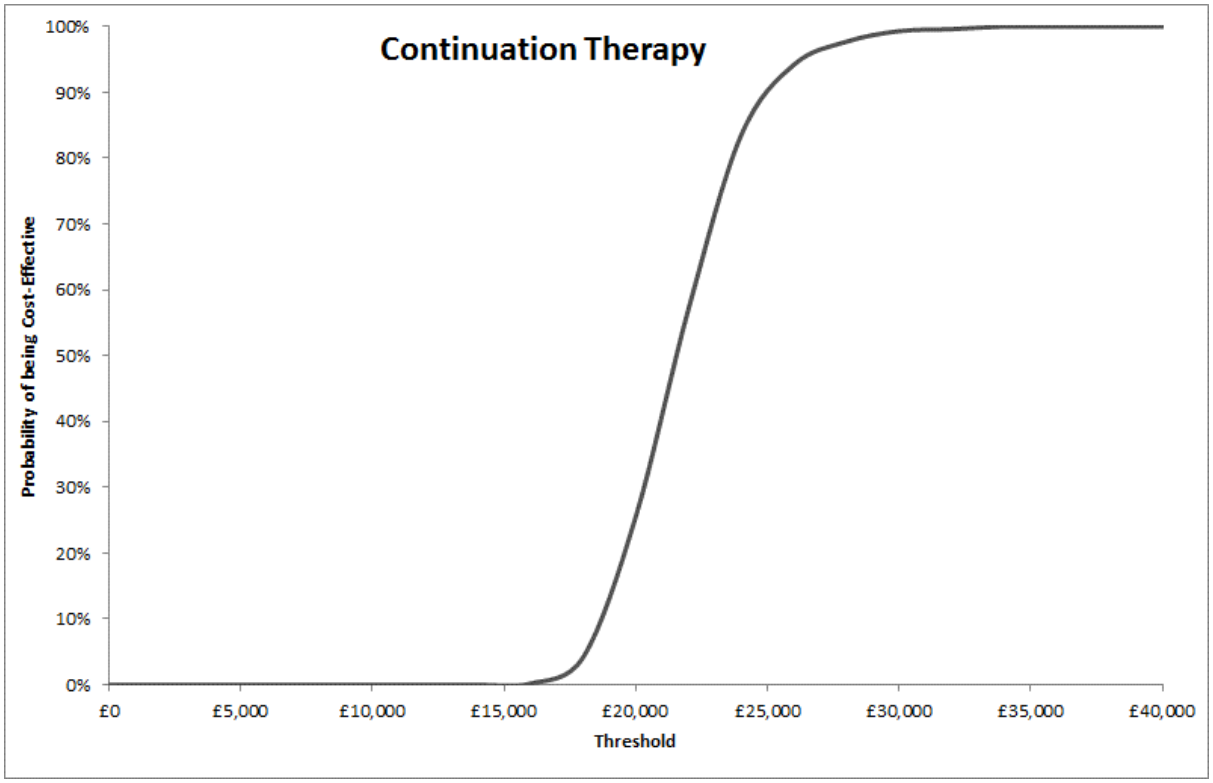


Figure 58: Continuation therapy CEAC



B. Diabetes

As per the NICE scope, we have analysed those patients with and without diabetes separately. Patients with diabetes are known to be at an increased risk (compared to the non-diabetic population) of cardiovascular comorbidities. Within the base-case population 2,741 patients had diabetes and 5,923 did not.

Patients with diabetes

For patients with diabetes, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.1003 QALYs at an incremental cost of £1,429, generating an ICER of £14,246.

Table 133: Diabetes (Yes) (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£13,509	8.9805			
Ticagrelor 60 mg BID + low-dose ASA	£14,938	9.0808	£1,429	0.1003	£14,246

Results for the PSA are shown in Table 134, Figure 59 and Figure 60.

Table 134: Diabetes (Yes) PSA results

	PSA performed on an individual patient (avg. ICER)
Incremental costs	£1,491
95% CI around costs	£1,434 to £1,540
Incremental QALYs	0.1033
95% CI around QALYs	0.0798 to 0.1289
Change in costs (%)	-3.83 to 3.28
Change in QALYs (%)	-21.99 to 25.95
ICER	£14,433*

*deterministic ICER for individual patient £14,572

Ticagrelor 60 mg BID + low-dose ASA has a 99.3% probability of being cost-effective at £20,000 per QALY gained, increasing to 100% at £30,000 per QALY gained.

Figure 59: Diabetes (Yes) PSA scatterplot

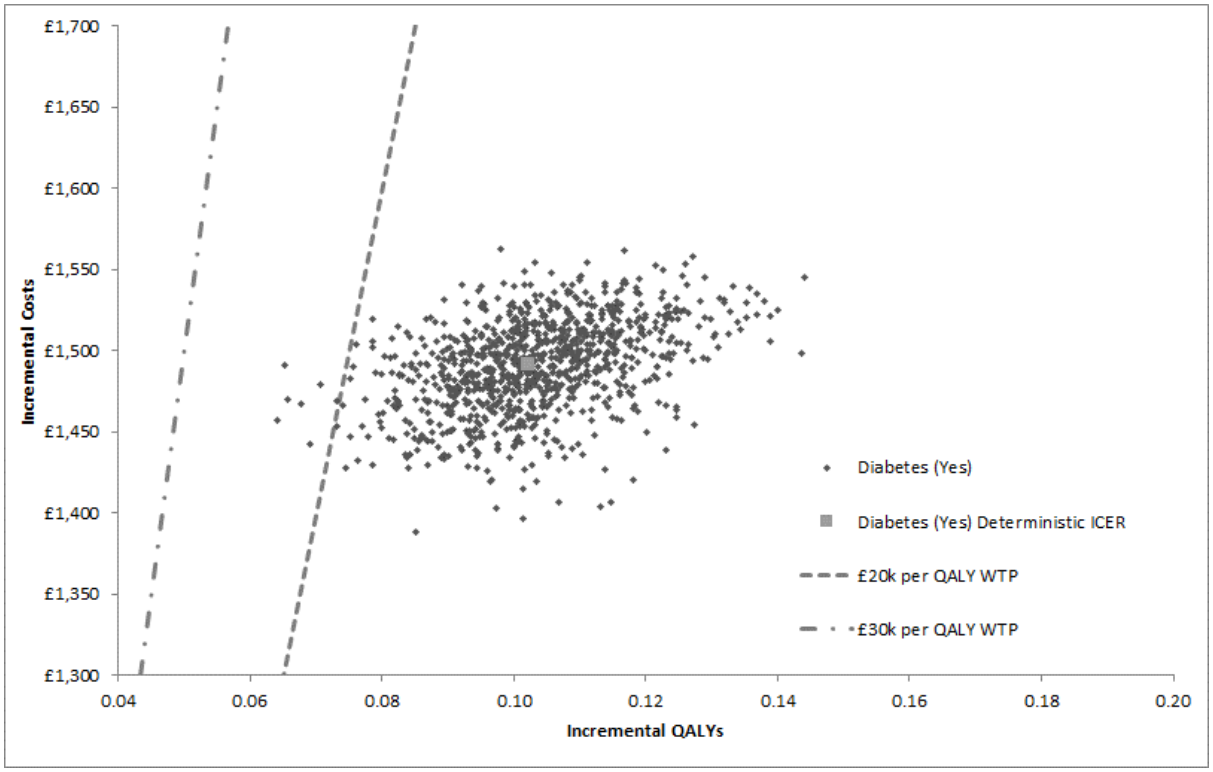
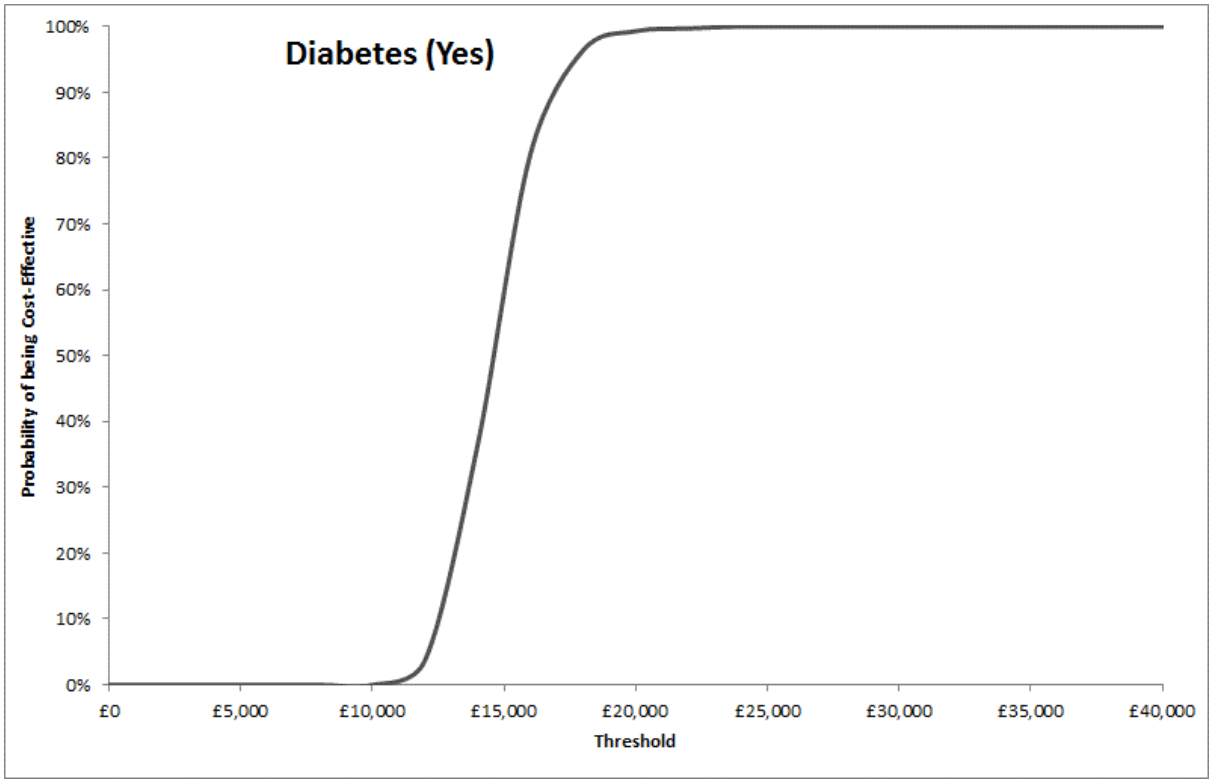


Figure 60: Diabetes (Yes) CEAC



Patients without diabetes

For patient without diabetes, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0572 QALYs at an incremental cost of £1,421, generating an ICER of £24,845.

Table 135: Diabetes (No) (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£12,792	9.3066			
Ticagrelor 60 mg BID + low-dose ASA	£14,214	9.3638	£1,421	0.0572	£24,845

Results for the PSA are shown in Table 136, Figure 61 and Figure 62.

Table 136: Diabetes (No) PSA results

	PSA performed on an individual patient (avg. ICER)
Incremental costs	£1,443
95% CI around costs	£1,411 to £1,473
Incremental QALYs	0.0582
95% CI around QALYs	0.0445 to 0.0706
Change in costs (%)	-2.35 to 1.94
Change in QALYs (%)	-21.37 to 21.65
ICER	£24,813*

*deterministic ICER for individual patient £24,916

ticagrelor 60 mg BID + low-dose ASA has a 1.5% probability of being cost-effective at £20,000 per QALY gained, increasing to 95.0% at £30,000 per QALY gained.

Figure 61: Diabetes (No) PSA scatterplot

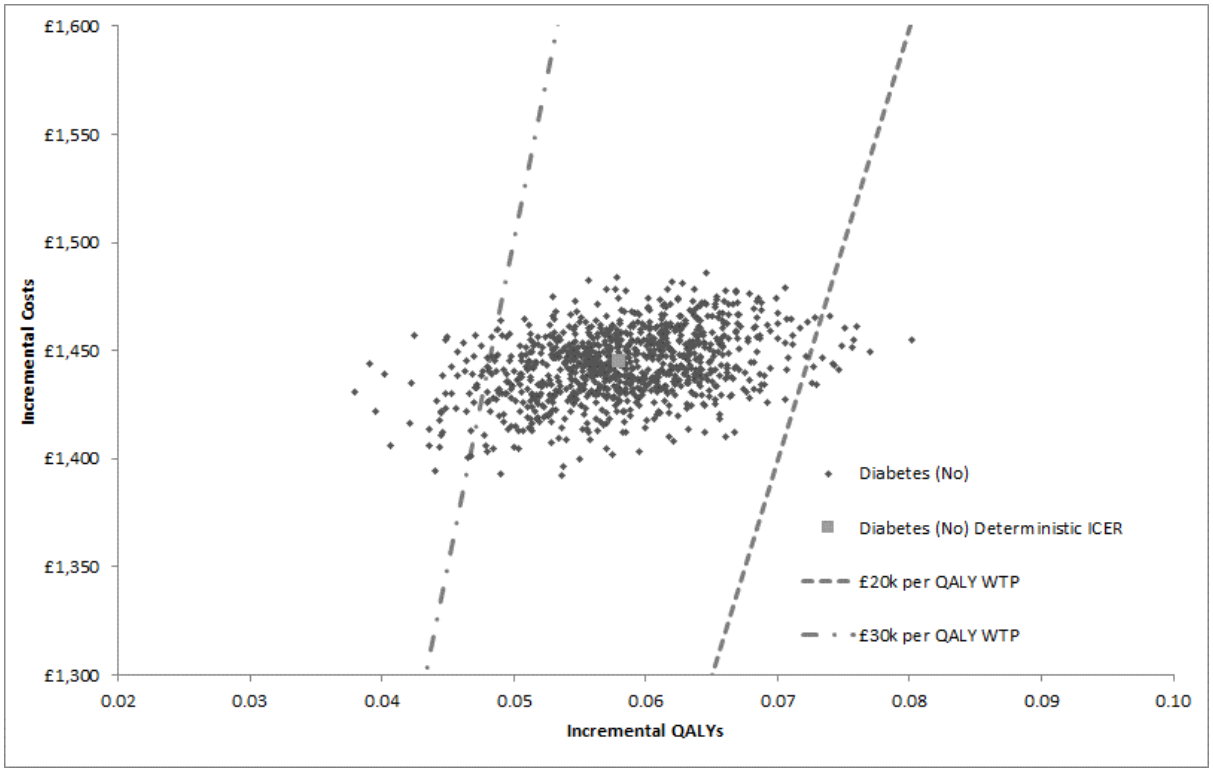
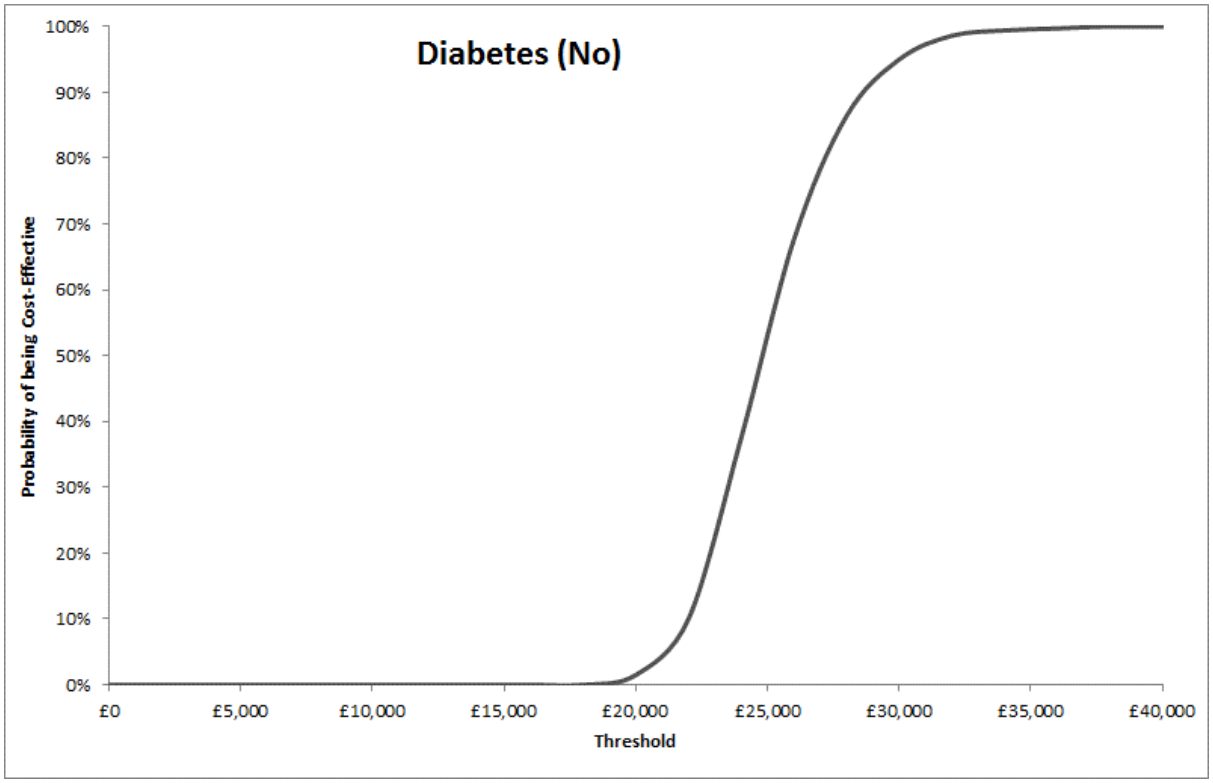


Figure 62: Diabetes (No) CEAC



C. History of PCI

The NICE scope requests stratification according to whether people have or have not had prior revascularisation. Since 'prior revascularisation' was not a prespecified subgroup of the trial, whereas 'history of PCI' was (the difference being history of coronary artery bypass grafting), we present analysis according to presence or absence of history of PCI. Within the base-case population 7,261 patients had a history of PCI whilst 1,401 did not. For two patients the status was unknown.

Patients with a history of PCI

For patients with a history of PCI, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0628 QALYs at an incremental cost of £1,419, generating an ICER of £22,600 (Table 137).

Table 137: History of PCI (Yes) (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£13,311	9.4436			
Ticagrelor 60 mg BID + low-dose ASA	£14,730	9.5064	£1,419	0.0628	£22,600

Results for the PSA are shown in Table 138, Figure 63 and Figure 64.

Table 138: History of PCI (Yes) PSA results

	PSA performed on an individual patient (avg. ICER)
Incremental costs	£1,437
95% CI around costs	£1,362 to £1,508
Incremental QALYs	0.0639
95% CI around QALYs	0.0462 to 0.0828
Change in costs (%)	-5.39 to 4.78
Change in QALYs (%)	-27.14 to 30.48
ICER	£22,488*

*deterministic ICER for individual patient £22,684

Ticagrelor 60 mg BID + low-dose ASA has a 18.0% probability of being cost-effective at £20,000 per QALY gained, increasing to 96.5% at £30,000 per QALY gained.

Figure 63: History of PCI (Yes) PSA scatterplot

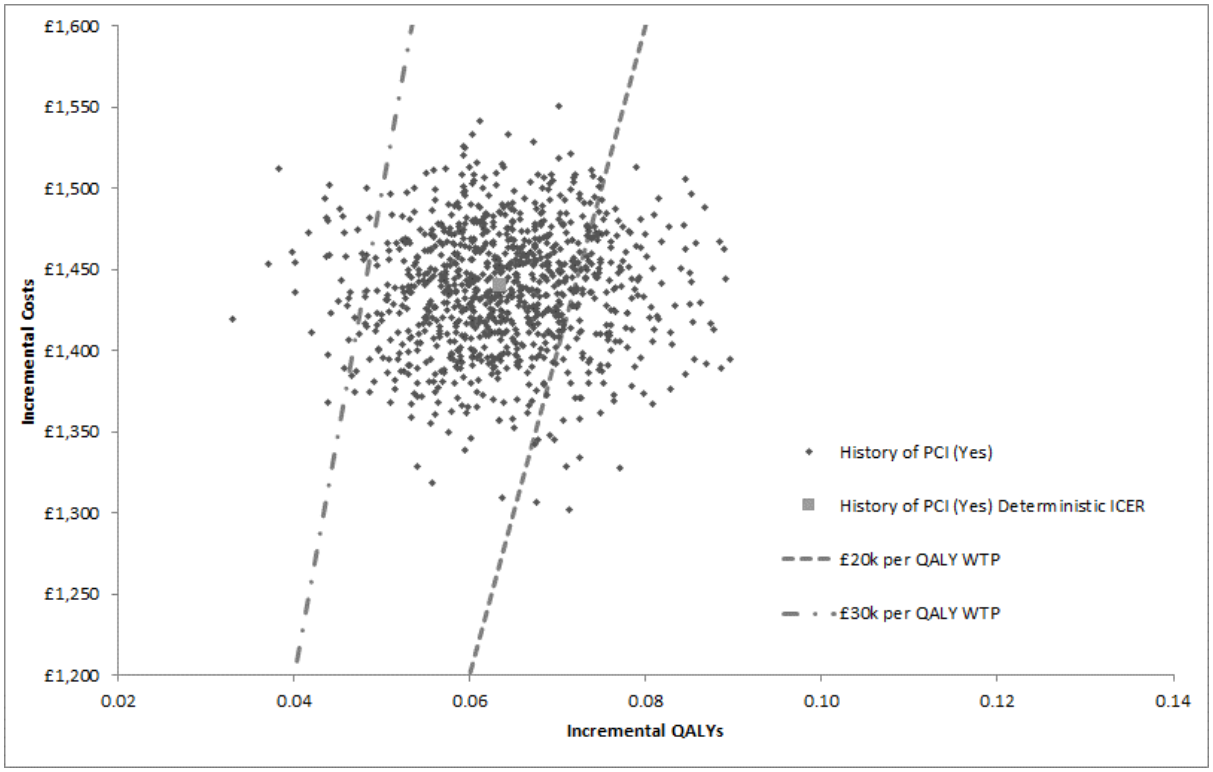
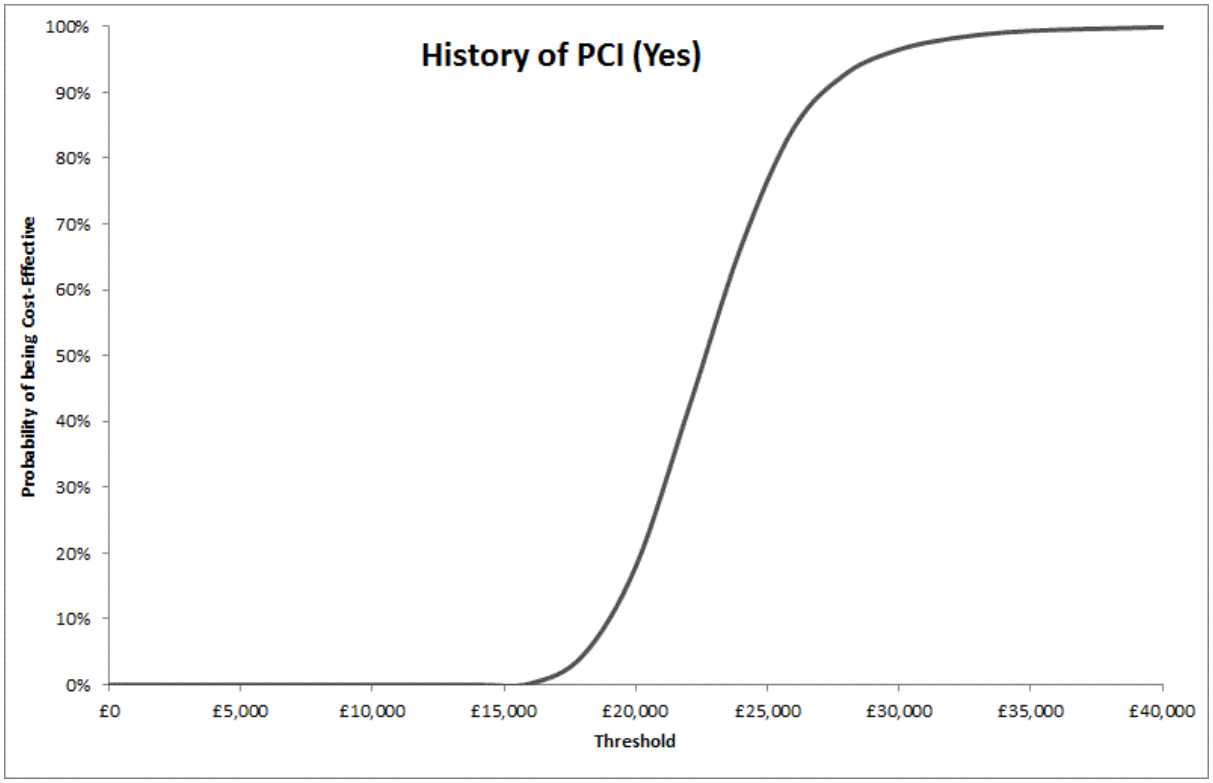


Figure 64: History of PCI (Yes) CEAC



Patients without a history of PCI

For patients without a history of PCI, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.1124 QALYs at an incremental cost of £1,445, generating an ICER of £12,856.

Table 139: History of PCI (No) (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£11,508	7.9600			
Ticagrelor 60 mg BID + low-dose ASA	£12,953	8.0724	£1,445	0.1124	£12,856

Results for the PSA are shown in Table 140, Figure 65 and Figure 66.

Table 140: History of PCI (No) PSA results

	PSA performed on an individual patient (avg. ICER)
Incremental costs	£1,126
95% CI around costs	£1,045 to £1,198
Incremental QALYs	0.1021
95% CI around QALYs	0.0714 to 0.1346
Change in costs (%)	-7.36 to 6.16
Change in QALYs (%)	-29.87 to 32.23
ICER	£11,026*

*deterministic ICER for individual patient £11,089

ticagrelor 60 mg BID + low-dose ASA has a 100% probability of being cost-effective at both £20,000 and £30,000 WTP per QALY gained.

Figure 65: History of PCI (No) PSA scatterplot

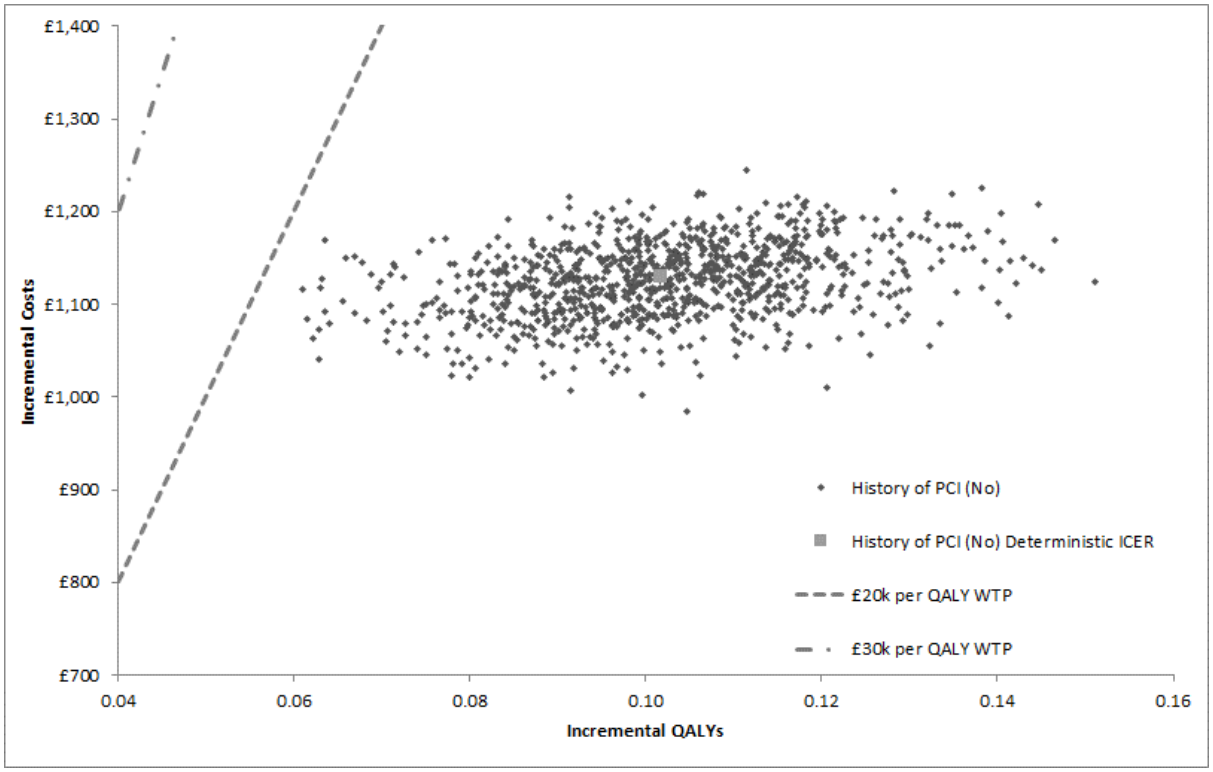
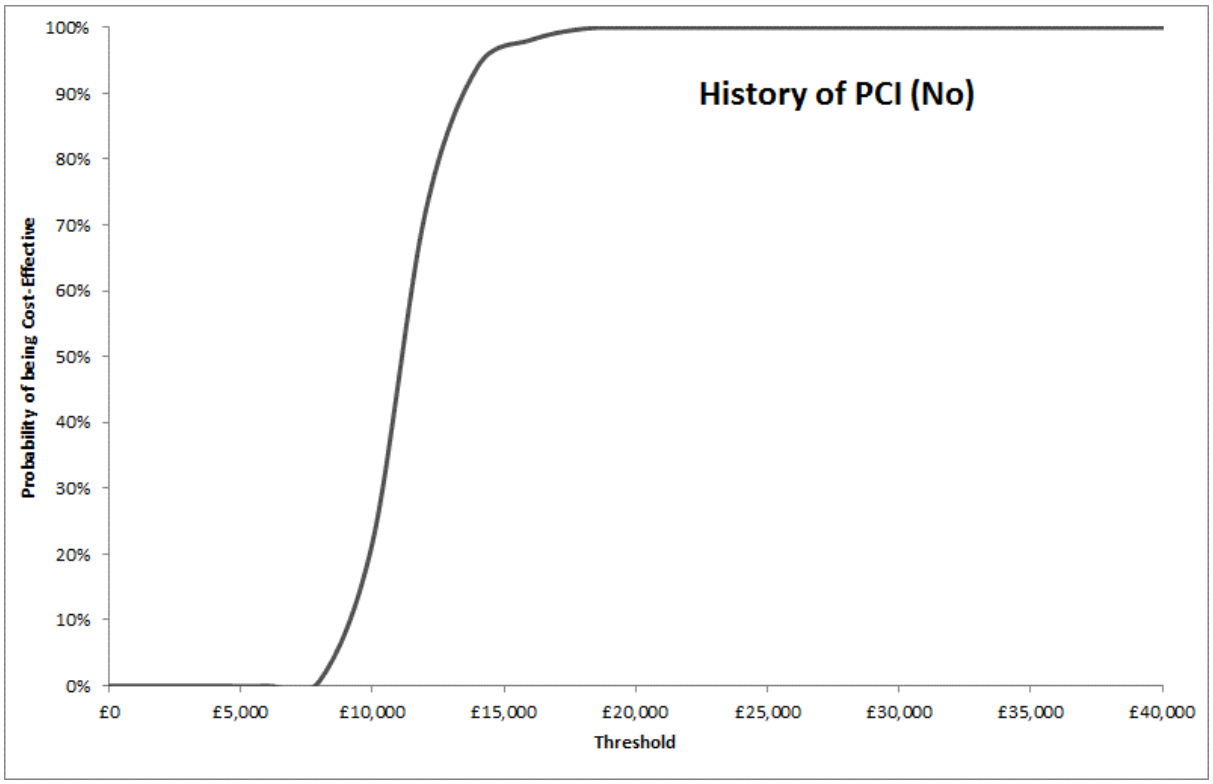


Figure 66: History of PCI (No) CEAC



Subgroups not considered

The decision problem at section 3 has been addressed. As detailed at section 5.9.2, we present analysis based on patient status in respect of 'history of PCI' as opposed to 'prior revascularisation', owing to the means by which patients were stratified in the trial.

5.10 Validation

Clinical validity

The model includes a validation of observed versus modelled clinical events (Table 141) which is based on the hazard functions selected by the user to describe time to first events and time to subsequent events. Using log–logistic survival functions for time to first events, the total number of events generated by the model closely matches the observed number of first events. The model slightly underestimates the total number of observed subsequent events.

Modelled AE outcomes for TIMI bleeds and grade 3–4 dyspnoea also closely match those observed in the ITT population while patients were on treatment. Adverse events are slightly over-estimated for ticagrelor 60 mg BID + low-dose ASA, while TIMI major bleeds are slightly underestimated for patients receiving low-dose ASA. In combination, these slightly bias the outcomes of the model against ticagrelor 60 mg BID + low-dose ASA, providing a conservative estimate for cost effectiveness.

The competing risks approach was used to estimate hazard functions representing the time to first component of the composite outcome, CV death, MI or stroke. In addition, MI or stroke events that occurred within 30 days of a CV death were recorded as CV deaths in order to accurately reflect the overall expected survival of patients. Nevertheless, the number of CV events modelled by the health economic model were similar with the number of CV events observed in the PEGASUS-TIMI 54 study (Table 141).

Table 141: Comparison of the number of observed vs. modelled events, during a period of the PEGASUS-TIMI 54 ('Label' population).

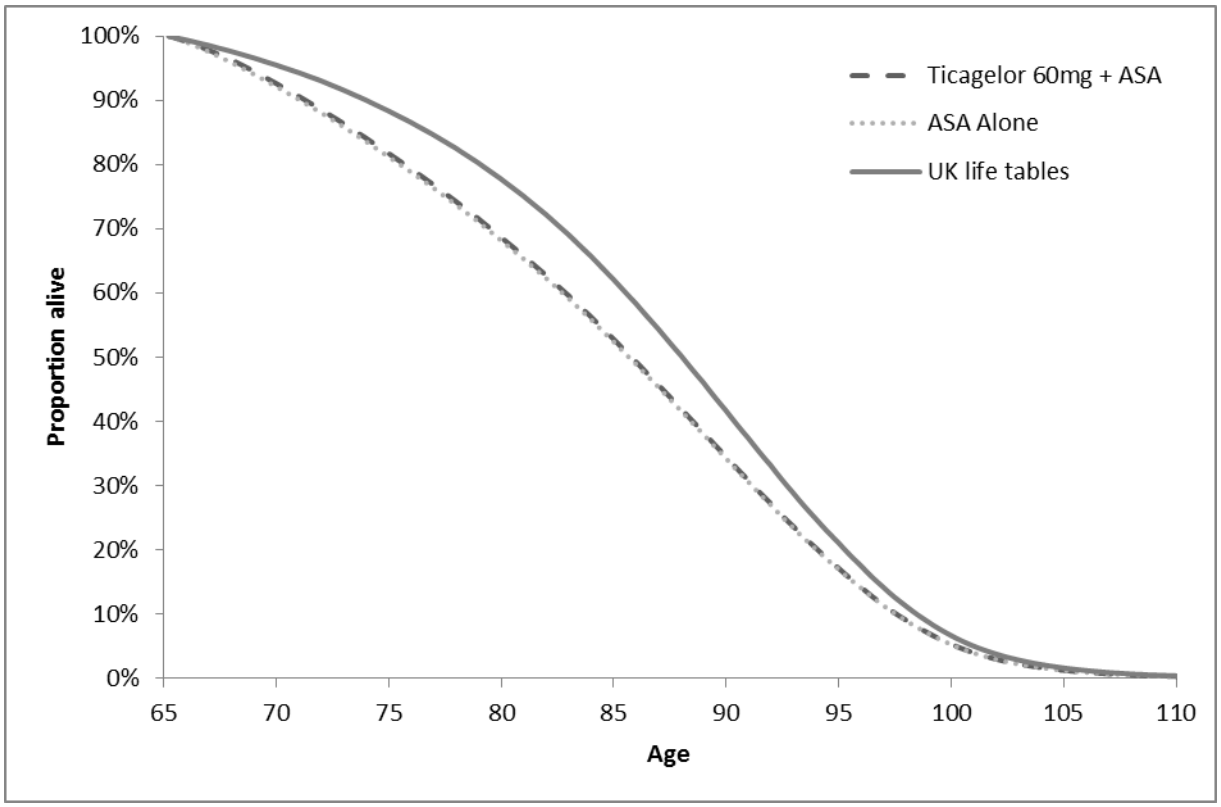
	Ticagrelor 60 mg BID + low-dose ASA	Low-dose ASA	Modelled vs. observed

	Observed	Modelled	Observed	Modelled	Ticagrelor 60 mg BID + LD ASA	Low-dose ASA
First event						
Non-fatal MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal CV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Composite outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other fatal event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent event						
Non-fatal MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal CV events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other fatal events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event						
TIMI Major bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The modelled events compared to the observed events are shown for patients included in the EMA indicated ‘label population’ (n=10,779). It is expected that the predictive accuracy of modelled events compared to observed events is comparable in patients with a qualifying MI <2 years ago (n=8,664).

A further check for validity was performed to ensure that the model predicted valid life expectancy. UK life tables were used to compare the survival probability by age in the economic model (Figure 67). Overall, the modelled survival curves for Ticagrelor 60 mg BID + low-dose ASA and low-dose ASA were in line with the UK life table survival curve although the linear curve from the model did not match completely with the life table data. The difference suggests that the model may underestimate the benefit of ticagrelor 60 mg BID + low-dose ASA as a larger number of CV events would be averted by ticagrelor 60 mg BID + low-dose ASA when the surviving population is larger.

Figure 67: Comparing the proportion of survival modelled for ticagrelor 60 mg BID + low-dose ASA and low-dose ASA with UK life tables



Technical validation

Tests were performed to check for errors that may have occurred in programming or during the incorporation of data into the model. In the simplest of these, a multi-way sensitivity analysis was performed where transition probabilities, costs and QALYs were set equal for both treatment strategies in the model. This exercise yielded the expected results (i.e. no difference in estimated long-term costs and QALYs between ticagrelor 60 mg BID + low-dose ASA and low-dose ASA).

5.11 Interpretation and conclusions of economic evidence

No published literature assessing the cost-effectiveness of ticagrelor 60 mg BID + low dose ASA were identified in the systematic review. As such, it is not possible to compare our results against published literature.

The economic model, which is compliant with the NICE reference case, was developed using patient level data on 21,162 patients who were enrolled into PEGASUS-TIMI 54 utilsing a competing risks framework which allows for different

impact of patient baseline characteristics for each separate endpoint. The risk equations model events directly, rather than composite events which are then apportioned using the probability of that event being of a certain type. The risk equations have been shown to predict the events observed within PEGASUS-TIMI 54 accurately. In order to control for patient hetrogeneity, the complete analysis runs each individual included within the 'label' population through the model one at a time, generating and storing results. This estimates the parametric functions for each patient individually using their specific characteristics. Once all patients have been run through the model, the average of the results is taken to estimate results for the cohort. Utilitising these approaches results in an accurate estimate of clinical events, costs and QALYs associated with each treatment, which would have not been possible without utilising the competing risks framework or in a standard cohort markov model framework.

The trade-off in using this approach is that the PSA and DSA have to be based on a single representative patient as the computational requirements of undertaking a PSA and DSA on an individual patient approach is great. Although some first order uncertainty may have not been captured, this has been controlled for by extensive scenario and sensitvity analyses and the use of appropriate costs and disutilities. Costs for health states, events and adverse events used within the model have been sourced from Evidence Review Group developed models for previous NICE technology appraisals of oral antiplatelets. Disutilities for health states, events and adverse events informed by in excess of 118,000 EQ-5D responses collected within PEGASUS-TIMI 54, weighted using UK tariff using general public preferences.

Due to data limitations an indirect comparison between ticagrelor 60 mg BID + low dose ASA and clopidogrel + low dose ASA was not possible. Therefore, this has not been included within the model although this is included within the NICE scope. However, it should be noted that clopidogrel has no marketing authorisation within this indication for use in conjunction with ASA and is arguably not a relevant comparator based on level of use in clinical practice in England and Wales.

Results from PEGASUS-TIMI 54 (full population) noted an increased risk of gout with ticagrelor 60 mg BID + low dose ASA compared to placebo + low dose ASA (HR 1.48, p = 0.01) (6).This was not included within the model due to the low overall

event rates and that unless gout is associated with a high mortality rate, which is not the case (138), this was not believed to materially impact on the ICER. Therefore, it is believed that the model captures all the relevant clinical events and associated costs and utility consequences of treatment.

Although the ICER varies across different patient subgroups; ticagrelor 60 mg BID + low dose ASA is cost-effective in all scenarios analysed (Table 142). Additionally, scenario analyses assessing potential variation in clincial practice (the impact of differential initition settings and starting ages) demonstrate that ticagrelor 60 mg BID + low dose ASA is cost-effective in all settings and that this is highly likely to be generalisable to clinical practice.

Table 142: Summary of results (complete analysis)

Analysis	ICER per QALY gained
Base-case	£20,098
Continuation therapy	£20,890
Patients with diabetes	£14,246
Patients without diabetes	£24,845
Patients with history of PCI	£22,600
Patients without history of PCI	£12,856

The analyses presented support the conclusion that ticagrelor 60 mg BID is a cost-effective use of NHS resources, when initiated for up to 3 years treatment duration in conjunction with aspirin, in patients with a history of MI (<2 years ago) and a high risk of developing an atherothrombotic event, including use as continuation therapy after the initial one year of dual antiplatelet treatment with an ADP receptor inhibitor therapy.

6 Assessment of factors relevant to the NHS and other parties

The budget impact analysis reflects the expectation that ticagrelor 60mg BID + low dose ASA will be used as continuation therapy, following the initial one-year treatment with dual antiplatelet therapy following myocardial infarction, in patients with a high risk of an atherothrombotic event.

The number of hospital admissions for ‘actual myocardial infarction’ (ICD10 code; I21) in England in the year 2014/15 was 78,397 (44). Each is assumed to represent one patient. Of these patients, 90% are assumed to receive aspirin-based DAPT in the first year following MI (45). Of the resultant cohort, 67% are expected to remain CV event-free over the next year (17). For the purposes of the budget impact analysis, it is assumed that all of these patients remain on DAPT for the year following MI. Of these patients, 59% are expected to meet the PEGASUS-TIMI 54 inclusion criteria and not meet the exclusion criteria (17).

This yields the estimate for the annual number of incident continuation therapy ticagrelor 60mg-eligible patients to be 27,887. The number of eligible patients is assumed to remain constant over the time horizon of the budget impact analysis, owing to the number of hospital admissions for actual myocardial infarction appearing stable over recent years.

The percentage of patients for each subgroup is taken from the PEGASUS-TIMI 54 trial (6) and is presented at Table 143.

Table 143: Continuation therapy, in-year incident cohort of patients eligible for treatment in England

		2016	2017	2018	2019	2020
Continuation therapy, in-year incident patients		27,887	27,887	27,887	27,887	27,887
Subgroups:						
Diabetes	32% (6)	8,969	8,969	8,969	8,969	8,969
No diabetes	68% (6)	18,918	18,918	18,918	18,918	18,918
History of PCI	83% (6)	23,115	23,115	23,115	23,115	23,115
No history of PCI	17% (6)	4,733	4,733	4,733	4,733	4,733

6.3 What assumption(s) were made about current treatment options and uptake of technologies?

Data taken from the cardiologists prescribing intention survey (45) is used to inform usage in the year 2016 and can be seen at Table 144.

6.4 What assumption(s) were made about future uptake?

Ticagrelor 60mg BID + low dose ASA usage is assumed to commence in 2017, owing to the expectation that cardiologists will prescribe long term therapy at discharge, consisting of a licensed DAPT regimen for the first year following MI, followed by ticagrelor 60mg BID + low dose ASA thereafter in some eligible continuation therapy patients. Usage of ticagrelor 60mg BID + low dose ASA is expected to grow such that it be used in 14% of in-year history of MI incident eligible patients by 2020, at the expense of ASA monotherapy. Uptake of other treatment options in in-year incident patients is assumed to remain constant over time (Table 144).

Patients initiated to ticagrelor 60mg BID + ASA and those on ticagrelor 90mg BID + low dose ASA are assumed to discontinue treatment at the rate observed in the corresponding arms of the PEGASUS-TIMI 54 trial (63). The same discontinuation rate is assumed to apply to patients receiving clopidogrel + ASA and prasugrel + ASA. Those reaching 3 years on ticagrelor 60mg BID + low dose ASA treatment are assumed to discontinue, in line with the specified duration of treatment for this single

technology appraisal submission. All patients who discontinue DAPT are assumed to move to ASA monotherapy.

Table 144: Current and future uptake, in-year incident patients

% Patient share	2016 (45)	2017	2018	2019	2020
ASA monotherapy	89%	87%	83%	79%	75%
Clopidogrel monotherapy	1%	1%	1%	1%	1%
Prasugrel monotherapy	0%	0%	0%	0%	0%
Clopidogrel + ASA	4%	4%	4%	4%	4%
Prasugrel + ASA	0%	0%	0%	0%	0%
Ticagrelor 60mg BID + LD ASA	**0%**	**2%**	**6%**	**10%**	**14%**
Ticagrelor 90mg BID + ASA	1%	1%	1%	1%	1%
No OAP	5%	5%	5%	5%	5%

Patients initiated to ASA monotherapy are assumed to discontinue at the rate observed in the corresponding arm of the PEGASUS-TIMI 54 trial (63). Patients initiated to other monotherapy regimens are assumed to discontinue at the same rate as patients on ASA monotherapy. All patients who discontinue monotherapy are assumed to move to no oral antiplatelet (OAP).

After applying discontinuation assumptions, the resultant share of patients incident from 2016 (cumulative), for ticagrelor 60mg BID + low dose ASA, can be seen at Table 145. These shares inform the total number of patients receiving ticagrelor 60mg BID + low dose ASA in any given year (i.e. patients initiated in the given year plus those initiated in prior years who remain on treatment).

Table 145: Current and future uptake of ticagrelor 60mg BID + low dose ASA, patients incident from 2016 (cumulative)

% Patient share	2016	2017	2018	2019	2020
Ticagrelor 60mg BID + LD ASA	0.0%	1.0%	2.6%	4.2%	5.5%

6.5 Other significant costs associated with treatment that may be of interest to commissioners

No significant costs associated to treatment with ticagrelor 60mg BID + low dose ASA are expected. The cost of managing adverse events has been included in the net budget impact at section 6.8.

6.6 Unit costs used in the budget impact analysis

The unit costs applied in the budget impact analysis are the same as those used in the cost-utility analysis model. Details can be found within sections 5.5.6 and 5.5.7.

6.7 Estimates of resource savings

Resource savings in the form of CV events averted were calculated from the Markov traces of ticagrelor 60mg BID + low dose ASA and ASA monotherapy. The same approach was used to calculate the likely costs associated to additional adverse events (bleeding and dyspnoea).

6.8 State the estimated annual budget impact on the NHS in England

The estimated net budget impact for the NHS in England is shown at Table 102. The total cost of ticagrelor 60mg BID + low dose ASA is made up of drug acquisition costs plus costs associated to treatment of adverse events (bleeding and dyspnoea) over and above that experienced by patients on ASA monotherapy, based on rates observed in the PEGASUS-TIMI 54 trial. Thereafter, drug acquisition costs for displaced ASA monotherapy and costs for CV events averted, based on rates observed in the PEGASUS-TIMI 54 trial are subtracted, to arrive at the net budget impact.

The net budget impact is expected to be £0.4m in 2017, rising to £5.4m in 2020.

Table 146. Budget Impact of ticagrelor 60mg BID in England

	2016	2017	2018	2019	2020
Continuation therapy, in-year incident patients	27,887	27,887	27,887	27,887	27,887
Continuation therapy, patients incident from 2016 (cumulative)	27,887	55,775	83,662	111,550	139,437
Ticagrelor 60mg BID + ASA:					
Share of in-year incident patients	0%	2%	6%	10%	14%
Share of patients incident from 2016 (cumulative)	0.0%	1.0%	2.6%	4.2%	5.5%
Patients treated	0	558	2,171	4,725	7,724
Drug acquisition costs	£0	£403,144	£1,569,080	£3,415,513	£5,582,794
Additional adverse event costs	£0	£643	£2,501	£5,444	£8,898
Ticagrelor 60mg BID + ASA Total Costs	**£0**	**£403,786**	**£1,571,581**	**£3,420,957**	**£5,591,692**
Less: **ASA monotherapy:**					
Drug acquisition costs	£0	£5,893	£22,937	£49,929	£81,611
CV events averted costs	£0	£6,826	£26,568	£57,832	£94,528
Total Cost Offset	**£0**	**£12,719**	**£49,505**	**£107,761**	**£176,139**
Net Budget Impact	**£0**	**£391,067**	**£1,522,076**	**£3,313,197**	**£5,415,553**

6.9 Other opportunities for resource savings or redirection of resources not quantified

No further opportunities for resource savings or redirection are identified.

6.10 Limitations of the budget impact analysis

The starting point for the estimate the number of eligible patients is hospital episode statistics (HES) data for the annual number of admissions for ‘actual myocardial infarction’ in England. HES does not report the number of patients experiencing MI. Since some patients who are hospitalised with MI would be expected to experience a recurrent hospitalised MI within the year, there is potential that the budget impact analysis overestimates on account of this.

The analysis assumes that all patients initiated to DAPT following MI, who remain CV event-free in the following year, remain on DAPT for the full year. This is likely to slightly overestimate the number of continuation therapy in-year incident patients, as further discontinuations unrelated to CV events would be expected.

7 References

1. (NICE) NIfHaCE. Guide to the methods of technology appraisal 2013. 2013.
2. Lewsey JD LK, Ford I, Fox KA, Ritchie LD, Tunstall-Pedoe H, Watt GC, Woodward M, Kent S, Neilson M, Briggs AH. . A cardiovascular disease policy model that predicts life expectancy taking into account socioeconomic deprivation. . Heart 2015;101:201-8.
3. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, et al. Vorapaxar in the Secondary Prevention of Atherothrombotic Events. New England Journal of Medicine. 2012;366(15):1404-13.
4. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine. 2007;357(20):2001-15.
5. Agency EM. SPC: Brilique 60 mg film-coated tablets. 2016.
6. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372(19):1791-800.
7. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007;50(7):e1-e157.
8. Medscape. Myocardial Infarction 2014, available at http://emedicine.medscape.com/article/155919-overview 2014 [cited 2014 4 August]. Available from: http://emedicine.medscape.com/article/155919-overview.
9. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60(16):1581-98.
10. Cohen M, Roubin G, Kuepper F. The challenge of ST-segment elevation myocardial infarction. International journal of clinical practice. 2007;61(12):2079-92.
11. Garcia-Garcia C, Subirana I, Sala J, Bruguera J, Sanz G, Valle V, et al. Long-term prognosis of first myocardial infarction according to the electrocardiographic pattern (ST elevation myocardial infarction, non-ST elevation myocardial infarction and non-classified myocardial infarction) and revascularization procedures. The American journal of cardiology. 2011;108(8):1061-7.
12. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.
13. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation. 2001;104(3):365-72.
14. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12(1):30-47.

15. Fuentes Q. E, Fuentes Q. F, Andrés V, Pello OM, de Mora JF, Palomo G. I. Role of platelets as mediators that link inflammation and thrombosis in atherosclerosis. Platelets. 2013;24(4):255-62.
16. Gawaz M. The evolving science of atherothrombotic disease2008 2008-11-01 00:00:00. I4-I7 p.
17. Rapsomaniki E, Thuresson M, Yang E, Blin P, Hunt P, Chung S-C, et al. Outcomes Among 140,887 Survivors of Acute Myocardial Infarction: comparison of health system data in 4 countries (JAMA submitted manuscript). 2014.
18. David M. Kern, Carl Mellström, Phillip R. Hunt, Ozgur Tunceli, Bingcao Wu, Mogens Westergaard, et al. Long-term cardiovascular risk and costs for myocardial infarction survivors in a US commercially insured population (Am J Cardiol submitted manuscript). 2014.
19. Yang E, Stokes M, Johansson S, Mellstrom C, Magnuson E, Cohen D, et al. Clinical and Economic Outcomes among Elderly Myocardial Infarction Survivors in United States (submitted manuscript, not yet approved). 2014.
20. Rapsomaniki ES, D. Emmas, C. Chung, S. Pasea, L. Denaxas, S. Shah, AD. Pujades-Rodriguez, M. Timmis, A. Hemingway, H. Health outcomes in patients with stable coronary artery disease following myocardial infarction; construction of a PEGASUS-TIMI-54 like population in UK linked electronic health records. 2013.
21. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180-9.
22. Khoury Z, Schwartz R, Gottlieb S, Chenzbraun A, Stern S, Keren A. Relation of coronary artery disease to atherosclerotic disease in the aorta, carotid, and femoral arteries evaluated by ultrasound. The American journal of cardiology. 1997;80(11):1429-33.
23. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226-35.
24. Kikkert WJ, Hoebers LP, Damman P, Lieve KV, Claessen BE, Vis MM, et al. Recurrent myocardial infarction after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. The American journal of cardiology. 2014;113(2):229-35.
25. Nakatani D, Sakata Y, Suna S, Usami M, Matsumoto S, Shimizu M, et al. Incidence, predictors, and subsequent mortality risk of recurrent myocardial infarction in patients following discharge for acute myocardial infarction. Circulation journal : official journal of the Japanese Circulation Society. 2013;77(2):439-46.
26. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J. 2010;31(22):2755-64.
27. Gulliksson M, Wedel H, Koster M, Svardsudd K. Hazard function and secular trends in the risk of recurrent acute myocardial infarction: 30 years of follow-up of more than 775,000 incidents. Circulation Cardiovascular quality and outcomes. 2009;2(3):178-85.
28. Figueras J, Missorici M, Lidon RM, Cortadellas J, Soler Soler J. Coincidental annual distribution of first and second acute myocardial infarction. The American journal of cardiology. 2002;89(12):1416-20.
29. Antithrombotic Trialists C, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease:

collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849-60.
30. Storey RF, Bliden KP, Patil SB, Karunakaran A, Ecob R, Butler K, et al. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. J Am Coll Cardiol. 2010;56(3):185-93.
31. Collet JP, Montalescot G. P2Y12 inhibitors: thienopyridines and direct oral inhibitors. Hamostaseologie. 2009;29(4):339-48.
32. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation. 2009;119(19):2553-60.
33. Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol. 2008;51(20):1925-34.
34. Jakubowski JA, Matsushima N, Asai F, Naganuma H, Brandt JT, Hirota T, et al. A multiple dose study of prasugrel (CS-747), a novel thienopyridine P2Y12 inhibitor, compared with clopidogrel in healthy humans. British journal of clinical pharmacology. 2007;63(4):421-30.
35. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009;120(25):2577-85.
36. Nylander S, Femia EA, Scavone M, Berntsson P, Asztely AK, Nelander K, et al. Ticagrelor inhibits human platelet aggregation via adenosine in addition to P2Y12 antagonism. Journal of thrombosis and haemostasis : JTH. 2013;11(10):1867-76.
37. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). 2016;37(3):267-315.
38. Merck. Vorapaxar Summary of Product Characteristics. 2015.
39. Merck. Zontivity® (vorapaxar) prescribing information. 2015.
40. BMS. Plavix Summary of Product Characteristics. 2015.
41. Bayer. Rivaroxaban Summary of Product Characteristics. 2014.
42. NICE. MI Secondary Prevention Guidelines: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (NICE clinical guideline 172). 2013.
43. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). 2012;33(20):2569-619.
44. HSCIC. Hospital Episode Statistics, Admitted Patient Care - England, 2014-15: Diagnosis Analysis. 2015.
45. Grime JA, A. Prescribing of Oral Antiplatelet Therapy: Results from a Representative Patient Records Survey into Cardiologist Prescribing Intentions for High Risk Post-MI Patients at Hospital Discharge. Data on File. 2016.

46. AstraZeneca. Real World Study into Post MI Prescribing to support NICE submission: 27th May 2015. Data on File. 2015.
47. (NICE) NIfHaCE. CG172: Myocardial infarction: cardiac rehabilitation and prevention of further MI. 2013.
48. SIGN. Guideline No. 93: Acute Coronary Syndromes. 2013.
49. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term use of ticagrelor in patients with prior myocardial infarction. New England Journal of Medicine. 2015;372(19):1791-800.
50. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol. 2007;49(19):1982-8.
51. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, et al. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. Journal of the American College of Cardiology. 2015;65(20):2211-21.
52. Bonaca MP. Abstract 11594: Reduction in Subtypes and Sizes of Myocardial Infarction With Ticagrelor in PEGASUS-TIMI 54. Circulation. 2015;132:(Suppl 3).
53. Bonaca MP. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS TIMI 54. European heart journal. 2015;DOI: http://dx.doi.org/10.1093/eurheartj/ehv531ehv531.
54. O'Donoghue ML, Bonaca MP, Magnani G, Bhatt DL, Cohen M, Steg PG, et al. The efficacy and safety of ticagrelor in women versus men with a prior myocardial infarction: Insights from the PEGASUS-TIMI 54 trial. European Heart Journal. 2015;36:549.
55. Murphy SA. Abstract 17121: Reduction in Total Cardiovascular Events With Long-term Use of Ticagrelor in Patients With Prior Myocardial Infarction in the PEGASUS-TIMI 54 Trial. Circulation. 2015;132:(Suppl 3).
56. Bonaca MP, Bhatt DL, Steg PG, Budaj A, Bansilal S, Storey RF, et al. TCT-78: Efficacy of Long-Term Ticagrelor in Stented Patients in PEGASUS-TIMI 54. JACC. 2015;66(15):Suppl B.
57. Magnani G, Sabatine MS, Bhatt DL, Choen M, Steg G, Storey RF, et al., editors. Efficacy and Safety of Ticagrelor for Long-Term Secondary Prevention of Atherothrombotic Events in Relation to Renal Function: Insights from the PEGASUS-TIMI 54 trial. European Society of Cardiology; 2015 Saturday 29th August to Wednesday 2nd Septemeber; London.
58. Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Am Heart J. 2004;148(2):263-8.
59. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371(23):2155-66.
60. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. New England Journal of Medicine. 2015;0(0):null.
61. Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF, et al. Design and rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of

Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. American Heart Journal. 2014;167(4):437-44.e5.
62. AstraZeneca. Data on file. 2015 14 February 2015. Report No.
63. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction (supplementary information). New England Journal of Medicine. 2015.
64. Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. New England Journal of Medicine. 2006;354(16):1706-17.
65. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J. 2006;27(9):1038-47.
66. AstraZeneca. Analysis of primary endpoint by categories of study drug compliance - FAS. 2015.
67. Bonaca MP, Storey RF, Theroux P, Steg PG, Bhatt DL, Im K, et al. Abstract 19642: Consistent Benefit of Ticagrelor Both Early and Late in Patients With Prior MI in PEGASUS-TIMI 54. Circulation. 2015;132(Suppl 3):A19642-A.
68. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (2011). Available at: http://handbook.cochrane.org/ [Last accessed 29/01/2016].
69. Bonaca MP, Wiviott SD, Morrow DA, Steg PG, Hamm C, Bhatt DL, et al. Abstract 11594: Reduction in Subtypes and Sizes of Myocardial Infarction With Ticagrelor in PEGASUS-TIMI 54. Circulation. 2015;132(Suppl 3):A11594-A.
70. Bonaca M, Bhatt D. Long-term tolerability of Ticagrelor in the PEGASUS-TIMI 54 trial (late-breaking clinical trial). American Heart Association. Scientific session.; 2015.
71. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2014;17(2):157-73.
72. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, et al. Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction. J Am Coll Cardiol. 2015;65(20):2211-21.
73. Mauri L, Kereiakes DJ, Normand SL, Wiviott SD, Cohen DJ, Holmes DR, et al. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. American heart journal. 2010;160(6):1035-41, 41 e1.
74. Bonaca MP, Bhatt DL, Steg PG, Storey RF, Cohen M, Im K, et al. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54. European Heart Journal. 2015.

75. Bonaca MP, Bhatt DL, Steg PG, Budaj A, Bansilal S, Storey RF, et al. TCT-78 Efficacy of Long-Term Ticagrelor in Stented Patients in PEGASUS-TIMI 54. Journal of the American College of Cardiology. 2015;66(15_S).
76. Smolina K WL, Rayner M, Goldacre MJ. Long-Term Survival and Recurrence After Acute Myocardial Infarction in England, 2004 to 2010. Circ Cardiovasc Qual Outcomes. 2012;5:532-40.
77. NICE. Myocardial infarction with ST-segment elevation overview (http://pathways.nice.org.uk/pathways/myocardial-infarction-with-st-segment-elevation). In: Excellence NIfHaC, editor. NICE Pathway2015.
78. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction - supplementary material. Online Supplement. 2015.
79. Cigolle CT, Blaum CS, Halter JB. Diabetes and Cardiovascular Disease Prevention in Older Adults. Clinics in Geriatric Medicine.25(4):607-41.
80. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in Older Adults. Diabetes Care. 2012;35(12):2650-64.
81. Bonaca MP, Storey RF, Theroux P, Steg PG, Bhatt DL, Im K, et al. Abstract 19642: Consistent Benefit of Ticagrelor Both Early and Late in Patients With Prior MI in PEGASUS-TIMI 54. Circulation. 2015;132(Suppl 3):A19642.
82. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA. 2010;304(12):1350-7.
83. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective2015 2015-01-13 00:00:00.
84. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Bmj. 1996;313(7052):275-83.
85. Banerjee S, Brown A, McGahan L, Asakawa K, Hutton B, Clark M, et al. Clopidogrel versus Other Antiplatelet Agents for Secondary Prevention of Vascular Events in Adults with Acute Coronary Syndrome or Peripheral Vascular Disease: Clinical and Cost-Effectiveness Analyses. CADTH Technol Overv. 2012;2(1):e2102.
86. Begum N, Stephens S, Schoeman O, Fraschke A, Kirsch B, Briere JB, et al. Cost-effectiveness Analysis of Rivaroxaban in the Secondary Prevention of Acute Coronary Syndromes in Sweden. Cardiol Ther. 2015;4(2):131-53.
87. Chen J, Bhatt DL, Dunn ES, Shi C, Caro JJ, Mahoney EM, et al. Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone for secondary prevention of cardiovascular events: results from the CHARISMA trial. Value Health. 2009;12(6):872-9.
88. Chen J, Shi C, Mahoney EM, Dunn ES, Rinfret S, Caro JJ, et al. Clinical research economic evaluation of clopidogrel plus aspirin for secondary prevention of cardiovascular events in Canada for patients with established cardiovascular disease: Results from the CHARISMA trial. Canadian Journal of Cardiology. 2011;27(2):222-31.
89. Gaspoz JM, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink MG, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. N Engl J Med. 2002;346(23):1800-6.
90. Banerjee, Brown, McGahan, Asakawa, Hutton, Clark, et al. Clopidogrel versus other antiplatelet agents for secondary prevention of vascular events in adults with acute coronary syndrome or peripheral vascular disease: clinical and cost-

effectiveness analyses (Structured abstract). Health Technology Assessment Database. 2015(4).
91. Stinnett AA, Mittleman MA, Weinstein MC. The cost-effectiveness of dietary and pharmacologic therapy for cholesterol reduction in adults. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Costeffectiveness in health and medicine. New York: Oxford University Press, 1996:349-91.
92. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. American journal of public health. 1987;77(11):1417-26.
93. Karnon J, Brennan A, Pandor A, Fowkes G, Lee A, Gray D, et al. Modelling the long term cost effectiveness of clopidogrel for the secondary prevention of occlusive vascular events in the UK. Current medical research and opinion. 2005;21(1):101-12.
94. Heeg B, Damen J, Van Hout B. Oral antiplatelet therapy in secondary prevention of cardiovascular events: an assessment from the payer's perspective. PharmacoEconomics. 2007;25(12):1063-82.
95. Sigvant B, Henriksson M, Lundin F, Wahlberg E. Asymptomatic peripheral arterial disease: is pharmacological prevention of cardiovascular risk cost-effective? European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2011;18(2):254-61.
96. Briggs A MB, Sculpher M, et al. . Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. . Heart. 2007;93:1081-6.
97. Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Fleeman N, et al. Prasugrel (Efient(R)) with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182): systematic review and economic analysis. Health Technol Assess. 2015;19(29):1-130.
98. Alabas OA, Dondo TB, Laut K, Van Laar M, Gale CP. Trajectories of quality of life after myocardial infarction: A national longitudinal study. European Heart Journal. 2015;36:11-2.
99. Nam J, Briggs A, Layland J, Oldroyd KG, Curzen N, Sood A, et al. Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction (FAMOUS-NSTEMI) developmental trial: cost-effectiveness using a mixed trial- and model-based methods. Cost Eff Resour Alloc. 2015;13:19.
100. Pockett RD, McEwan P, Beckham C, Shutler S, Martin S, Yousef Z, et al. Health utility in patients following card iovascular events. Value in Health. 2014;17 (7):A328.
101. Stafford M, Soljak M, Pledge V, Mindell J. Socio-economic differences in the health-related quality of life impact of cardiovascular conditions. European journal of public health. 2012;22(3):301-5.
102. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Medical decision making : an international journal of the Society for Medical Decision Making. 2011;31(6):800-4.
103. Bach JP, Riedel O, Pieper L, Klotsche J, Dodel R, Wittchen HU. Health-related quality of life in patients with a history of myocardial infarction and stroke. Cerebrovascular Diseases. 2011;31(1):68-76.
104. Goss F, Haerer W, Brachmann J, Hamm CW, Reifart N, Levenson B. Low mortality and rate of cardiac events in patients after acute coronary syndrome

systematically managed by office-based cardiologists in germany: 1-year outcomes of the proacor study. Circulation Conference: American Heart Association's. 2015;132.
105. Seidl H, Hunger M, Leidl R, Meisinger C, Wende R, Kuch B, et al. Cost-effectiveness of nurse-based case management versus usual care for elderly patients with myocardial infarction: results from the KORINNA study. European Journal of Health Economics. 2015;16(6):671-81.
106. Kim MJ, Jeon DS, Gwon HC, Kim SJ, Chang K, Kim HS, et al. Health-related quality-of-life after percutaneous coronary intervention in patients with UA/NSTEMI and STEMI: The Korean multicenter registry. Journal of Korean Medical Science. 2013;28(6):848-54.
107. Park SJ, Ahn S, Woo SJ, Park KH. Extent of exacerbation of chronic health conditions by visual impairment in terms of health-related quality of life. JAMA Ophthalmology. 2015;133(11):1267-75.
108. Varnfield M, Karunanithi M, Lee CK, Honeyman E, Arnold D, Ding H, et al. Smartphone-based home care model improved use of cardiac rehabilitation in postmyocardial infarction patients: results from a randomised controlled trial. Heart. 2014;100(22):1770-9.
109. van Stel HF, Busschbach JJ, Hunink MG, Buskens E. Impact of secondary cardiovascular events on health status. Value in Health. 2012;15(1):175-82.
110. Koltowski L, Koltowska-Haggstrom M, Filipiak KJ, Kochman J, Golicki D, Pietrasik A, et al. Quality of life in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention - Radial versus femoral access (from the OCEAN RACE trial). American Journal of Cardiology. 2014;114(4):516-21.
111. Abdin E, Subramaniam M, Vaingankar JA, Luo N, Chong SA. Population norms for the EQ-5D index scores using Singapore preference weights. Qual Life Res. 2015;24(6):1545-53.
112. Henriksson C, Larsson M, Herlitz J, Karlsson JE, Wernroth L, Lindahl B. Influence of health-related quality of life on time from symptom onset to hospital arrival and the risk of readmission in patients with myocardial infarction. Open Heart. 2014;1(1):e000051.
113. De Smedt D, Clays E, Annemans L, De Bacquer D. EQ-5D versus SF-12 in coronary patients: Are they interchangeable? Value in Health. 2014;17(1):84-9.
114. Dreyer RP, Smolderen KG, Strait KM, Beltrame JF, Lichtman JH, Lorenze NP, et al. Gender differences in pre-event health status of young patients with acute myocardial infarction: A VIRGO study analysis. European heart journal Acute cardiovascular care. 2016;5(1):43-54.
115. Lewis EF, Li Y, Pfeffer MA, Solomon SD, Weinfurt KP, Velazquez EJ, et al. Impact of cardiovascular events on change in quality of life and utilities in patients after myocardial infarction: a VALIANT study (valsartan in acute myocardial infarction). Jacc. 2014;Heart failure. 2(2):159-65.
116. Alonso A, Gore JM, Awad HH, Quill AL, Montalescot G, van de Werf F, et al. Management and outcomes of patients presenting with STEMI by use of chronic oral anticoagulation: results from the GRACE registry. European heart journal Acute cardiovascular care. 2013;2(3):280-91.
117. Hermanides RS, Ottervanger JP, ten Berg JM, Gosselink AT, van Houwelingen G, Dambrink JH, et al. Net clinical benefit of prehospital glycoprotein IIb/IIIa inhibitors in patients with ST-elevation myocardial infarction and high risk of

bleeding: effect of tirofiban in patients at high risk of bleeding using CRUSADE bleeding score. The Journal of invasive cardiology. 2012;24(3):84-9.
118. (NICE) NIfHaCE. TA182: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. 2009.
119. (NICE) NIfHaCE. TA210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events 2010. Available from: https://www.nice.org.uk/guidance/ta210.
120. (NICE) NIfHaCE. TA236: Ticagrelor for the treatment of acute coronary syndromes. Manufacturer's submission 2011. Available from: https://www.nice.org.uk/guidance/ta236/chapter/3-the-manufacturers-submission.
121. (NICE) NIfHaCE. TA317: Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes. 2014.
122. (NICE) NIfHaCE. TA335: Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. 2015.
123. Pandor A, Pollard D, Chico T, Henderson R, Stevenson M. Rivaroxaban for Preventing Atherothrombotic Events in People with Acute Coronary Syndrome and Elevated Cardiac Biomarkers: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. PharmacoEconomics. 2015.
124. Greenhalgh J, Bagust A, Boland A, Martin Saborido C, Oyee J, Blundell M, et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis. Health Technol Assess. 2011;15(31):1-178.
125. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Bmj. 1998;316(7133):736-41.
126. Dorian P, Kongnakorn T, Phatak H, Rublee DA, Kuznik A, Lanitis T, et al. Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation. Eur Heart J. 2014;35(28):1897-906.
127. Guerriero C, Cairns J, Roberts I, Rodgers A, Whittaker R, Free C. The cost-effectiveness of smoking cessation support delivered by mobile phone text messaging: Txt2stop. The European journal of health economics : HEPAC : health economics in prevention and care. 2013;14(5):789-97.
128. Lip GY, Kongnakorn T, Phatak H, Kuznik A, Lanitis T, Liu LZ, et al. Cost-effectiveness of apixaban versus other new oral anticoagulants for stroke prevention in atrial fibrillation. Clin Ther. 2014;36(2):192-210.e20.
129. McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, et al. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. Eur Heart J. 2014;35(5):290-8.
130. Thokala P, Kruger J, Brennan A, Basarir H, Duenas A, Pandor A, et al. Assessing the cost-effectiveness of type 1 diabetes interventions: the Sheffield type 1 diabetes policy model. Diabet Med. 2014;31(4):477-86.
131. Zheng Y, Sorensen SV, Gonschior AK, Noack H, Heinrich-Nols J, Sunderland T, et al. Comparison of the cost-effectiveness of new oral anticoagulants for the prevention of stroke and systemic embolism in atrial fibrillation in a UK setting. Clin Ther. 2014;36(12):2015-28.e2.
132. Curtis L. Unit costs of health and social care. 2013.
133. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabet Med. 2003;20(6):442-50.

134. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. PharmacoEconomics. 2003;21 Suppl 1:43-50.
135. Squibb S-aaB-M. The use of clopidogrel hydrogen sulphate (Plavix) in patients with atherosclerotic disease-Manufacturer submission. 2009.
136. British National Formulary (online) [Internet]. BMJ Group and Pharmaceutical Press.
137. NHS reference costs 2014/15 [Internet]. 2015.
138. Sacks JJ, Helmick CG, Langmaid G. Deaths from arthritis and other rheumatic conditions, United States, 1979-1998. The Journal of rheumatology. 2004;31(9):1823-8.

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Single technology appraisal

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Dear Kevin,

The Evidence Review Group, Kleijnen Systematic Reviews Ltd., and the technical team at NICE have looked at the submission received on 11 April 2016 from Astrazeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Tuesday 17 May 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Nicola Hay, Technical Analyst nicola.hay@nice.org.uk. Any procedural questions should be addressed to Stephanie Yates, Project Manager stephanie.yates@nice.org.uk.

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Analysis

A1. **Priority request:** In line with the final scope, please include an indirect comparison of ticagrelor co-administered with aspirin to clopidogrel in combination with aspirin.[2]

- Please update the methods accordingly.
- Please provide all results specified in the final scope for this indirect comparison for both the intention-to-treat (ITT) population and the population of interest specified in the CS which is a subgroup of the ITT population ('label population').
- Please discuss the uncertainties of this indirect comparison, e.g. how the uncertainties described in the company submission impact on any effect estimates from this indirect comparison.

A2. **Priority request:** According to page 67 of the company submission, the pre-specified primary safety analysis was based on an on-treatment analysis population. Please provide results for all safety outcomes for both, the ITT and the label populations.

A3. Figure 15 (page 89) of the submission reports the effect of ticagrelor on patients with ST-elevation myocardial infarction (STEMI). Please provide the corresponding results for non-ST-elevation myocardial infarction (NSTEMI).

A4. Table 33 (page 98) of the submission includes a row for all cause mortality but no results are provided, the row is blank. Please provide the corresponding results.

A5. Please clarify the positioning of ticagrelor 60 mg in the treatment pathway. The indication summarised in table 2 (page 17) of the company submission states that 'treatment may be started without interruption following one year of ticagrelor 90 mg or other ADP receptor inhibitor.[1]

- Please clarify how patients are treated after experiencing a subsequent non-fatal event, i.e. a myocardial infarction (MI) or a stroke >12 months after the index event.
- Do patients continue to receive ticagrelor 60 mg or if not what treatment do they typically receive?

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Literature searching

A6. Please provide search strategies, date of searches, and number of records retrieved for the clinical trials register searches (section 4.1, page 50: Identification and selection of relevant studies - clinical trial registry).

A7. Please provide more details for the searches of conference proceedings, including the specific conference proceedings searched, the search strategies or search terms used, website addresses, and results (sections 2.4, 11.4 and 13.4 in the appendices: Additional searches).

A8. Please provide details of the search strategy used to search EconLit (section 11.1, page 52 in the appendices: Databases searched and service provider).

Supporting references

A9. A brief summary of the summary of product characteristics (SmPC) is provided in table 2 (page 17) of the company submission .[1] Page 27 of the company submission states that the *"SmPC is provided in a PDF format"*. Please provide the PDF or refer to the relevant document in the references already provided.

A10. In section 4.10 (page 117) the company submission mentions an *"advisory board of clinical and statistical experts"*.[1] Please provide relevant documents such as meeting minutes of the advisory board.

Selection of relevant studies

A11. The inclusion criteria reported in table 15 (page 52) of the company submission state that only studies with ≥ 18 months of dual antiplatelet therapy (DAPT) would be included.[1] Please explain the justification for choosing 18 months for the cut off.

Quality assessment of included studies

A12. Table 24 (Page 77) of the company submission states that there was insufficient information to assess the risk of bias in the PEGASUS-TIMI study. Please explain why this information was unavailable for the primary study of the main intervention in the submission.

Section B: Clarification on cost-effectiveness data

B1. **Priority request:** Please use the indirect comparisons presented in question A1 to incorporate clopidogrel in combination with aspirin as a comparator in the economic model.

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Model structure

B2. **Priority request:** Disabling and non-disabling strokes seem to have different clinical and economic impacts on the model.

- Please provide a breakdown of the number of disabling and non-disabling strokes for each arm of the trial separately.
- Please implement treatment-specific utility values and costs for stroke in the cost-effectiveness model based on the breakdown of disabling and non-disabling strokes provided in the previous bullet point.

B3. Subsequent events and adverse events (AE) are not explicitly modelled, as a result of this simplification the occurrence of subsequent event and AE does not impact survival. Subsequent events and AE only have a temporary (3 months) impact costs and quality of life. Moreover, difference in AEs between treatments was incorporated until ticagrelor treatment discontinuation only.

- Please adjust the economic model to incorporate the impact of subsequent events and AE on survival and costs and quality of life beyond 3 months, e.g. impact of non-fatal bleeding such as intra-cerebellar bleeds.
- Please explain the statement, that this simplification does not impact health outcomes and costs, with a scenario analysis explicitly incorporating subsequent events and the potential impact on survival.
- Please provide a scenario analysis incorporating difference in AEs between treatments after ticagrelor treatment discontinuation only.

B4. Please add a scenario analysis incorporating treatment with ticagrelor 60 mg, starting 12 months after having experienced a subsequent MI (consistent with the response to question A11).

B5. Please add a scenario analysis replacing clopidogrel treatment 1 to 12 months after experiencing a subsequent MI by treatment with tricagrelor 90 mg.

Risk equations for first and subsequent event

B6. **Priority request:** The risk equations incorporated in the economic model are based on the ITT population of the PEGASUS-TIMI 54 trial, while the population of interest specified by the company is a subgroup of this population, termed the 'label population'.[1] Only the risk equations for first non-fatal MI and fatal cardiovascular (CV) events (as first event) are adjusted (in part) to represent the label population.

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- Please provide all risk equations for first event, subsequent event, adverse events, treatment discontinuation and hospitalisation for the label subpopulation only (instead of the ITT population).

- Please use these risk equations in a scenario analysis and present the cost-effectiveness results using the average outcomes (i.e. costs and quality-adjusted life years (QALYs)) obtained from the probabilistic sensitivity analysis (PSA; using the 'simple'/cohort analysis).

B7. **Priority request:** In the following cases, variables and/or interaction terms were excluded from the risk equations without providing objective decision criteria for this:

(1) Company submission page 178 *"Variables were excluded if proportionality was not observed and interaction effects could not be established."*

- Please provide more details of the test for interaction used to assess the proportional hazards (PH) assumption. Was it the interaction between the variable and time (or log time) and what significant level was used? Please also provide details for each risk equation of which variables (if any) were dropped from the model due to doubts about the PH assumption.

(2) Company submission page 180 *"similar variables dropped from the analysis to isolate the effect of being in the label population"*

- Please provide the significance level used to assess the interaction between off-label and other variables. If it was < 0.05 then this seems to be low for assessing an interaction term (0.10 or higher is usually used due) so please justify your choice. Please also provide details of what you mean by "similar variables", i.e. how the decision was made to drop them, and give details of the variables which were dropped in each risk equation (if any).

(3) Company submission page 181 *"Where multicollinearity was suspected to have occurred between the 'offlabel' variable and either the 'qev2rnd' or 'tADP_12mplus' variables, the label population variable was prioritised and retained in the model, and the collinear variables dropped as the label population variable was of greater importance."*

- Please clarify the statistical method used to assess multicollinearity (such as tolerance or variance inflation factor) and the threshold used to decide whether variables were collinear (e.g. VIF >10). Please also specify which (if any) variables were dropped from each risk equation model.

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B8. Treatment (Tic60/ pMI_Tic60 variable) was not included in the estimation of transition probabilities using the risk equations to estimate subsequent events and both first and for "fatal other" this was applicable to the estimation of the first events.

- Please clarify why the treatment variable was not included in these risk equations.

- Please examine the impact of not including the treatment variable for "non-fatal stroke" in a sensitivity analysis (by including the treatment variable in the risk equations).

B9. In order to avoid underestimation of mortality in the base case, the company has derived the probability of non-CV related mortality from UK life tables. As life tables reflect all-cause mortality, including deaths from CV-related causes, CV-specific mortality was excluded from the standard life tables used in the model using a component of contribution for non-CV death compared to all-cause mortality. The Evidence Review Group (ERG) would like to be able to validate the values set out in table 91 of the CS but is unable to do so without specific references and methods of adjustment.

- Please supply a proper reference (with an active web link) for "the UK Government Actuarial Department's 2004–2006 interim life tables and the Office for National Statistics mortality by cause data".

- Please supply references for any adjustments made (in relation to ICD-10 codes: I11, I13, I20-I26, I30-I49, I50-I74, I81-I82 and I85) if they are not detailed in the aforementioned reference.

Adverse events and hospitalisations

B10. TIMI bleeds and dyspnoea were considered as AE in the model (incorporated using an exponential parametric model).

- Please examine other parametric distributions than exponential (i.e. Weibull, Gompertz, Log-Normal and Log-Logistic) for implementing AE and incorporate the optimal model (selection based on AIC) in a sensitivity analysis.

  According to the company submission (page 264) *"A small excess of gout was observed in PEGASUS-TIMI 54 for ticagrelor 60mg BID vs. placebo (0.46% ARI; HR 1.48; 95% CI 1.10 to 2.00; p=0.01)"*.[1] Nevertheless, gout was not considered in the economic model, this is unlikely to be a conservative assumption.

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- Please examine the impact of this assumption by incorporating the impact of gout on costs and quality of life in the economic analyses.

B11. The rate of hospitalisation is estimated using a Poisson regression model.

- Please examine whether the Poisson model is over-dispersed and whether it is zero inflated.
- If the Poisson model is over-dispersed or zero inflated, provide a corrected regression model (and economic model) to estimate the rate of hospitalisation.
- Please clarify how the variables for the Poisson regression were selected.
- Please justify why treatment (Tic60) is not incorporated as covariate in the Poisson regression model and examine the impact of this while including Tic60 in the Poisson regression in a sensitivity analysis.

Health related quality of life

B12. **Priority request:** As explained by the company, the use of a linear random effect panel data analysis allowed for utility values > 1(Table 98, page 262, company submission[1]). Therefore, the company capped the utility value from the PEGASUS TIMI 54 to 1. However, utility decrements used in the model are still based on the same linear model. Naïvely capping the maximal utility value will presumably bias the utility decrements since the scale on which utility decrements are based is different than 0-1.

- Please justify why capping the maximal value is considered appropriate instead of using a model providing utility estimates between 0-1.
- Please justify why applying (multiple) utility decrements was considered more appropriate than calculating utility values for the different health states.
- Recalculate the utility values using a model providing utility values between 0-1 bounds (e.g. a probit model) and provide details on:
    a. The number of events, patients and EQ-5D questionnaires used to calculate the utility estimates and utility decrements, if applicable.
    b. The methodology used to determine utility estimates and utility decrements, e.g. variable selection and assumptions underlying the model.
    c. The uncertainty around each utility estimate and each utility decrement (e.g. standard deviation, standard error, lower and upper bounds).

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d. Include these new utility values in the cost-effectiveness model (provide the methods and results)

B13. Table 96 (page 256) of the company submission displays utility decrements from the current and previous assessments.[1] The difference between the decrements is also provided.

- Please describe the calculations to obtain utility decrements from previous assessments (methods + results).

Resource use and costs

B14. **Priority request:** The company submission states that the cost data from ERG review of TA317 inflated to 2015 values were adopted for the base case. However, TA317 used inflated values from TA182 and, as table 104 shows, TA182 used NHS reference costs. Therefore, please provide, for each cost estimate presented in table 103 of the company submission[1]: the primary source, the NHS reference costs number(s) and name(s) as well as the uncertainty around the estimate from TA182. In addition, please provide the same information using the reference costs from the latest schedule i.e. 2014/15. Provide this information as in Table 1.

- Please incorporate the reported costs in the cost-effectiveness model with their measures of uncertainty and describe the methods used to do so

- Please provide the results of including these costs and their measures of uncertainty.

- Please also explain why the latest NHS reference costs (2014/15) were not used.

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Table 1: List of resource use and associated costs in the economic model (CS[1], table 103)

Resource use	Value in CS	National Average Unit Cost, TA182	Lower Quartile Unit Cost, TA182	Upper Quartile Unit Cost, TA182	HRG code from NHS reference costs, TA182	National Average Unit Cost, 2014/15 schedule	Lower Quartile Unit Cost, 2014/15 schedule	Upper Quartile Unit Cost, 2014/15 schedule	HRG code from NHS reference costs, 2014/15 schedule
Inpatient									
Non-fatal MI	£4,476.18								
Non-fatal stroke	£4,925.76								
Fatal events (CAD and non-CAD)	£2,497.83								
'No event'	£2,497.83								
Outpatient and maintenance									
Post non-fatal MI (0-3 months)	£639.45								
Post non-fatal MI (3-6 months)	£639.45								
Post non-fatal MI (6-9 months)	£319.73								
Post non-fatal MI (9-12 months)	£319.73								
Post non-fatal MI (12+ months, every cycle)	£160.31								
Post non-fatal stroke (0-3 months)	£1,343.39								
Post non-fatal stroke (3-6 months)	£1,119.49								
Post non-fatal stroke (6-9 months)	£877.57								
Post non-fatal stroke (9-12 months)	£689.71								
Post non-fatal stroke (12+	£689.71								

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Resource use	Value in CS	National Average Unit Cost, TA182	Lower Quartile Unit Cost, TA182	Upper Quartile Unit Cost, TA182	HRG code from NHS reference costs, TA182	National Average Unit Cost, 2014/15 schedule	Lower Quartile Unit Cost, 2014/15 schedule	Upper Quartile Unit Cost, 2014/15 schedule	HRG code from NHS reference costs, 2014/15 schedule
months, every cycle)									
'No event' (every cycle)	£160.31								
Adverse events									
Grade 3-4 Dyspnoea	£732.98								
Major TIMI bleed	£2,206.87								
Minor TIMI bleed	£122.48								

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B15. In table 112 (page 282) of the company submission[1], costs for dyspnoea grade 3-4 are provided and based on a weighted average of DZ 19 'Other Respiratory Disorders' from National Health Service (NHS) reference costs 14/15.

- Please justify why these reference costs were chosen for dyspnoea and are adequate for such a calculation.
- Please provide details on how the weighted average was obtained (methods + results).
- Please provide the standard error, the lower and the upper bounds of this estimate from table 112 (page 282) of the company submission[1].

B16. Please provide a description of the 'No event' health state.

- Justify the assumption that 'No event' inpatient costs are equal to the inpatient costs for inpatient costs of a fatal events "*due to the potential range of 'no event' inpatient costs"*.[1]
- Provide an overview of which events produced inpatient costs in the 'No event' health state (events name + number of events)

B17. The costs of non-fatal MI and non-fatal stroke are spread on a one year period with respectively 70% and 55% of the costs being accounted for as inpatient costs ('event' costs) and the rest being accounted for as outpatient costs (divided across the following tunnel states).

- Please justify the rationale between these 70% and 55%.
- Please justify why this methodology has been adopted.

Results and sensitivity analyses

B18. The probabilistic sensitivity analyses are based on a single individual, this is methodologically incorrect, see for instance Halpern et al. how to represent both 1st and 2nd order uncertainty (using an inner and outer loop).[3]

- Please provide probabilistic sensitivity analyses based on the cohort analysis (i.e. the 'simple' analysis) for the base case.
- Please provide a summary of LY gained by health state using the format of table 115 from the company submission.[1]
- According to the NICE Methods Guide[4], probabilistic methods provide the best estimates of mean costs and outcomes in non-linear decision models.

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Please provide probabilistic sensitivity analyses based on the cohort analysis (i.e. the 'simple' analysis) for all scenario and subgroup analyses presented in the company submission.

Transparency and validity

B19. The company submission presents a description of the external and technical validation of the model in section 5.10.[1] However, other aspects of validity are not addressed in the company submission.

- Please describe which steps have been undertaken to assess the face validity of the cost-effectiveness model.
- Please provide a comparison of the observed and modelled TIMI minor bleeds events, and grade 1-2 dyspnoea as it is provided for the other events (Table 141, company submission[1]).
- Please provide a comparison regarding input parameters, model structure, assumptions and outcomes of the current assessment with previous studies identified in the systematic literature review of the company and relevant TA's (i.e. studies included in table 51, page 157 of the company submission and TA182, TA210, TA236, TA317, TA335).
- Please provide a comparison of the number of MI's, strokes, other CV events, and survival with an external, preferably UK, database (e.g. http://www.isdscotland.org/Health-Topics/, https://indicators.hscic.gov.uk/webview/, https://www.ucl.ac.uk/nicor/audits/minap).
- In figure 67 (page 193) of the company submission [1], the company compares the survival probabilities by age as modelled in the cost-effectiveness analysis with the survival probabilities according to UK life tables. Please provide the exact reference for the UK life tables (with an active web link).

Section C: Textual clarifications and additional points

C1. Table 10 (page 44) of the company submission[1]: Please confirm that the "mean, %" under "Percentage of professional time spent in direct patient care" for "England and Wales (n=85)" is 85.7.

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References

[1] AstraZeneca. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]: AstraZeneca evidence submission to National Institute of Health and Clinical Excellence. Single technology appraisal (STA)*: AstraZeneca, 2016

[2] National Institute for Health and Care Excellence. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]. Final scope [Internet]*. London: National Institute for Health and Care Excellence, 2016 [accessed 18.4.16] Available from: https://www.nice.org.uk/guidance/GID-TA10016/documents/final-scope

[3] Halpern EF, Weinstein MC, Hunink MG, Gazelle GS. Representing both first- and second-order uncertainties by Monte Carlo simulation for groups of patients. *Med Decis Making* 2000;20(3):314-22.

[4] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [Internet]*. London: NICE, 2013 [accessed 14.4.16] Available from: http://publications.nice.org.uk/pmg9

Response to Clarification Questions

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID813_Ticagrelor_ClarificationQuestions_AZResponse_Final	Final	Yes	May 17, 2016

AstraZeneca UK Ltd
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Please note that all tables copied from the original submission are reproduced here (with appropriate amendments) with the original Table and Figure numbers.

Section A: Clarification on effectiveness data

Analysis

A1. **Priority request:** In line with the final scope, please include an indirect comparison of ticagrelor co-administered with aspirin to clopidogrel in combination with aspirin.(1)

- Please update the methods accordingly.
- Please provide all results specified in the final scope for this indirect comparison for both the intention-to-treat (ITT) population and the population of interest specified in the CS which is a subgroup of the ITT population ('label population').
- Please discuss the uncertainties of this indirect comparison, e.g. how the uncertainties described in the company submission impact on any effect estimates from this indirect comparison.

The Decision Problem for this appraisal specifies the outcome measures to be considered as:

- non-fatal myocardial infarction (STEMI and NSTEMI)
- non-fatal stroke
- urgent coronary revascularisation
- bleeding events
- mortality
- adverse effects of treatment
- health-related quality of life.

The only sources of data on the use of Clopidogrel +ASA vs ASA potentially available to provide an indirect comparison of clopidogrel + ASA with ticagrelor + ASA in line with the final scope, is the post-hoc analysis of the DAPT study focussing on the subgroup of patients presenting with an MI (2) and a post-hoc analysis of the CHARISMA study (3) .

Table 1 below summarizes the available single component outcome measures specified in the Decision Problem from NICE for prior MI patients in the post-hoc analyses of both DAPT and CHARISMA studies, as well as the full population in the PEGASUS-TIMI 54 study. It is also important to highlight that other outcome measures are commonly reported in studies exploring cardiovascular endpoints, but were not specified in the Decision Problem by NICE. The availability of some of these is also summarised in Table 1 below.

It is clear from Table 1 that the available data for the subgroup of the CHARISMA trial does not provide any information on the single component outcomes specifically requested by NICE in the Decision Problem.

Table 1: Outcome measures available for prior MI patients in three potentially relevant studies.

Study	DAPT MI subgroup			CHARISMA MI subgroup	PEGASUS-TIMI 54
Treatment	**Thienopyridine (n=3576)**	**Clopidogrel* (n=2361)**	**Prasugrel* (n=1251)**	**Clopidogrel (n=3846)**	**Ticagrelor** (n=14,112)**
Outcome measures specified in Decision Problem					
Non-fatal MI	(AVAILABLE)[#]	(AVAILABLE)[#]	(AVAILABLE)[#]	-	AVAILABLE
Non-fatal stroke	-	-	-	-	AVAILABLE
Urgent coronary revascularisation	-	-	-	-	AVAILABLE
Bleeding events	GUSTO	GUSTO	GUSTO	-	TIMI, PLATO, GUSTO
Death	AVAILABLE	-	-	-	AVAILABLE
Adverse effects of treatment	-	-	-	-	AVAILABLE
HRQoL	-	-	-	-	AVAILABLE
Other Outcome measures of interest					
Baseline characteristics	AVAILABLE	-	-	-	AVAILABLE
Composite of CV death, MI or stroke	-	-	-	AVAILABLE	AVAILABLE
Composite of (All-cause) death, MI or stroke	AVAILABLE	-	-	-	AVAILABLE

* Available in Table 3 of the Supplementary Materials to Yeh 2015. -: Data not available. ** Based on full analysis population from PEGASUS-TIMI 54 study for patients in the ticagrelor 60 mg and placebo arms, [#] Reported as MI

As shown in Table 1, data for clopidogrel + ASA vs ASA alone is only available for two of the seven outcome measures specified by the Decision Problem: incidence of MI and bleeding events (specifically moderate/severe GUSTO bleeding) from the DAPT study as provided in Table 3 of the Supplementary Materials to **Yeh 2015**. However, this small subset (n=2361) of the available data is compromised since it is derived from a subgroup (i.e. subjects presenting with an MI) of a subgroup (according to thienopyridine type) and the analyses were not pre-specified nor powered to assess interactions. Therefore, these outcome analyses are hypothesis-generating at best, and cannot be regarded as a robust source of evidence.

There are significant differences between the design of the DAPT and PEGASUS-TIMI 54 studies that also presents barriers to indirect comparison of clopidogrel + ASA with ticagrelor 60 mg + ASA.

Patients included in the DAPT study were patients undergoing percutaneous coronary intervention with drug-eluting stent or bare-metal stent. After enrolment, all of these patients received 12 months of open-label thienopyridine treatment in addition to aspirin. After this observational period, subjects with MI, stroke, repeat revascularisation, GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) moderate or severe bleeding or non-adherent patients were removed from the study. All other patients who met the inclusion criteria were then randomised to receive 18 additional months of either clopidogrel or prasugrel (30 month DAPT arm) or placebo (12 month DAPT arm) plus aspirin.

In contrast, the PEGASUS-TIMI 54 study consists of patients who had suffered a MI one to three years prior to enrolment and had concomitant risk factors for future events. All patients were randomised to either 60mg or 90mg doses of ticagrelor twice daily, plus aspirin, or aspirin alone. Risk factors included being over 65 years of age, diabetes mellitus, prior MI, multivessel coronary artery disease, chronic non-end stage renal dysfunction.

Table 2 demonstrates that patients recruited to and randomised in the two studies are not comparable in terms of baseline characteristics expected to impact risk of future events and relative treatment effect of continued DAPT (e.g. age, hypertension, congestive heart failure, thienopyridine treatment at randomisation, type of stent). This is an important source of heterogeneity to consider when combining trials in a meta-analysis.

Table 2: Selected baseline characteristics of patients in DAPT and PEGASUS-TIMI 54 studies (all % unless stated)

	DAPT (MI subgroup)		PEGASUS-TIMI 54 (full population)	
	Thienopyridine	Placebo	Ticagrelor 60 mg	Placebo
Patients	(n=1805)	(n=1771)	(n=7045)	(n=7067)
Age (yrs)	57.9	57.7	65.2	65.4
Female	22.4	21.2	23.6	24.3
Non-white race	8.9	7.9	13.7	13.3
Weight (kg)	89.7	90.8	82.0	81.8
BMI	29.8	30.0	28.5	28.4
Diabetes mellitus	20.8	21.0	32.8	31.9
Hypertension	59.8	56.4	77.5[+]	77.6[+]
Smoker	41.8	41.8	17.7 (current)	16.2 (current)

			48.5 (former)	48.0 (former)
Congestive heart failure	3.0	2.9	19.5	20.6
Peripheral arterial disease	2.6	3.2	5.2	5.7
Prior MI	19.1	20.0	16.6*	16.8*
Index MI	100	100	100	100
STEMI	46.8	47.2	53.3	53.9
NSTEMI	53.2	52.9	40.3	40.2
Unknown	-	-	6.2	5.7
Thienopyridine at randomisation	100	100	26.2[!]	26.2[!]
Clopidogrel	66.4	65.6	24.0[!]	23.9[!]
Prasugrel	33.6	34.4	2.0[!]	1.8[!]
PCI at index event	100	100	83.4	82.6
BMS	NR	NR	42.7	41.6
DES	72.6	72.2	39.3	39.4
Type of DES				
Sirolimus	8.3	7.8	5.3	6.0
Zotarolimus	12.0	11.4	6.6	5.9
Paclitaxel	28.3	30.2	5.5	5.4
Everolimus	49.8	48.5	15.3	15.7

* History of >1 MI, [+] Hypertension requiring medication, [!] Treatment received within 7 days prior to randomisation

In summary, we stand by our position in the submission that there is a lack of solid evidence regarding prolonged treatment with clopidogrel + ASA compared to ASA alone (defined as greater than 12 months) in this patient population. The little evidence that does exist cannot be used to construct a robust network with the PEGASUS-TIMI 54 study, due to differences between the patients in the two studies, the clinically implausible assumptions required to conduct the analysis and the lack of common endpoints.

A2. **Priority request:** According to page 67 of the company submission, the pre-specified primary safety analysis was based on an on-treatment analysis population. Please provide results for all safety outcomes for both, the ITT and the label populations.

Updated version of Tables 41, 43 and 44 (from pages 126, 129 and 131) from the original submission are presented below.

The OT analysis of the full study population presented in the original submission is supplemented with an ITT analysis.

Copies of each of Tables 41, 43 and 44 are also provided containing similar ITT analyses of the base case population (i.e. MI < 2years) in Tables 41b, 43b and 44b, respectively.

Table 41: Analysis of bleeding events using TIMI definitions – full analysis set (on treatment vs ITT analysis)

	Ticagrelor 60 mg BID				Placebo	
Characteristic	**Patients (%) with events**	**KM%**	**HR (95% CI)**	**p-value**	**Patients (%) with events**	**KM%**
OT	**(N=6958)**				**(N=6996)**	
TIMI Major bleeding	115 (1.7%)	2.3%	2.32 (1.68, 3.21)	<.0001	54 (0.8%)	1.1%
Fatal	11 (0.2%)	0.3%	1.00 (0.44, 2.27)	1.0000	12 (0.2%)	0.3%
ICH	28 (0.4%)	0.6%	1.33 (0.77, 2.31)	0.3130	23 (0.3%)	0.5%
Other Major	83 (1.2%)	1.6%	3.61 (2.31, 5.65)	<.0001	25 (0.4%)	0.5%
TIMI Major or Minor bleeding	168 (2.4%)	3.4%	2.54 (1.93, 3.35)	<.0001	72 (1.0%)	1.4%
ITT	**(N=7045)**				**(N=7067)**	
TIMI Major bleeding	138 (2.0%)	2.20%	1.78 (1.35, 2.35)	<.0001	78 (1.1%)	1.30%
Fatal	13 (0.2%)	0.20%	0.87 (0.41, 1.82)	0.7049	15 (0.2%)	0.30%
ICH	35 (0.5%)	0.50%	1.06 (0.66, 1.71)	0.8051	33 (0.5%)	0.60%
Other Major	98 (1.4%)	1.60%	2.53 (1.74, 3.66)	<.0001	39 (0.6%)	0.60%
TIMI Major or Minor bleeding	201 (2.9%)	3.20%	1.91 (1.51, 2.42)	<.0001	106 (1.5%)	1.70%

Table 41b: Analysis of bleeding events using TIMI definitions – base case population (ITT analysis)

	Ticagrelor 60 mg BID (N=4331)				Placebo (N=4333)	
Characteristic	**Patients (%) with events**	**KM%**	**HR (95% CI)**	**p-value**	**Patients (%) with events**	**KM%**
TIMI Major bleeding	82 (1.9%)	2.10%	1.50 (1.06, 2.11)	0.0208	55 (1.3%)	1.50%
Fatal	10 (0.2%)	0.30%	1.00 (0.42, 2.40)	0.9954	10 (0.2%)	0.30%
ICH	20 (0.5%)	0.50%	0.91 (0.50, 1.67)	0.7581	22 (0.5%)	0.70%
Other Major	59 (1.4%)	1.60%	2.19 (1.39, 3.46)	0.0007	27 (0.6%)	0.60%
TIMI Major or Minor bleeding	129 (3.0%)	3.40%	1.73 (1.30, 2.30)	0.0002	75 (1.7%)	2.00%

Table 43: Most common AEs (including bleeding) by preferred term (with frequency >1%) - full analysis set (on treatment vs ITT analysis)

	OT analysis				ITT analysis			
	Ticagrelor 60 mg BID (N - 6958)		Placebo (N = 6996)		Ticagrelor 60mg BID (N=7045)		Placebo (N=7067)	
Preferred term	**Number of patients (%)**	**Event rate (per 100 pt years)**	**Number of patients (%)**	**Event rate (per 100 pt years)**	**Number(%) of patients**	**Event rate (per 100 pt years)**	**Number(%) of patients**	**Event rate (per 100 pt years)**
Patients with any AE	5268 (75.7%)	35.93	4837 (69.1%)	30.55	5342 (75.8%)	36.43	4941 (69.9%)	31
Dyspnoea	865 (12.4%)	5.9	309 (4.4%)	1.94	895 (12.7%)	6.1	335 (4.7%)	2.1
Dyspnoea SAE					24 (0.3%)	0.16	11 (0.2%)	0.07
Dyspnoea non-SAE					877 (12.4%)	5.98	327 (4.6%)	2.05
Epistaxis	422 (6.1%)	2.88	156 (2.2%)	0.98	432 (6.1%)	2.95	164 (2.3%)	1.03
Increased tendency to bruise	419 (6.0%)	2.86	62 (0.9%)	0.39	418 (5.9%)	2.85	63 (0.9%)	0.4
Contusion	349 (5.0%)	2.38	108 (1.5%)	0.68	356 (5.1%)	2.43	107 (1.5%)	0.67
Nasopharyngitis	347 (5.0%)	2.37	349 (5.0%)	2.19	347 (4.9%)	2.37	363 (5.1%)	2.28
Non-cardiac chest pain	341 (4.9%)	2.33	374 (5.3%)	2.35	393 (5.6%)	2.68	414 (5.9%)	2.6
Dizziness	290 (4.2%)	1.98	261 (3.7%)	1.64	311 (4.4%)	2.12	270 (3.8%)	1.69
Spontaneous haematoma	218 (3.1%)	1.49	41 (0.6%)	0.26	221 (3.1%)	1.51	46 (0.7%)	0.29
Hypertension	282 (4.1%)	1.92	290 (4.1%)	1.82	300 (4.3%)	2.05	305 (4.3%)	1.91

Bronchitis	187 (2.7%)	1.28	180 (2.6%)	1.13	201 (2.9%)	1.37	186 (2.6%)	1.17
Diarrhoea	228 (3.3%)	1.55	173 (2.5%)	1.09	239 (3.4%)	1.63	186 (2.6%)	1.17
Back pain	226 (3.2%)	1.54	226 (3.2%)	1.42	243 (3.4%)	1.66	235 (3.3%)	1.47
Traumatic haematoma	160 (2.3%)	1.09	45 (0.6%)	0.28	160 (2.3%)	1.09	51 (0.7%)	0.32
Headache	175 (2.5%)	1.19	182 (2.6%)	1.14	185 (2.6%)	1.26	186 (2.6%)	1.17

Table 43b: Most common AEs (including bleeding) by preferred term (with frequency >1%) - base case population (ITT analysis)

	Ticagrelor 60mg bd (N=4331)		**Placebo (N=4333)**	
Preferred term	**Number(%) of patients**	**Event rate (per 100 pt years)**	**Number(%) of patients**	**Event rate (per 100 pt years)**
Patients with any AE	3261 (75.3%)	36.49	3022 (69.7%)	31.4
Dyspnoea	524 (12.1%)	5.86	213 (4.9%)	2.21
Dyspnoea SAE	17 (0.4%)	0.19	7 (0.2%)	0.07
Dyspnoea non-SAE	512 (11.8%)	5.73	208 (4.8%)	2.16
Epistaxis	264 (6.1%)	2.95	93 (2.1%)	0.97
Increased tendency to bruise	252 (5.8%)	2.82	45 (1.0%)	0.47
Contusion	209 (4.8%)	2.34	53 (1.2%)	0.55
Nasopharyngitis	199 (4.6%)	2.23	211 (4.9%)	2.19
Non-cardiac chest pain	248 (5.7%)	2.77	262 (6.0%)	2.72

Dizziness	202 (4.7%)	2.26	149 (3.4%)	1.55
Spontaneous haematoma	136 (3.1%)	1.52	24 (0.6%)	0.25
Hypertension	176 (4.1%)	1.97	194 (4.5%)	2.02
Bronchitis	118 (2.7%)	1.32	115 (2.7%)	1.19
Diarrhoea	146 (3.4%)	1.63	102 (2.4%)	1.06
Back pain	150 (3.5%)	1.68	148 (3.4%)	1.54
Traumatic haematoma	101 (2.3%)	1.13	27 (0.6%)	0.28
Headache	112 (2.6%)	1.25	104 (2.4%)	1.08

Table 44 Safety endpoints as 3-year Kaplan-Meier estimates - full population set (on-treatment vs ITT analysis)

AE	**Ticagrelor 60 mg BID**	**Placebo**	**Ticagrelor 60 mg vs placebo**	
	n (%)	**n (%)**	**HR (95% CI)**	**p value[a]**
OT analysis	**(n=6,958)**	**(n=6,996)**		
Dyspnoea	987 (15.84)	383 (6.38)	2.81 (2.50–3.17)	<0.001
Event leading to study drug discontinuation	297 (4.55)	51 (0.79)	6.06 (4.50–8.15)	<0.001
Serious AE	23 (0.45)	9 (0.15)	2.70 (1.25–5.84)	0.01
Renal event	173 (3.43)	161 (2.89)	1.17 (0.94–1.45)	0.15
Bradyarrhythmia	121 (2.32)	106 (1.98)	1.24 (0.96–1.61)	0.10
Gout	101 (1.97)	74 (1.51)	1.48 (1.10–2.00)	0.01

ITT analysis	(N=7045)	(N=7067)		
Dyspnoea	1019 (14.5%)	418 (5.9%)	2.60 (2.32, 2.91)	<0.001
Event leading to study drug discontinuation	297 (4.2%)	51 (0.7%)	5.95 (4.42, 8.01)	<.0001
Serious AE	27 (0.4%)	13 (0.2%)	2.08 (1.07, 4.02)	0.0305
Renal event	216 (3.1%)	210 (3.0%)	1.03 (0.85, 1.25)	0.7528
Bradyarrhythmia	147 (2.1%)	124 (1.8%)	1.19 (0.94, 1.51)	0.1535
Gout	114 (1.6%)	86 (1.2%)	1.33 (1.01, 1.76)	0.0455

- AE: adverse event; BID: twice daily; CI: confidence interval; HR: hazard ratio; TIMI: thrombolysis in myocardial infarction
- Note: there are minor differences between numbers for discontinuations due to bleeding and dyspnoea between this table from NEJM and the KM plots that follow (taken from the CSR)
- a Safety endpoints were evaluated on an exploratory basis; the p-values for these endpoints were considered descriptive and not indicative of statistical significance.

Table 44b: Safety endpoints as 3-year Kaplan-Meier estimates - base case population (ITT analysis)

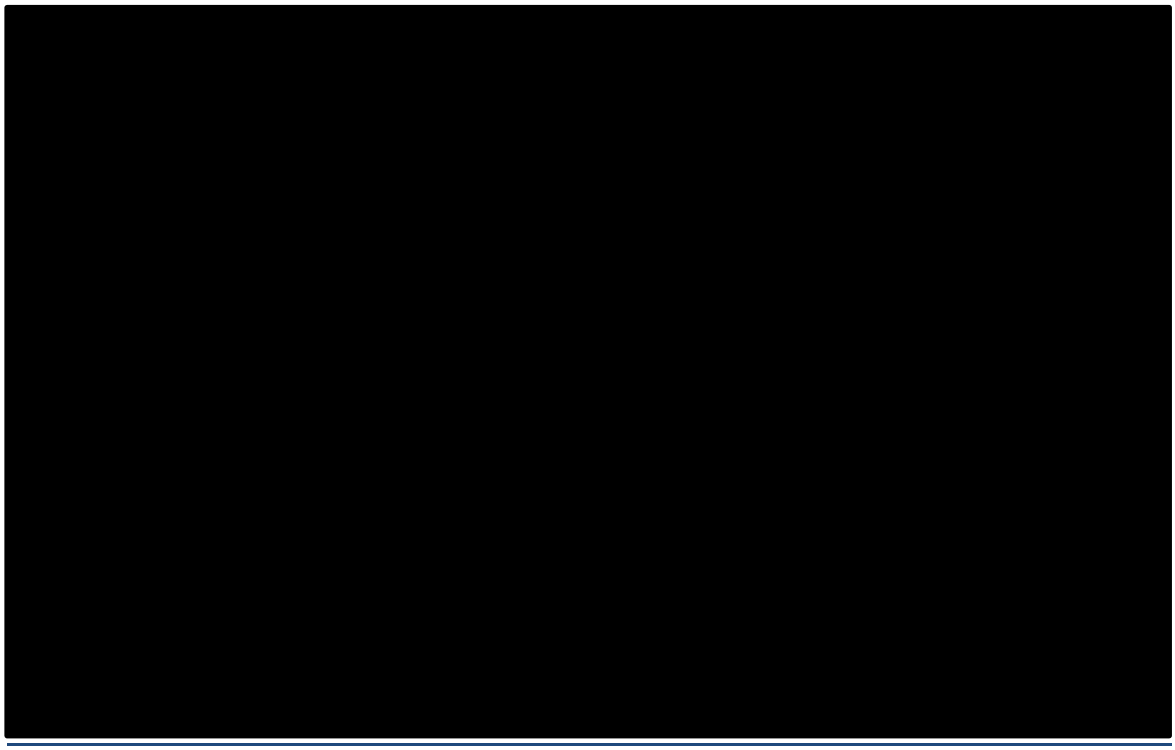
AE	Ticagrelor 60 mg BID (n=4331)	Placebo (n=4333)	Ticagrelor 60 mg vs placebo	
	n (%)	n (%)	HR (95% CI)	p value[a]
Dyspnoea	593 (13.7%)	259 (6.0%)	2.41 (2.09, 2.79)	<.0001
Event leading to study drug discontinuation	176 (4.1%)	29 (0.7%)	6.18 (4.17, 9.15)	<.0001
Serious AE	19 (0.4%)	7 (0.2%)	2.71 (1.14, 6.46)	0.0239
Renal event	128 (3.0%)	126 (2.9%)	1.02 (0.79, 1.30)	0.9006
Bradyarrhythmia	107 (2.5%)	75 (1.7%)	1.43 (1.07, 1.92)	0.0171
Gout	67 (1.5%)	54 (1.2%)	1.24 (0.87, 1.78)	0.2389

- AE: adverse event; BID: twice daily; CI: confidence interval; HR: hazard ratio; TIMI: thrombolysis in myocardial infarction
- Note: there are minor differences between numbers for discontinuations due to bleeding and dyspnoea between this table from NEJM and the KM plots that follow (taken from the CSR)
- a Safety endpoints were evaluated on an exploratory basis; the p-values for these endpoints were considered descriptive and not indicative of statistical significance.

A3. Figure 15 (page 89) of the submission reports the effect of ticagrelor on patients with ST-elevation myocardial infarction (STEMI). Please provide the corresponding results for non-ST-elevation myocardial infarction (NSTEMI).

A KM plot for this analysis is provided below.

Figure 1: Effect of ticagrelor on NSTEMI (Commercial in Confidence)



A4. Table 33 (page 98) of the submission includes a row for all cause mortality but no results are provided, the row is blank. Please provide the corresponding results.

The complete table, including the missing data, is provided below.

Table 33: Composite and individual component primary efficacy endpoint for patient subgroup: Time from qualifying MI as 3-year Kaplan-Meier estimates (full analysis) (62)

Sub group		Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID vs placebo		
	Patients	KM %	KM %	HR (95% CI)	p value	p value for interaction
CV death, MI or Stroke						
MI <2 years ago	8,664	7.8	9.7	0.77 (0.66, 0.90)	0.0010*	
MI > 2 - 3 years ago	5,428	7.8	7.9	0.96 (0.79, 1.17)	0.6945*	0.0868
CV death						
MI <2 years ago	8,664	[redacted]	[redacted]	[redacted]	[redacted]	
MI > 2 - 3 years ago	5,428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI						
MI <2 years ago	8,664	[redacted]	[redacted]	[redacted]	[redacted]	
MI > 2 - 3 years ago	5,428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke						
MI <2 years ago	8,664	[redacted]	[redacted]	[redacted]	[redacted]	
MI > 2 - 3 years ago	5,428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All cause mortality						
MI <2 years ago	8,664	[redacted]	[redacted]	[redacted]	[redacted]	
MI > 2 - 3 years ago	5,428	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARR: absolute risk reduction; BID: twice daily; CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier; MI: myocardial infarction

* Nominal p-value

A5. Please clarify the positioning of ticagrelor 60 mg in the treatment pathway. The indication summarised in table 2 (page 17) of the company submission states that 'treatment may be started without interruption following one year of ticagrelor 90 mg or other ADP receptor inhibitor.(4)

As stated by the ERG, treatment may be started without interruption as continuation therapy after the initial one-year treatment with ticagrelor 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment.

- Please clarify how patients are treated after experiencing a subsequent non-fatal event, i.e. a myocardial infarction (MI) or a stroke >12 months after the index event.

Following a subsequent non-fatal event (i.e. an MI or stroke), patients are expected to be treated as appropriate for the event experienced. In the case of an MI, patients will be 'reset' as new ACS patients according to NICE pathways (http://pathways.nice.org.uk/pathways/myocardial-infarction-secondary-prevention#path=view%3A/pathways/myocardial-infarction-secondary-prevention/myocardial-infarction-secondary-prevention-overview.xml&content=view-index). With respect to oral antiplatelet therapy, this equates to dual antiplatelet therapy for 12 months followed by ASA monotherapy or return to 60 mg ticagrelor + ASA for 3 years and ASA monotherapy indefinitely thereafter.

In the case of a non-fatal stroke, patients will be admitted to a specialist stroke unit and treated according to the relevant NICE pathway (http://pathways.nice.org.uk/pathways/stroke#path=view%3A/pathways/stroke/acute-stroke.xml&content=view-index).

- Do patients continue to receive ticagrelor 60 mg or if not what treatment do they typically receive?

Ticagrelor 60mg BID is not licenced for use immediately after an MI event or following a stroke. As such, in the event of a patient having a non-fatal MI or non-fatal stroke whilst on ticagrelor 60mg + ASA, ticagrelor 60 mg would be withdrawn and oral antiplatelet treatment as described above would be initiated.

Literature searching

A6. Please provide search strategies, date of searches, and number of records retrieved for the clinical trials register searches (section 4.1, page 50: Identification and selection of relevant studies - clinical trial registry).

The requested data is presented in Table 3.

Table 3. Summary of registry searching methodology

Registry	Date searched	Source	Search terms	Number of hits	Trial details
ClinicalTrials.gov	10/10/2014	https://clinicaltrials.gov/	Acute Coronary Syndrome AND Clopidogrel	165	• Completed trials with results, n=17 • Completed trials without results, n=29 Single trial identified where study inclusion criteria reported that patients had to have an MI > 12 months prior to study enrolment(3)
			Acute Coronary Syndrome AND Prasugrel	70	
			Acute coronary Syndrome AND Ticagrelor	70	
			Acute Coronary Syndrome AND Rivaroxaban	8	
			Acute Coronary Syndrome AND Vorapaxar	3	
EU Clinical Trials register	10/10/2014	https://www.clinicaltrialsregister.eu/	Acute Coronary Syndrome AND Clopidogrel	39	• Completed trials, n=18
			Acute Coronary Syndrome AND Prasugrel	24	
			Acute Coronary Syndrome AND Rivaroxaban	3	
			Acute Coronary Syndrome AND Ticagrelor	15	
			Acute Coronary Syndrome AND Vorapaxar	0	
Australian New Zealand Clinical Trials registry (ANZCTR)	10/10/2014	http://www.anzctr.org.au/	Clopidogrel	34	• No unique trials completed
			Prasugrel	8	
			Ticagrelor	11	
			Rivaroxaban	24	
			Vorapaxar	0	

Abbreviations: MI, myocardial infarction

A7. Please provide more details for the searches of conference proceedings, including the specific conference proceedings searched, the search strategies or search terms used, website addresses, and results (sections 2.4, 11.4 and 13.4 in the appendices: Additional searches).

Table 4. Summary of hand searching methodology

Conference	Date searched	Source	Additional methodology details	Search terms	Number of hits	Number downloaded
European Society of Cardiology (ESC)						
ESC Congress 2015	13/01/2016	Online library: http://congress365.escardio.org/	Library was searched using search facility and filtered according to year	Acute coronary syndrome	132	0
				Myocardial infarction	389	2
				Dual antiplatelet therapy	21	1
				Utility	12	0
				Cost	22	0
ESC Congress 2014 (Barcelona, Spain)	13/01/2016	Online library: http://congress365.escardio.org/	Library was searched using search facility and filtered according to year	Acute coronary syndrome	191	0
				Myocardial infarction	413	0
				Dual antiplatelet therapy	17	0
				Utility	17	0
				Cost	30	0
ESC Congress 2013 (Amsterdam, Netherlands)	13/01/2016	Online library: http://congress365.escardio.org/	Library was searched using search facility and filtered according to year	Acute coronary syndrome	145	0
				Myocardial infarction	352	0
				Dual antiplatelet therapy	20	0
				Utility	16	0
				Cost	13	0
American Heart Association (AHA)						
AHA Scientific Sessions and Resuscitation Science	13/01/2016	Circulation 2015; 132(Suppl 3) (available online): http://circ.ahajournals.org/content/132/Suppl_3	Searched by session	Acute and Chronic Coronary Artery Disease: Quality Care and Outcomes I/II/III	26	0
				Acute Coronary Syndromes:	7	0

Symposium 2015 (Orlando, Florida)				Controversies and Opportunities in Management		
				Acute Coronary Syndromes: Opportunities for Improvement	4	0
				Chronic and Acute Ischemic Heart Disease I/II/III/IV/VII	23	1
				eAbstract Session: Chronic and Acute Ischemic Heart Disease I/II/III	19	2
				Medical Therapies for ACS	9	0
AHA Scientific Sessions and Resuscitation Science Symposium 2014 (Chicago, Illinois)	13/01/2016	Circulation 2014; 130(Suppl 2) (available online): http://circ.ahajournals.org/content/130/Suppl_2	Searched by session	Chest Pain and Acute Coronary Syndromes: Presentation and Representation	5	0
				Rhythms, Myocardial Infarction and Acute Coronary Syndrome	10	0
				Assessing and Improving the Quality of Care for Acute Coronary Syndromes	10	0
				Insights into the Treatment and Outcomes of Patients with Acute Coronary Syndromes	10	0
				New Developments in Acute Coronary Syndromes	9	0
				Novel Therapies and Treatment Strategies for Patients with Acute Coronary Syndromes	5	0
AHA Scientific Sessions and Resuscitation Science Symposium 2013 (Dallas, Texas)	13/01/2016	Circulation 2013; 128(24) PDF (abstract booklet): http://circ.ahajournals.org/content/128/24/2704.full.pdf	Searched using CTRL+F search facility	Acute coronary syndrome	NA	0
				Myocardial infarction	NA	0
				Dual antiplatelet therapy	NA	0
				Cost	NA	0
				Utility	NA	0
American College of Cardiology (ACC)						
American College of Cardiology Annual	13/01/2016	Journal of American College of Cardiology March 17, 2015, Vol. 65, No. 10_S (available online): http://content.onlinejacc.org/issue.a	Searched using advanced search facility and restricting by date	Acute coronary syndrome	361	0
				Myocardial infarction	0	0
				Dual antiplatelet therapy	40	0

Scientific Session 2015 (San Diego, California)		spx?journalid= 101&issueID=933568&direction=P		Cost	93	0
				Utility	0	0
American College of Cardiology Annual Scientific Session 2014	13/01/2016	Journal of American College of Cardiology April 01, 2014, Vol. 63, No. 12_S (available online): http://content.onlinejacc.org/issue.aspx?journalid =101&issueid=929967	Searched using advanced search facility and restricting by date	Acute coronary syndrome	452	0
				Myocardial infarction	564	0
				Dual antiplatelet therapy	55	0
				Cost	106	0
				Utility	174	0
American College of Cardiology Annual Scientific Session 2013 (San Francisco, CA)	13/01/2016	Journal of American College of Cardiology March 12, 2013, Vol. 61, No. 10_S (available online): http://content.onlinejacc.org/issue.aspx?journalid =101&issueID=926556&direction=P	Searched using advanced search facility and restricting by date	Acute coronary syndrome	315	0
				Myocardial infarction	421	0
				Dual antiplatelet therapy	26	0
				Cost	107	0
				Utility	181	0
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)						
20th Annual International Meeting 2015 (Philadelphia, US)	14/01/2016	Website searched, abstracts unavailable: http://www.ispor.org/Event/Index/2015Philadelphia	Not searched	NA	NA	NA
19th Annual International Meeting 2014 (Montreal, Canada)	14/01/2016	Value in Health, Volume 17:3 (May 2014) (abstract book): http://www.ispor.org/publications/value/VIH_17-3_final.pdf	Searched using CTRL+F search facility	Acute coronary syndrome	NA	1
				Myocardial infarction	NA	0
				Dual antiplatelet therapy	NA	0
18th Annual International Meeting 2013 (New Orleans, US)	14/01/2016	Value in Health, Volume 16:3 (May 2013) (abstract book): http://www.ispor.org/publications/value/JVAL_16-3_FINAL.pdf	Searched using CTRL+F search facility	Acute coronary syndrome	NA	5
				Myocardial infarction	NA	0
				Dual antiplatelet therapy	NA	0

Abbreviations: AHA, American Heart Association; CA, California; ESC, European Society of Cardiology; NA, not available; US, United States.

Table 5. Summary of potentially relevant abstracts identified and downloaded during hand searching

Conference	Author	Title	Comments
ESC 2015	O'Donoghue	The efficacy and safety of ticagrelor in women versus men with a prior myocardial infarction: insights from the PEGASUS-TIMI 54 trial	Clinical – identified by electronic database
ESC 2015	Storey	Ticagrelor 60 mg twice-daily provides effective platelet inhibition in patients with prior myocardial infarction: the PEGASUS-TIMI 54 platelet function sub-study	Clinical – identified by electronic database
ESC 2015	Udell	Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in patients with previous myocardial infarction: a collaborative meta-analysis of randomised trials	Excluded – full publication identified and assessed for eligibility (not included)
AHA 2015	Bonaca	Abstract 19642: Consistent Benefit of Ticagrelor Both Early and Late in Patients With Prior MI in PEGASUS-TIMI 54	Excluded – full publication identified and included in clinical review
AHA 2015	Murphy	Abstract 17121: Reduction in Total Cardiovascular Events With Long-term Use of Ticagrelor in Patients With Prior Myocardial Infarction in the PEGASUS-TIMI 54 Trial	Included in clinical review
AHA 2015	Bonaca	Abstract 11594: Reduction in Subtypes and Sizes of Myocardial Infarction With Ticagrelor in PEGASUS-TIMI 54	Included in clinical review
ISPOR 2014	Reyes-Lopez	Economic evaluation of clopidogrel versus ticagrelor, in patients with acute coronary syndrome, from the perspective of the Mexican public health care system	Economic –identified by electronic database
ISPOR 2014	Deger	The cost–effectiveness of rivaroxaban for the prevention of cardiovascular (CV) events in patients with acute coronary syndrome (ACS) in Turkey	Excluded based on patient population
ISPOR 2013	Coleman	Cost-effectiveness of universal versus assay-driven antiplatelet therapy in acute coronary syndrome patients	Economic – identified by electronic database
ISPOR 2013	Kim	Cost-effectiveness of ticagrelor in patients with acute coronary syndrome	Excluded based on patient population
ISPOR 2013	Grima	Cost-effectiveness of ticagrelor versus generic clopidogrel in patients with acute coronary syndromes in Canada	Economic – full publication identified by electronic database
ISPOR 2013	Polanco	Cost effectiveness analysis of ticagrelor in the treatment of patients with acute coronary syndrome in Mexico: outcomes for specific groups	Economic – identified by electronic database
ISPOR 2013	Wu	Economic evaluation of ticagrelor in treating patients with acute coronary syndrome in Hong Kong: a cost-utility analysis	Economic – identified by electronic database

Abbreviations: AHA, American Heart Association; ESC, European Society of Cardiology; ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

A8. Please provide details of the search strategy used to search EconLit (section 11.1, page 52 in the appendices: Databases searched and service provider).

Search strategy

EconLIT was searched via the OVID platform:

OVID EconLit, 1886 to present day

The searches were conducted on the 1st December 2015.

Econlit 1886 to December 2015

#	Searches	Results
1	coronary thrombosis.mp. [mp=heading words, abstract, title, country as subject]	0
2	myocardial isch?emi*.mp. [mp=heading words, abstract, title, country as subject]	1
3	heart infarction.mp. [mp=heading words, abstract, title, country as subject]	0
4	myocardial infarction.mp. [mp=heading words, abstract, title, country as subject]	131
5	unstable angina.mp. [mp=heading words, abstract, title, country as subject]	4
6	(STEMI or NONSTEMI or NON-STEMI or NSTEMI).mp. [mp=heading words, abstract, title, country as subject]	1
7	coronary syndrome.mp. [mp=heading words, abstract, title, country as subject]	8
8	unstable coronary.mp. [mp=heading words, abstract, title, country as subject]	0
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	140

The 140 citations retrieved by this search were reviewed as part of the citation screening process and there were no unique citations in the EconLIT search. There were 3 potentially relevant citations but these were duplicated in the other databases.

Supporting references

A9. A brief summary of the summary of product characteristics (SmPC) is provided in table 2 (page 17) of the company submission .(4) Page 27 of the company submission states that the *"SmPC is provided in a PDF format"*. Please provide the PDF or refer to the relevant document in the references already provided.

A PDF copy of the SmPC was provided in the CD-ROM sent to NICE (file name 5_Brilique SPC.pdf).

A10. In section 4.10 (page 117) the company submission mentions an *"advisory board of clinical and statistical experts"*.(4) Please provide relevant documents such as meeting minutes of the advisory board.

The meeting minutes of the advisory board and a copy of the slides used in the relevant section of the meeting are attached separately. Attendee names and certain discussion points not relevant to this request are redacted in accordance with contractual obligations and commercial sensitivity.

Selection of relevant studies

A11. The inclusion criteria reported in table 15 (page 52) of the company submission state that only studies with ≥ 18 months of dual antiplatelet therapy (DAPT) would be included.(4) Please explain the justification for choosing 18 months for the cut off.

The purpose of the systematic literature review was to compare studies exploring long-term treatment of patients who had experienced an MI at least 1 year ago. The use of a lower limit for treatment duration was employed to help exclude studies investigating short-term treatment which were known to be irrelevant (e.g. PLATO; 12 months, TRITON-TIMI 38; 15 months) and was a pragmatic way of retrieving potentially useful studies which recruited patients immediately following an MI.

Quality assessment of included studies

A12. Table 24 (Page 77) of the company submission states that there was insufficient information to assess the risk of bias in the PEGASUS-TIMI study. Please explain why this information was unavailable for the primary study of the main intervention in the submission.

This was a mistake in the report and this should be recorded as 'Low risk' since the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.

The corrected table is presented here:

Table 24. Results of quality assessment using the Cochrane Collaboration's tool for assessing risk of bias

Domain	Bonaca 2015 (5)	
	Support for judgement	**Review authors' judgement**
Selection bias.		
Random sequence generation.	Randomisation was performed using a central computerised telephone or web-based system	Low risk
Allocation concealment.	Randomisation was performed using a central computerised telephone or web-based system	Low risk
Performance bias.		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes).	Assignment was double-blinded; a modified study drug option (blinded, double-dummy ticagrelor or clopidogrel) was provided to investigators for patients with an indication for ADP receptor blockade	Low risk
Detection bias.		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes).	A central clinical-events committee, whose members were unaware of treatment assignments, adjudicated all efficacy end points and bleeding episodes	Low risk
Attrition bias.		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes).	Missing outcome data balanced across groups and similar reasons for missing data across groups (trial CONSORT diagram provided in Supplementary appendix)	Low risk
Reporting bias.		
Selective reporting.	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest have been reported in the pre-specified way.	Low risk
Other bias.		
Other sources of bias.	The study appears to be free of other sources of bias	Low risk

Section B: Clarification on cost-effectiveness data

B1. **Priority request:** Please use the indirect comparisons presented in question A1 to incorporate clopidogrel in combination with aspirin as a comparator in the economic model.

An indirect comparison to clopidogrel in combination with aspirin has not been incorporated into the model. Please see explanation provided in response to question A1 for more details.

Model structure

B2. **Priority request:** Disabling and non-disabling strokes seem to have different clinical and economic impacts on the model.

- Please provide a breakdown of the number of disabling and non-disabling strokes for each arm of the trial separately.

A full breakdown of the number of disabling and non-disabling strokes for each arm of PEGASUS-TIMI 54 is provided in Table 6.

Table 6. Breakdown of the number of disabling (Rankin score 3-5) and non-disabling (Rankin score 0-2) strokes for each trial arm separately 30 days or more after the event

		Number of patients (%)							
		Ticagrelor 60mg bd (N=6958) On treatment		Placebo (N=6996) On treatment		Ticagrelor 60mg bd (N=6958) Off treatment		Placebo (N=6996) Off treatment	
Rankin score		N	%	N	%	N	%	N	%
Number of patients with event		82		104		40		32	
Patients with event and Rankin score available		44		67		25		17	
0	No symptoms at all	13	29.5%	19	28.4%	7	28.0%	3	17.6%
1	No significant disability despite symptoms; able to carry out all usual duties and activities	14	31.8%	22	32.8%	5	20.0%	2	11.8%
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	7	15.9%	11	16.4%	7	28.0%	2	11.8%
3	Moderate disability; requiring some help, but able to walk without assistance	5	11.4%	6	9.0%	2	8.0%	3	17.6%
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	0	0.0%	1	1.5%	1	4.0%	2	11.8%
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention	1	2.3%	2	3.0%	1	4.0%	2	11.8%
6	Dead	4	9.1%	6	9.0%	2	8.0%	3	17.6%

The results summarised in Table 7 demonstrate that patients treated with ticagrelor 60mg BID +ASA are associated with a numerically lower percentage of disabling non-fatal strokes (given the occurrence of a non-fatal stroke).

Table 7: Summary of occurrence of non-fatal stroke by treatment arm 30 days or more after the event (combined on treatment and off treatment)

	Ticagrelor 60mg BID (N=6958)	Placebo (N=6996)
Number of non-fatal strokes	63	75
Number of non-fatal strokes – non disabling	53	59
Number of non-fatal strokes – disabling	10	16
% disabling	15.9%	21.3%

- Please implement treatment-specific utility values and costs for stroke in the cost-effectiveness model based on the breakdown of disabling and non-disabling strokes provided in the previous bullet point.

Post stroke costs and disutilities have been estimated on an event basis, therefore the disutility estimated from the individual patient data analyses are reflective of the overall proportion of disabling and non-disabling stroke events in the PEGASUS-TIMI 54 trial (for placebo + ASA, ticagrelor 60mg BID + ASA and ticagrelor 90mg BID + ASA combined). The same cost and disutility have been applied to patients receiving ticagrelor 60mg BID + ASA or placebo + ASA when the occurrence of a non-fatal stroke event has been modelled.

In light of the evidence provided in Table 6 and Table 7 above, where patients treated with ticagrelor 60mg BID +ASA are associated with a numerically lower percentage of disabling non-fatal strokes (given the occurrence of a non-fatal stroke), it is reasonable to expect that both the disutility and cost associated with non-fatal stroke would lower for those treated with ticagrelor 60mg BID + ASA and conversely higher for those treated with placebo + ASA. Therefore the application of disutility and costs in the model in the current manner is conservative for ticagrelor 60mg BID + ASA.

B3. Subsequent events and adverse events (AE) are not explicitly modelled, as a result of this simplification the occurrence of subsequent event and AE does not impact survival. Subsequent events and AE only have a temporary (3 months) impact costs and quality of life. Moreover, difference in AEs between treatments was incorporated until ticagrelor treatment discontinuation only.

- Please adjust the economic model to incorporate the impact of subsequent events and AE on survival and costs and quality of life beyond 3 months, e.g. impact of non-fatal bleeding such as intra-cerebellar bleeds.

- Please explain the statement, that this simplification does not impact health outcomes and costs, with a scenario analysis explicitly incorporating subsequent events and the potential impact on survival.

- Please provide a scenario analysis incorporating difference in AEs between treatments after ticagrelor treatment discontinuation only.

Subsequent events

Subsequent events for the primary outcomes from PEGASUS-TIMI are modelled (see original submission pages 171, 195 to 207). Differential rates for the subsequent occurrence of CV events (non-fatal MI, non-fatal stroke and CV death) were modelled with a number of considerations:

- First, multiple failure risk equations were applied to account for the fact that more than one primary event could occur during the acute and long-term stable phase. These models kept patients in the 'at risk' population and allowed for the occurrence of subsequent events to be incorporated.
- Second, variables were included in the subsequent event risk equations which captured whether the first event was either a non-fatal MI (pMI_Tic60) or a non-fatal stroke (prevEvent). These variables showed that the risk of having a subsequent non-fatal MI was higher if the first event was a non-fatal MI, likewise, the risk of a subsequent non-fatal stroke event was higher if the first event was a non-fatal stroke.

A pragmatic decision was made to simplify the health states needed to model transition probabilities through the acute and stable phase subsequent events, without losing important information. Therefore the risk equations were designed to capture the likelihood of multiple subsequent events (during the acute and stable phase) in addition to the greater risk of a subsequent given the occurrence of a first event.

Should the model slightly underpredict the occurrence of 3rd events (and beyond), this would represent a conservative modelling approach from the perspective of ticagrelor 60mg BID + ASA, owing to the treatment effect observed for first events in PEGASUS-TIMI 54 and the influence of first events on subsequent events.

The occurrence of the 3rd event (and beyond) in the model represents (at least) the 4th event (and beyond) in the patient's history, given the qualifying MI.

Adverse events

The occurrence of TIMI Major/Minor Bleeds and Dyspnoea (Grade 3-4) and (Grade 1-2) were modelled dependent on being 'on treatment' but independent of other events in the model, which is consistent with safety analyses from the PEGASUS-TIMI 54 trial. A comparison of OT and ITT analyses of TIMI bleeding and dyspnoea events, as presented in Table 8 illustrates that the magnitude of the treatment effect on both a relative and absolute basis, is greater for the OT analysis than the ITT analysis. Therefore incorporating AEs into the model on an OT basis represents a conservative modelling approach from the perspective of ticagrelor 60mg BID + ASA. As a result, the requested scenario analysis incorporating difference in AEs between treatments after ticagrelor treatment discontinuation only is not provided.

Table 8: Main AEs endpoints for cost-effectiveness model by OT and ITT analyses (base case population)

	Ticagrelor 60 mg BID				Placebo	
Characteristic	**Patients (%) with events**	**KM%**	**HR (95% CI)**	**p-value**	**Patients (%) with events**	**KM%**
OT	**(N=4279)**				**(N=4287)**	
TIMI Major bleeding	72 (1.7%)	2.40%	2.05 (1.38, 3.03)	0.0004	38 (0.9%)	1.20%
TIMI minor bleeding	42 (1.0%)	1.50%	3.22 (1.76, 5.90)	0.0001	14 (0.3%)	0.50%
Dyspnoea all*	573 (13.4%)	15.20%	2.57 (2.21, 2.99)	<.0001	241 (5.6%)	6.50%
Dyspnoea grade 3-4	17 (0.4%)	0.50%	4.49 (1.51, 13.35)	0.0069	4 (0.1%)	0.10%
Dyspnoea grade 1-2						
ITT	**(N=4331)**				**(N=4333)**	
TIMI Major bleeding	82 (1.9%)	2.10%	1.50 (1.06, 2.11)	0.0208	55 (1.3%)	1.50%
TIMI minor bleeding	50 (1.2%)	1.30%	2.17 (1.33, 3.56)	0.002	23 (0.5%)	0.70%
Dyspnoea all*	593 (13.7%)		2.41 (2.09, 2.79)	<.0001	259 (6.0%)	
Dyspnoea grade 3-4	19 (0.4%)		2.71 (1.14, 6.46)	0.0239	7 (0.2%)	
Dyspnoea grade 1-2	580 (13.4%)		2.41 (2.08, 2.79)	<.0001	254 (5.9%)	

* Not an endpoint in the model but included here due to absence of dyspnoea information grade 1-2.

The risk of TIMI major/minor bleeds or dyspnoea (grade 3-4) or dyspnoea (grade 1-2), were modelled using multiple failure risk models. By way of contrast to standard risk equations, a multiple failure risk model does not remove an individual from being 'at risk' until the evaluation period is reached (e.g. treatment cessation), as such patients are allowed to have multiple events in the model, whilst on treatment.

With regards to the modelling of AEs and in particular TIMI major bleeding as a temporal event, as presented in Table 41 (page 126) of the original submission, it should be noted that within PEGASUS-TIMI 54, ticagrelor 60mg BID + ASA was not associated with an increase in fatal bleeding or intracranial haemorrhage (ICH) meaning the observed excess related to TIMI major non-fatal and non-ICH bleeds. Therefore we feel it appropriate to model AEs including TIMI major bleeding as a temporal event. The impact on HRQoL is captured in the disutility applied when an event occurs in the model and an inpatient hospital cost is applied.

B4. Please add a scenario analysis incorporating treatment with ticagrelor 60 mg, starting 12 months after having experienced a subsequent MI (consistent with the response to question A11).

In the time available to respond to clarification questions, it has not been possible to meet this request directly, owing to the fact that it brings quite substantial structural implications for the model - it would be necessary to build in further post non-fatal MI tunnel states up to 4 years after the MI event. Were such a change implemented, it would be expected to result in a (marginally) lower ICER for ticagrelor 60mg BID vs. that presented for base case within the original submission, owing to additional cost being captured in post non-fatal MI health states in years 2 to 4 following an MI event. To illustrate the direction of the change, a new scenario analysis will be provided separately whereby the cost associated to the post non-fatal MI (12+ months) health state is increased by £178.06 per cycle (the cost of ticagrelor 60mg BID per 3 months). This is similar to assuming ticagrelor 60mg BID is given for remaining lifetime from 12 months following an MI event. As such, this scenario analysis overstates the impact on the ICER opposite the requested analysis but is illustrative of directional impact on the ICER. This scenario analysis will be provided separately.

B5. Please add a scenario analysis replacing clopidogrel treatment 1 to 12 months after experiencing a subsequent MI by treatment with tricagrelor 90 mg.

The requested scenario analysis will be provided separately.

Risk equations for first and subsequent event

B6. **Priority request:** The risk equations incorporated in the economic model are based on the ITT population of the PEGASUS-TIMI 54 trial, while the population of interest specified by the company is a subgroup of this population, termed the 'label population'.(4) Only the risk equations for first non-fatal MI and fatal cardiovascular (CV) events (as first event) are adjusted (in part) to represent the label population.

First event

Following a restriction to the eligible patient population being incorporated into the SmPC late in the EU regulatory process, the 'original' time to first event risk equations (i.e. those derived using the ITT population of the PEGASUS-TIMI 54 trial) were analysed to observe whether an interaction effect existed between the treatment effect and being in the (new) 'label' population. The reason for taking this approach, as opposed to an alternative approach whereby the risk equations be reformulated using only data for patients corresponding to the 'label' population, was so as to preserve 'power' in the equations to detect the factors that influence relatively rarely occurring events and thus maintain the level of precision of the model. Adopting the alternative approach would have reduced the number of patient profiles used in the derivation of the equations by almost 50% (10,779 patients in the 'label' population vs. 21,162 patients in the trial) and thus reduced precision.

The derivation of (all) original risk equations gave consideration to variables relating to time since qualifying MI (*qev2rnd*) and time since previous ADP treatment (*tADP_30dless, tADP_30d12m and tADP_12mplus*). This is important because the qualifying factors for being in the 'label' population were:

- time since qualifying MI of less than 2 years or;
- previous ADP treatment within 1 year prior to study enrolment.

For those original risk equations that did not contain the above variables, we can conclude that these factors did not have any significant influence upon the outcome of the interest (and therefore nor would it be expected that being in the 'label' population, or not, would).

Following the analysis to test for interaction effect between treatment effect and being in the 'label' population for first event risk equations. Only two of the equations required adaption in this regard (non-fatal MI and fatal CV) as there was no evidence of an interaction between the treatment effect and inclusion in the 'label' population for non-fatal stroke and fatal other (see Appendix Table 38 and Table 46 where p-values for offlabel, Tic60offlabel and Tic90offlabel are all greater than 0.05).

We go on to describe the methodology used to assess whether the 'base' variables should be retained or dropped, having incorporated the interaction term, under the heading 'Decision to drop similar variables' below.

Other events

Other risk equations (subsequent events, adverse events, hospitalisations and discontinuations) were not analysed to observe whether an interaction effect existed, as the effect on the outcome of interest of being in the 'label' population or not was thought to be adequately explained by considering the time since qualifying MI and time since previous ADP treatment-related variables in the derivation of the original risk equations. Taking TIMI

major bleeding as an example, there is no evidence to suggest that ticagrelor 60mg treatment effect is modified by time since qualifying MI **(ref Bonaca supplementary)** or time since previous ADP inhibitor treatment (**ref time since ADP subgroup publication**). Taking subsequent events as a second example, for base case no treatment effect is assumed, so it was not deemed important to investigate the possibility of an interaction effect.

In summary, we believe that the risk equations adequately capture the effect of being in the 'label' population and that the approach taken maximises power in the equations and thus the precision of the model (as demonstrated via observed vs. modelled events in Table 141 within the original submission).

- Please provide all risk equations for first event, subsequent event, adverse events, treatment discontinuation and hospitalisation for the label subpopulation only (instead of the ITT population).

The risk equations requested are not provided based on the response above.

- Please use these risk equations in a scenario analysis and present the cost-effectiveness results using the average outcomes (i.e. costs and quality-adjusted life years (QALYs)) obtained from the probabilistic sensitivity analysis (PSA; using the 'simple'/cohort analysis).

The scenario analysis requested is not provided based on the response above.

B7. **Priority request:** In the following cases, variables and/or interaction terms were excluded from the risk equations without providing objective decision criteria for this:

(1) Company submission page 178 *"Variables were excluded if proportionality was not observed and interaction effects could not be established."*

- Please provide more details of the test for interaction used to assess the proportional hazards (PH) assumption. Was it the interaction between the variable and time (or log time) and what significant level was used? Please also provide details for each risk equation of which variables (if any) were dropped from the model due to doubts about the PH assumption.

Proportional hazards for both original variables and interaction variables were analysed using the Schoenfeld residuals test. Additional analyses were performed observing log–log plots of survival and a plot of Kaplan–Meier and predicted survival, if deemed necessary.

For the Schoenfeld residuals test, a variable was considered to require further analysis for proportional hazards where $p<0.05$. For such variables, proportional hazards were subsequently assessed by observing log-log plots (log-log survival compared vs. log time). The proportional hazard assumption can be deemed to hold when the lines are parallel, demonstrating that log hazards are constant over time. In addition to this, analysis of the observed survival (Kaplan-Meier plots) vs. predicted survival was observed to consider how well the predicted outcomes of the regression model fit the observed data. Increasing disparity between the observed and predicted data was considered as another indicator that the proportional hazards assumption did not hold.

No variables were dropped from the analysis due to the proportional hazards assumption. The variable 'NthAmerica' in the time to first event, non-fatal MI analysis and 'creatinine_cl'

in the time to first event, fatal other analysis were assessed as they fulfilled the criteria outlined above. Upon visual inspection of the log-log and Kaplan-Meier plots (Appendix 16, Figure 1 and Figure 5), the proportional hazards assumption was deemed to hold (parallel lines with agreement with between the observed and predicted data) for both variables and they remained in their respective analyses.

(2) Company submission page 180 *"similar variables dropped from the analysis to isolate the effect of being in the label population"*

- Please provide the significance level used to assess the interaction between off-label and other variables. If it was < 0.05 then this seems to be low for assessing an interaction term (0.10 or higher is usually used due) so please justify your choice. Please also provide details of what you mean by "similar variables", i.e. how the decision was made to drop them, and give details of the variables which were dropped in each risk equation (if any).

The significance level for the interaction term was p<0.05, when attempting to observe an interaction term between variables Tic60 (60mg ticagrelor) and offlabel (for the label population). Where the p-value for an interaction term fell between 0.05 and 0.1, the treatment arms were combined (i.e. *Tic60* and *Tic90)* for additional power and an attempt made to observe whether an interaction term existed between ticagrelor treatment (any dosage) and the label population. This methodology is detailed on page 180 of the submission.

"*If the p-value fell between 0.05 and 0.1, then the two separate interaction terms (t60offlabel and t90offlabel) were collapsed to one variable (i.e. a new interaction variable encoding ticagrelor of any dosage and patients not included in the label population). An interaction effect was then analysed by the [log rank] test approach using this collapsed variable, increasing the power to detect an interaction effect where one existed*".

Furthermore, the stepwise approach taken to consider whether an interaction term should be included in the risk equation is detailed within tables in the appendix (e.g. table 42, page 137, relating to first-event: fatal CV). This table displays this methodology, since the introduction of the interaction terms (*Tic60offlabel* and *Tic90offlabel* variables) produced p-values of 0.023 and 0.075, respectively. When combining the treatment effect to observe an interaction term, the p-value observed was 0.02, supporting the inclusion of both the *Tic60offlabel* and *Tic90offlabel* variables in the regression model.

Decision to drop similar variables

The decision to drop 'similar variables' was performed due to the high probability that variables *qev2rnd*, and tADP (*tADP_30dless*, *tADP_30d12m* and *tADP_12mplus*) would be highly associated with any variable encoding patients included in the label population, given that these variables are qualifying factors for the label population.

Evidence to support this can be observed in Section A16.1, in which the *qev2rnd* variable in the original regression model for 'time to first event: non-fatal MI' becomes unstable with the introduction of the label population variable: the *qev2rnd* variable hazard ratio moves from 1.0005 (p=0.003) to 1.0003 (p=0.157) with the introduction of the label population variable (*offlabel*) and interaction terms (*Tic60offlabel* and *Tic90offlabel*). This loss of stability is observed in the increase in the standard error associated with this variable (26% increase in

standard error), which introduces model instability and lack of precision in estimating the impact of individual variables in the model (as observed by the p-value).

An additional example can be observed in Section A16.2 (Table 38), in which the introduction of the label population variable and interaction terms reduces the hazard ratio for *tADP_12mplus* variable from 0.705 (p=0.033) to 0.687 (p=0.084). The change in the p-value is a consequence of the increased standard error for this variable (29% increase in the standard error, data not shown), increasing model instability, and reducing the ability of the regression to isolate the effect of inclusion in the label population.

Table 9 demonstrates that Time since MI (*qev2rnd*) varies according to being in the label population or not and Table 10 demonstrates the association between time since previous ADP inhibitor treatment (e.g. *tADP_12mplus)* and being in the label population or not.

Table 9: Summary of qev2rnd variable, for patients included and not included in the label population

Patient population	N	Time since previous MI (days)
Label population	16,153	581.7
Non-label population	5,009	922.5

Table 10: Summary of tADP_12mplus variable, for patients included and not included in the label population

Time since previous ADP treatment	Label population (%)	Non-label population
≤12 months	15,071 (93.3%)	1,109 (22.1%)
>12 months	1,082 (6.7%)	3,900 (77.9%)
Total	16,153 (100%)	5,009 (100%)

(3) Company submission page 181 *"Where multicollinearity was suspected to have occurred between the 'offlabel' variable and either the 'qev2rnd' or 'tADP_12mplus' variables, the label population variable was prioritised and retained in the model, and the collinear variables dropped as the label population variable was of greater importance."*

- Please clarify the statistical method used to assess multicollinearity (such as tolerance or variance inflation factor) and the threshold used to decide whether variables were collinear (e.g. VIF >10). Please also specify which (if any) variables were dropped from each risk equation model.

The term 'multicollinearity' used in the submission was used interchangeably with 'similar variables', which is described extensively above. There was no statistical test performed to assess multicollinearity, and therefore for clarity this should be considered to be describing the same issue as 'similar variables'.

B8. Treatment (Tic60/ pMI_Tic60 variable) was not included in the estimation of transition probabilities using the risk equations to estimate subsequent events and both first and for "fatal other" this was applicable to the estimation of the first events.

- Please clarify why the treatment variable was not included in these risk equations.

For base case, the treatment effects observed for subsequent events have been excluded as a conservative estimate of the impact of treatment with ticagrelor 60mg BID.

One of the scenario analyses included within the submissions allows for the inclusion of the treatment effect for subsequent events as a scenario after a non-fatal event in the model. The impact of including subsequent treatment effects is to decrease the ICER compared to the base case analysis. As such, the exclusion of subsequent treatment effects does not conceal any 'catch-up' effect that is often observed in clinical trials.

"*In this analysis (Table 127) ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0767 QALY at an incremental cost of £1,443, generating an ICER of £18,817. This demonstrates that our initial assumption was the more conservative*."

- Please examine the impact of not including the treatment variable for "non-fatal stroke" in a sensitivity analysis (by including the treatment variable in the risk equations).

As requested an additional sensitivity analysis has been undertaken to assess the removal of the treatment variable in the "non-fatal stroke" risk equation. The results will be provided separately. It should be noted that a consequence of the removal of the treatment effect for non-fatal stroke is an underestimate of the treatment effect for the composite primary endpoint. Thus, AstraZeneca believes that it is not appropriate to remove the treatment effect for non-fatal stroke in the base case.

B9. In order to avoid underestimation of mortality in the base case, the company has derived the probability of non-CV related mortality from UK life tables. As life tables reflect all-cause mortality, including deaths from CV-related causes, CV-specific mortality was excluded from the standard life tables used in the model using a component of contribution for non-CV death compared to all-cause mortality. The Evidence Review Group (ERG) would like to be able to validate the values set out in table 91 of the CS but is unable to do so without specific references and methods of adjustment.

- Please supply a proper reference (with an active web link) for "the UK Government Actuarial Department's 2004–2006 interim life tables and the Office for National Statistics mortality by cause data".

Mortality Statistics: Cause, England and Wales (Series DH2: discontinued), No. 32, 2005 can be accessed at:
http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/vsob1/mortality-statistics--cause--england-and-wales--series-dh2--discontinued-/index.html

- Please supply references for any adjustments made (in relation to ICD-10 codes: I11, I13, I20-I26, I30-I49, I50-I74, I81-I82 and I85) if they are not detailed in the aforementioned reference.

The adjustments are made in a number of steps:

- Using the above source, all cause, all age deaths by ICD code were calculated
- ICD codes included in the definition of CV death within PEGASUS-TIMI 54 were:
    - I11; I13; I20-26; I30-49; I50:74; I81-82; I85
- The number of deaths due to these causes (as reported in source above) were calculated
- General population mortality was then adjusted to take into account the causes of death already accounted for within PEGASUS-TIMI 54 (by excluding the deaths caused by these ICD codes from that of the general population).
- Adjusted rates and relative risks for eliminated causes and all deaths are thus calculable.

All calculations are detailed in the "Mortality Sheet", cells AN13:BL36

Adverse events and hospitalisations

B10. TIMI bleeds and dyspnoea were considered as AE in the model (incorporated using an exponential parametric model).

- Please examine other parametric distributions than exponential (i.e. Weibull, Gompertz, Log-Normal and Log-Logistic) for implementing AE and incorporate the optimal model (selection based on AIC) in a sensitivity analysis.

AE functional forms:

To meet the ERG request, we have examined other parametric distributions (Weibull, Gompertz, log-normal and log-logistic) functions for implementing AEs (Table 11 to Table 14).

Table 11: AIC and BIC by functional form, Major TIMI Bleeds

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exponential	20,816	-1498.554	-1445.519	12	2915.038	3010.36
weibull	20,816	-1498.516	-1445.519	13	2917.038	3020.303
gompertz	20,816	-1498.195	-1445.343	13	2916.687	3019.952
lognormal	20,816	-1499.167	-1445.719	13	2917.438	3020.703
loglogistic	20,816	-1498.474	-1445.395	13	2916.79	3020.055

Table 12: AIC and BIC by functional form, Minor TIMI Bleeds

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exponential	20,698	-817.652	-778.5649	10	1577.13	1656.508
weibull	20,698	-814.9497	-776.4525	11	1574.905	1662.221
gompertz	20,698	-812.9374	-774.6487	11	1571.297	1658.613
lognormal	20,698	-813.0481	-774.445	11	1570.89	1658.206
loglogistic	20,698	-814.9263	-776.3622	11	1574.724	1662.04

Table 13: AIC and BIC by functional form, Dyspnoea (Grade 3 to 4)

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exponential	20,745	-351.0424	-328.1443	9	674.2886	745.7491
weibull	20,745	-341.9057	-320.0169	10	660.0337	739.4344
gompertz	20,745	-349.2008	-326.6267	10	673.2534	752.654
lognormal	20,745	-342.2008	-320.5281	10	661.0563	740.4569
loglogistic	20,745	-341.9087	-320.0305	10	660.061	739.4616

Table 14: AIC and BIC by functional form, Dyspnoea (Grade 1 to 2)

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exponential	21,686	-17865.92	-17087.66	18	34211.32	34355.04
weibull	21,686	-14935.24	-14259.46	19	28556.92	28708.62
gompertz	21,686	-16212.42	-15514.63	19	31067.27	31218.97
lognormal	21,686	-14810.53	-14104.6	19	28247.19	28398.9
loglogistic	21,686	-14916.93	-14219.57	19	28477.14	28628.84

Using AIC as the decision criteria, the following functional forms were determined to be the optimal model by adverse event:

- Major TIMI Bleeds: Exponential
- Minor TIMI Bleeds: Log-Normal

- Dyspnoea (Grade 3 to 4): Weibull
- Dyspnoea (Grade 1 to 2): Log-Normal

These functional forms were adopted into the model for (new) base case. A table showing the stepwise impact of all changes to the model adopted for (new) base case are presented in Table 28.

According to the company submission (page 264) *"A small excess of gout was observed in PEGASUS-TIMI 54 for ticagrelor 60mg BID vs. placebo (0.46% ARI; HR 1.48; 95% CI 1.10 to 2.00; p=0.01)"*.(4) Nevertheless, gout was not considered in the economic model, this is unlikely to be a conservative assumption.

- Please examine the impact of this assumption by incorporating the impact of gout on costs and quality of life in the economic analyses.

Gout

To meet the ERG request, we have incorporated gout as an AE into the model. The rate of gout events for patients in the placebo + ASA arm were estimated (74 events with 5,662,696 on treatment days at risk). Gout was incorporated into the model as a simple rate per cycle for patients receiving placebo + ASA and applying the hazard ratio for the full PEGASUS-TIMI 54 population (HR=1.48; 95%CI: 1.10 to 2.00) to estimate the number of gout events for patients receiving ticagrelor 60mg BID + ASA. This is likely to be an over estimation of the relative difference between treatment arms for patients treated <2 years following their qualifying MI, where the total number of gout events observed were 67 for those receiving placebo + ASA and 81 for those receiving ticagrelor 60mg BID + ASA. Furthermore, gout is assumed to be a chronic condition in the model, with the total number of patients with incident cases of gout aggregating over the time horizon of the model. Given a minor imbalance of medical history of gout at baseline, 227 (5.3%) of the patients in the ticagrelor 60 mg group versus 204 (4.8%) in ASA alone arm, this additional analysis should be interpreted with caution.

All of the gout events which occurred during the PEGASUS-TIMI 54 trial were non-serious in nature (grade 1 to 2) except for 1 serious event in the placebo arm. It is assumed that the disutility associated with a non-serious gout event is equivalent to dyspnoea (grade 1 to 2). This disutility is applied chronically in the case of gout occurring and patients with gout are assumed to have two GP visits per year.

Gout was adopted into the model for (revised) base case. A table showing the stepwise impact of all changes to the model adopted for (revised) base case is presented in Table 28.

B11. The rate of hospitalisation is estimated using a Poisson regression model.

- Please examine whether the Poisson model is over-dispersed and whether it is zero inflated.
- If the Poisson model is over-dispersed or zero inflated, provide a corrected regression model (and economic model) to estimate the rate of hospitalisation.
- Please clarify how the variables for the Poisson regression were selected.

- Please justify why treatment (Tic60) is not incorporated as covariate in the Poisson regression model and examine the impact of this while including Tic60 in the Poisson regression in a sensitivity analysis.

Over-dispersion with regard to Poisson regressions are an issue when the variance is larger than the mean in the observed data. Summary statistics for hospitalisation events within 3 monthly period (akin to the modelled cycles) are outlined in Table 15. It is clear from these data that the Poisson is a good fit, given that the mean value (0.0282) is only marginally greater than the variance (0.0274).

Table 15: Summary statistics for hospitalisation data

Statistic	Measure
Observations	214,358
Mean	0.0282
Standard Deviation	0.1656
Variance	0.0274

In addition to these summary statistics a goodness-of-fit analysis was completed to empirically test whether the Poisson regression was appropriate. If the deviance statistic or the Pearson statistic are statistically significant then the Poisson regression is inappropriate and a negative binomial model should be used. These goodness-of-fit tests confirm that the Poisson is an appropriate fit for the hospitalisation data (Table 16).

Table 16: Goodness of fit statistical tests for Poisson regression

Deviance goodness-of-fit	34,845.64
Prob > chi2(214323)	1.0000
Pearson goodness-of-fit	183,510.7
Prob > chi2(214323)	1.0000

Zero-inflated models are used in applied circumstances where there are an excess of zeros within a data set. The model first predicts the probability of an event occurring (using a logit regression) and then the rate of that event (given that the event has occurred). Nominally, with respect to the hospitalisation data within the PEGASUS datasets, there are a number of time periods evaluated in which a hospitalisation event did not occur. Therefore zero-inflated Poisson model is a reasonable candidate for this model, although an assessment with respect to the efficiency between a Poisson regression and a Zero-Inflated Poisson is warranted given the additional complexity of the latter.

A zero-inflated Poisson regression was estimated using the same covariates as the Poisson model. A Voung test of Zero-Inflated versus Standard Poisson regression was also completed which indicated that a zero-inflated model might be appropriate ($p < 0.001$). However a comparison between the predictive performance of the Poisson and Zero-Inflated model (Table 17) showed that the Poisson model provided a better estimate of the mean hospitalisations.

Table 17: Comparison of model efficiency (Poisson vs Zero-Inflated)

Model	Observations	Mean	Standard Deviation
Observed	214,358	0.9718	0.1656
Poisson	214,358	0.9747	0.0409
Zero inflated	214,358	0.9752	0.0487

In consideration of these results, the original Poisson regression model has been retained.

Health related quality of life

B12. **Priority request:** As explained by the company, the use of a linear random effect panel data analysis allowed for utility values > 1(Table 98, page 262, company submission(4)). Therefore, the company capped the utility value from the PEGASUS TIMI 54 to 1. However, utility decrements used in the model are still based on the same linear model. Naïvely capping the maximal utility value will presumably bias the utility decrements since the scale on which utility decrements are based is different than 0-1.

- Please justify why capping the maximal value is considered appropriate instead of using a model providing utility estimates between 0-1.
- Please justify why applying (multiple) utility decrements was considered more appropriate than calculating utility values for the different health states.
- Recalculate the utility values using a model providing utility values between 0-1 bounds (e.g. a probit model) and provide details on:
    a. The number of events, patients and EQ-5D questionnaires used to calculate the utility estimates and utility decrements, if applicable.
    b. The methodology used to determine utility estimates and utility decrements, e.g. variable selection and assumptions underlying the model.
    c. The uncertainty around each utility estimate and each utility decrement (e.g. standard deviation, standard error, lower and upper bounds).
    d. Include these new utility values in the cost-effectiveness model (provide the methods and results)

By way of clarification the restriction applied to utilities (capping the value to 1.0) applies to the estimation of the baseline utility, from which disutilities are applied if an event occurs. In the original submission the baseline utility estimates were sourced from reported national norms as published by Kind et al (6) and will not have been impacted by a capping of the baseline utility. A scenario analysis whereby the cap associated with baseline utilities be removed will be provided.

ERG requested that baseline utilities be estimated using a model which has properties that naturally restrict to a value of 1. The suggested probit (or presumably logit) models were deemed to be inappropriate as these models are used to estimate the probability of a binary

outcome. Instead a gamma model (using a log-link) was estimated after transforming the baseline EQ-5D-3L estimates using the following function (1 – utility), outputs from this regression are shown in Figure 2. Applying this functional form to the transformed utility estimates, naturally allows the utility to be capped at 1 but also allows utility estimates to be lower than zero, as is possible for outcomes using the EQ-5D tool. Baseline covariate selection was also performed using an identical process to that previously undertaken in the original submission (as reported on p177-178) and the total number of baseline respondents are reported in Table 97 p261 of the original submission.

A re-estimation of utility models beyond the baseline has not been completed. A panel data analysis controlling for baseline characteristics, and the occurrence of events is a superior analytical approach compared to the suggested analysis that purely estimates utility values for health states that are occupied at the time of EQ-5D data collection, for the following reasons:

- A panel data analysis allows for each individual to act as a control for themselves since a series of cross-sectional analyses suggested by the ERG would draw data from a different set of individuals at each time point. A rationale for this was outlined in the original submission p258-261 including Figure 47.
- The number of health states modelled would have to increase significantly, as the approach suggested by the ERG would need to consider patients who have had an MI (within and outside of 91 days) with and without TIMI Bleeding Major/Minor, other adverse events and subsequent events (such as other non-fatal MI's or non-fatal stroke).
    - The complexity of such a model would be very onerous as transitions between each of the combinations of health states would require estimation, in addition to hospital admission rates for each combination of health states.
    - Segmentation of the PEGASUS trial data to support such an analysis would reduce the statistical power, and increase the level of uncertainty.
- Utility decrements estimated as part of the panel data analyses accord very closely with utility decrements reported in the literature (p257 Table 96 of the original submission).

By including multiple events in the panel data regression, as per the original submission, the reduction in utility associated with an event can be clearly estimated, and allows greater flexibility with respect to modelling.

A scenario analysis whereby baseline utilities be derived using a gamma model (using a log-link) as described will be provided separately.

Figure 2: Baseline utility estimates using a log transformed gamma model on 1 – utility values

```
Generalized linear models                         No. of obs      =     20,573
Optimization     : ML                             Residual df     =     20,549
                                                  Scale parameter =   1.618544
Deviance         =  8599.358008                   (1/df) Deviance =   .4184806
Pearson          =  33259.45268                   (1/df) Pearson  =   1.618544

Variance function: V(u) = u^2                     [Gamma]
Link function    : g(u) = ln(u)                   [Log]

                                                  AIC             =  -1.931434
Log pseudolikelihood =  19891.70058               BIC             =  -195487.9
```

yvar_glm	Coef.	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
sex	-.4114762	.0195363	-21.06	0.000	-.4497666	-.3731857
age	-.0844568	.0138828	-6.08	0.000	-.1116667	-.0572469
age2	.0006971	.0001045	6.67	0.000	.0004922	.000902
bmi	.0230549	.0018766	12.29	0.000	.0193769	.0267329
dmtype	.0965591	.0194756	4.96	0.000	.0583877	.1347306
MI_HIST	.1033513	.0228149	4.53	0.000	.0586349	.1480678
smk_his1	.0556938	.0211691	2.63	0.009	.0142031	.0971846
smk_his2	.2209548	.0278885	7.92	0.000	.1662944	.2756151
stentany1	-.2476466	.0212597	-11.65	0.000	-.2893147	-.2059784
anpect	.2389557	.0185444	12.89	0.000	.2026093	.2753022
qevtyp2	-.0462675	.0182709	-2.53	0.011	-.0820778	-.0104572
MEDTDDOS_n	.0016841	.0005276	3.19	0.001	.0006501	.0027181
dbpsup	.0023658	.0009294	2.55	0.011	.0005442	.0041874
hyp	-.0435253	.0217446	-2.00	0.045	-.0861439	-.0009067
hypchol	.1606081	.0250697	6.41	0.000	.1114725	.2097437
cohdhist	.0403069	.0194547	2.07	0.038	.0021763	.0784374
stroke	.3370755	.1151704	2.93	0.003	.1113457	.5628054
tria	.3049262	.0691149	4.41	0.000	.1694635	.4403889
chf	.3141598	.0194726	16.13	0.000	.2759943	.3523254
Asia_Australia	-.5901457	.0427591	-13.80	0.000	-.673952	-.5063395
tClop_7dplus	-.0326337	.0185941	-1.76	0.079	-.0690775	.0038101
histPAD	.3086902	.0319216	9.67	0.000	.246125	.3712554
creatinine_cl	-.0936972	.0253877	-3.69	0.000	-.1434562	-.0439382
_cons	-.161652	.4697306	-0.34	0.731	-1.082307	.759003

B13. Table 96 (page 256) of the company submission displays utility decrements from the current and previous assessments.(4) The difference between the decrements is also provided.

- Please describe the calculations to obtain utility decrements from previous assessments (methods + results).

Table 18 Methodology applied to utility values found in the literature

Literature reference	Methodology
Sullivan et al 2011	Panel data from EQ-5D descriptive questionnaire responses from the US-based Medical Expenditure Panel Survey (MEPS) based on community based UK preferences. Ordinary least squares (OLS), Tobit, and censored least absolute deviations (CLAD) regression methods were used to estimate the 'marginal disutility' of each condition controlling for covariates.
TA182	Reference to Sullivan et al., 2006:
TA210	Study by Delea et al., 2003: The utility values were taken from this CE analysis and were derived from published, population-based studies employing either time trade-off or standard gamble techniques.
TA236	In PLATO the EQ-5D was administered and the conversion of the EQ-5D questionnaire scores to utility values was performed as per the UK time-trade-off value set as recommended in the NICE methods guide. A multiple linear regression model was used to study the association between treatment, demographic and clinical factors, and the end-point EQ-5D questionnaire single index. In addition, a relevant literature search was also performed to ensure consistency. These utility values were used within the sensitivity analysis. All utility scores from both the PLATO HECON sub-study and published literature were adjusted downwards by 0.0328 to reflect characteristics of the UK population
TA317	Reference to Sullivan et al., 2006:
TA335	The utility values associated with long-term health states were obtained from the literature, primarily from NICE's technology appraisal guidance on ticagrelor for the treatment of acute coronary syndromes (TA236). Ara and Brazier, 2010: Panel data from the Health Survey for England were used to utilities in the stroke health states. Utility values were assumed to be the same for both rivaroxaban and standard care following any event.
Lewis et al 2014	Utility values were taken from the VALIANT HRQL substudy using EQ-5D questionnaire and VAS. The trajectory of EQ-5D scores was developed by using linear mixed effects regression models with calculation of deviation from this trajectory after nonfatal CV events. Patients who died before the next EQ-5D assessment were excluded.
Stafford et al	Panel data from Health survey of England.

Literature reference	Methodology
2011	Regression modelling was used to estimate the relationship between EQ5D index scores with each condition independently and differentially by socio-economic position
TA335	Health related quality of life data was collected in the ATLAS 2 trial. EQ-5D data were collected from sites in eight countries (Australia, Canada, Spain, Netherlands, Korea, the United Kingdom, Sweden, and Japan). The descriptive part of the questionnaire was used to generate utility scores (0 to 1) by applying weights derived from the general UK population. The visual analog scale followed the descriptive questions. Health related quality of life data were collected at baseline, 4 weeks, 24 weeks, 48 weeks, 72 weeks and 96 weeks. Data were also collected in early study withdrawal patients. The table below details the average utility values of patients after each event. Utility data following revascularization was not specifically collected. Further, due to the low numbers of IS and HS/ICH events in the trial, the average utility after a stroke is estimated, which incorporates both IS and HS/ICH. The utility estimates for stroke and TIMI major bleed are based on fewer than 35 observations. The utility values reported in the trial do not differentiate between the tunnel states defined in the model hence the improvement following an event is not captured instead an average before and after the event is taken. The low numbers of observations for some of the estimates from the trial also mean the data are not robust enough for use in the base case analyses. No mapping techniques were used.

Table 19. Utility Decrement Calculations

Health state/ Event	Value from literature	Methodology to calculate utility decrement	Literature reference
Non-fatal MI	-0.0626	Value sourced directly from literature	Sullivan et al 2011
	-0.0524	Value sourced directly from literature	TA182
	-0.0820	Value sourced directly from literature	TA210
	-0.0630	Value sourced directly from literature	TA236
	-0.0370	Value sourced directly from literature	TA317
	-0.0630	No further ACS event (0.842) - MI (0.779)	TA335
Non-fatal stroke	-0.0524	Value sourced directly from literature	TA182
	-0.2480	Value sourced directly from literature	TA210
	-0.1390	No event (0.842) - Non-fatal stroke (0.703)	TA236
	-0.1390	No event (0.842) - Non-fatal stroke (0.703)	TA335
Post non-fatal MI	-0.1800	Value sourced directly from literature	Lewis et al 2014
	-0.1390	Value sourced directly from literature	Stafford et al 2011
	-0.0368	Value sourced directly from literature	Sullivan et al 2011
	0	No Event (0.87) - After MI (0.87)	TA210
	-0.0210	No event (0.842) - Post MI (0.821)	TA236
	0	Post MI utility in health state = event free utility in health state	TA317
	-0.0210	No ACS event (0.842)- MI later (0.821)	TA335
Post non-fatal stroke	-0.0600	Value sourced directly from literature	Lewis et al 2014
	-0.1600	Value sourced directly from literature	Stafford et al 2011
	-0.1009	Value sourced directly from literature	Sullivan et al 2011
	-0.1390	No event (0.842) - Non-fatal stroke (0.703)	TA236
	-0.2600	This is a calculation error	TA317
	-0.0500	No event (0.842) - IS later (0.792)	TA335
Dyspnoea (Grade 3-4)	N/A		N/A
Dyspnoea (Grade 1-2)	N/A		N/A
TIMI minor bleed	-0.0010	No event (0.842) - IS later (0.792)	TA210
	-0.0400*	No event (0.88) – TIMI minor bleed (0.84)	TA335
TIMI major bleed	-0.0070	Value sourced directly from literature	TA182
	-0.3000	See Table 95 (p254-255) in the original submission	TA210
	-0.1100[#]	No event (0.88) – TIMI major bleed excluding ICH (0.77)	TA335

*Read -0.0420 in error within original submission document
#Read -0.0920 in error within original submission document

Resource use and costs

B14. **Priority request:** The company submission states that the cost data from ERG review of TA317 inflated to 2015 values were adopted for the base case. However, TA317 used inflated values from TA182 and, as table 104 shows, TA182 used NHS reference costs. Therefore, please provide, for each cost estimate presented in table 103 of the company submission(4): the primary source, the NHS reference costs number(s) and name(s) as well as the uncertainty around the estimate from TA182. In addition, please provide the same information using the reference costs from the latest schedule i.e. 2014/15. Provide this information as in Table 1.

- Please incorporate the reported costs in the cost-effectiveness model with their measures of uncertainty and describe the methods used to do so
- Please provide the results of including these costs and their measures of uncertainty.
- Please also explain why the latest NHS reference costs (2014/15) were not used.

Regarding the derivation of unit costs for the ERG-derived model for TA317, at page 83 of the ERG report for TA317 it is stated that “Unit costs used in the AG’s report for TA182 have been uplifted using the Hospital and Community Health Services (HCHS) inflation index to 2012 prices“ (7). However this is inaccurate, it was actually the ERG-derived model for TA210 (8), which formed the basis of event/health state costs for the ERG-derived model for TA317. In both TA317 and TA210 an ERG-derived model was developed (which was not the case in TA182 (9)) and in both cases the ERG was the Liverpool Reviews and Implementation Group.

The primary sources for event/health state costs within TA210 (and thus the TA317 ERG model) were Youman et al 2003 (10) for stroke-related events/health states and UKPDS (11) for MI-related endpoints, i.e. NHS reference costs were not used.

We demonstrate the similarity in event/health state costs between the ERG-derived models for TA317 and TA210 (the difference being inflation) in Table 20.

Table 20. Event and health state costs of ERG TA317 and ERG TA210 reports

Event	ERG TA317 values (y)	ERG TA210 values (x)	y/x
Fatal MI	£2,373.68	£2,218.39	1.07
Non-fatal MI	£6,165.21	£5,761.88	1.07
Fatal stoke	£9,381.43	£8,767.69	1.07
Non-fatal non-disabling stroke	£6,858.64	£6,409.94	1.07
Non-fatal disabling stroke	£14,602.70	£13,647.38	1.07
Other vascular death	£2,407.50	£2,225.00	1.08
Non vascular death	£2,407.50	£2,225.00	1.08
Annual cost in health state			
Event free/ post non-fatal MI	£618.03	£0.00 / £577.60	NA / 1.07
Post non-fatal non-disabling stroke	£1,804.06	£1,686.04	1.07
Post non-fatal disabling stroke	£5,537.72	£5,175.44	1.07

The TA182-related unit costs as presented within table 104 of the current submission relate to the manufacturer's model. Whilst the ERG did make some enhancements to the manufacturer's model, none were related to unit costs (TA182 ERG report, page 72 (9)).

Within the manufacturer's submission for TA182, it is not specified which HRG codes were used in the derivation of each event/health state cost.

For non-fatal MI and non-fatal-stroke, it should be noted that NHS reference costs, by their nature, provide information for costing the inpatient hospitalisation (i.e. the acute event) but not for costing the outpatient and maintenance settings (i.e. the tunnel states and post non-fatal event health states in the case of the current model). A key reason for not using NHS reference costs was that the NHS reference costs for "actual or suspected myocardial infarction" do not capture costs related to procedures that are carried out following MI, specifically percutaneous coronary intervention (PCI) (regularly carried out) and coronary artery bypass grafting (CABG) (sometimes carried out).

However subsequent to making the original submission, AstraZeneca has identified that separate NHS reference cost codes are available for PCI and CABG procedures which can be used to more accurately model the inpatient costs associated to MI.

Thus we present the methods and results associated to the implementation of a NHS reference costs 2014/15 (12) costing approach for acute events to meet the request of the clarification questions.

Inpatient costs

Non-fatal MI:

NHS reference costs relating to actual or suspected MI and PCI and CABG procedures were used to calculate a weighted average cost for non-fatal MI. The currency codes used, their unit cost and resultant weighted average cost can be seen at Table 21. The weighted average cost was derived by calculating the total cost across the 27 codes (activity multiplied by unit cost) and dividing through by only the sum of activity for actual or suspected MI-related codes (total activity = 116,772), the assumption inherent to this approach being that all patients with non-fatal MI incur a 'standard' cost relating to actual or suspected MI hospitalisation but only a subset also incur the cost of a PCI (60%) or a CABG (12%).

Non-fatal stroke:

The weighted average unit cost can be seen at Table 22. Activity multiplied by unit cost was calculated across relevant codes, summed and divided through by total activity to derive the weighted average unit cost.

Table 21: Currency codes, unit costs and resultant weighted average unit cost for non-fatal MI

Cost Area	Currency	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
MI hospitalisation (no procedure)	EB10A	Actual or Suspected Myocardial Infarction, with CC Score 13+	6,805	£3,153	£2,212	£3,819
	EB10B	Actual or Suspected Myocardial Infarction, with CC Score 10-12	16,111	£2,207	£1,614	£2,528
	EB10C	Actual or Suspected Myocardial Infarction, with CC Score 7-9	26,483	£1,573	£1,189	£1,825
	EB10D	Actual or Suspected Myocardial Infarction, with CC Score 4-6	36,255	£1,202	£927	£1,397
	EB10E	Actual or Suspected Myocardial Infarction, with CC Score 0-3	31,118	£939	£723	£1,061
CABG (for MI)	ED22A	Complex, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 11+	151	£19,125	£14,032	£21,975
	ED22B	Complex, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 6-10	211	£14,654	£11,659	£16,794
	ED22C	Complex, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 0-5	181	£12,853	£10,663	£14,651
	ED23A	Standard, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 11+	411	£18,200	£14,107	£21,304
	ED23B	Standard, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 6-10	814	£13,401	£11,027	£15,053
	ED23C	Standard, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 0-5	1,300	£11,681	£9,270	£13,123
	ED26A	Complex Coronary Artery Bypass Graft with CC Score 10+	306	£15,110	£11,131	£17,592
	ED26B	Complex Coronary Artery Bypass Graft with CC Score 5-9	486	£12,026	£9,269	£14,099
	ED26C	Complex Coronary Artery Bypass Graft with CC Score 0-4	593	£10,005	£8,402	£10,813

Cost Area	Currency	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
	ED27A	Major Coronary Artery Bypass Graft with CC Score 10+	279	£12,824	£9,812	£16,118
	ED27B	Major Coronary Artery Bypass Graft with CC Score 5-9	906	£11,034	£8,972	£12,451
	ED27C	Major Coronary Artery Bypass Graft with CC Score 0-4	1,549	£9,904	£8,058	£11,470
	ED28A	Standard Coronary Artery Bypass Graft with CC Score 10+	827	£12,419	£10,369	£13,322
	ED28C	Standard Coronary Artery Bypass Graft with CC Score 0-4	5,841	£9,009	£7,249	£10,523
PCI (for MI)	EY40A	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	492	£7,266	£5,164	£8,921
	EY40B	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	1,084	£5,339	£4,130	£6,358
	EY40C	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	4,949	£3,794	£2,874	£4,467
	EY40D	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	11,054	£2,981	£2,259	£3,698
	EY41A	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	844	£6,968	£5,216	£8,489
	EY41B	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	2,804	£4,430	£3,359	£5,549
	EY41C	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	14,509	£3,194	£2,444	£3,737
	EY41D	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	34,825	£2,557	£1,909	£2,918
Total/weighted average*			**116,772**	**£4,593**	**£3,521**	**£5,342**

* 'Total' and denominator within the calculation of weighted average unit cost reflects only activity for the sum of activity for actual or suspected MI-related codes. Further explanation above.

Table 22: Currency codes, unit costs and resultant weighted average unit cost for non-fatal stroke

Currency	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
AA35A	Stroke with CC Score 16+	4,967	£8,762	£5,043	£11,343
AA35B	Stroke with CC Score 13-15	10,392	£6,331	£3,725	£7,983
AA35C	Stroke with CC Score 10-12	18,426	£4,677	£3,039	£5,862
AA35D	Stroke with CC Score 7-9	31,069	£3,314	£2,407	£4,054
AA35E	Stroke with CC Score 4-6	43,479	£2,435	£1,811	£2,820
AA35F	Stroke with CC Score 0-3	36,402	£1,773	£1,335	£2,001
Total/weighted average		**144,735**	**£3,239**	**£2,223**	**£3,930**

Fatality events (CAD and non-CAD) and 'No event':

Unit costs as used in the original submission were retained owing to absence of relevant unit costs within NHS reference costs.

TIMI major bleeding:

The weighted average unit cost can be seen at Table 23. Since the majority of both TIMI major bleeding and TIMI minor bleeding events within the PEGASUS-TIMI 54 trial were of gastrointestinal (GI) origin, GI bleed related currency codes have been used to derive the unit cost in each case. Major bleeds were deemed to correspond with currency codes for GI bleed with single or multiple interventions. Activity multiplied by unit cost was calculated across relevant codes, summed and divided through by total activity to derive the weighted average unit cost.

TIMI minor bleeding:

The weighted average unit cost can be seen at

Table 24. Minor bleeds were deemed to correspond with currency codes for GI bleed without interventions. Activity multiplied by unit cost was calculated across relevant codes, summed and divided through by total activity to derive the weighted average unit cost.

Dyspnoea grade 3-4:

NHS reference costs were used in the derivation of the cost for dyspnoea grade 3-4 within the original submission. The weighted average unit cost can be seen at

Table 25. Activity multiplied by unit cost was calculated across relevant codes, summed and divided through by total activity to derive the weighted average unit cost

Table 23: Currency codes, unit costs and resultant weighted average unit cost for TIMI major bleeding

Currency	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
FZ38G	Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+	1,037	£5,470	£3,217	£6,709
FZ38H	Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4	1,284	£3,271	£2,043	£3,939
FZ38J	Gastrointestinal Bleed with Single Intervention, with CC Score 8+	1,212	£4,000	£2,300	£4,809
FZ38K	Gastrointestinal Bleed with Single Intervention, with CC Score 5-7	2,111	£2,829	£2,016	£3,293
FZ38L	Gastrointestinal Bleed with Single Intervention, with CC Score 0-4	6,827	£2,129	£1,609	£2,369
Total/weighted average		**12,471**	**£2,825**	**£1,923**	**£3,285**

Table 24: Currency codes, unit costs and resultant weighted average unit cost for TIMI minor bleeding

Currency	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
FZ38M	Gastrointestinal Bleed without Interventions, with CC Score 9+	3,021	£2,060	£1,318	£2,481
FZ38N	Gastrointestinal Bleed without Interventions, with CC Score 5-8	13,134	£1,341	£1,023	£1,507
FZ38P	Gastrointestinal Bleed without Interventions, with CC Score 0-4	62,199	£804	£638	£884
Total/weighted average		**78,354**	**£942**	**£728**	**£1,050**

Table 25: Currency codes, unit costs and resultant weighted average unit cost for dyspnoea grade 3-4

Currency	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
DZ19H	Other Respiratory Disorders with Multiple Interventions	385	£4,641	£2,016	£5,271
DZ19J	Other Respiratory Disorders with Single Intervention, with CC Score 5+	844	£3,012	£1,543	£3,702
DZ19K	Other Respiratory Disorders with Single Intervention, with CC Score 0-4	1,612	£1,694	£827	£2,248
DZ19L	Other Respiratory Disorders without Interventions, with CC Score 11+	1,886	£1,316	£838	£1,474
DZ19M	Other Respiratory Disorders without Interventions, with CC Score 5-10	22,386	£804	£607	£913
DZ19N	Other Respiratory Disorders without Interventions, with CC Score 0-4	42,764	£554	£413	£634
Total/weighted average		**69,877**	**£733**	**£519**	**£846**

Outpatient and maintenance costs

As described above, NHS reference costs, by their nature, are not useful in informing unit costs for the outpatient and maintenance settings. Within the original submission, costs for the post non-fatal MI and post non-fatal stroke tunnel states were calculated based on the residual value between the (1 year) event cost from the ERG model for TA317 (inflated to 2015 values) and the percentage of the cost assumed to have been incurred from the inpatient setting. A similar approach is adopted for the 'revised base case', whereby the tunnel state costs are derived using the residual of the (1 year) event cost from the ERG model for TA317 (inflated to 2015 values) and the NHS reference cost derived inpatient cost, with diminishing cost applied over time across the tunnel states. However it is recognised that this has the effect of nullifying the implementation of NHS reference costs to inform non-fatal MI and non-fatal stroke inpatient costs (since the 1 year total cost is the same), so an additional sensitivity analysis will be provided separately whereby the costs for the tunnel states are retained at the values from the original submission document. An additional sensitivity analysis whereby, for efficacy events, the lower quartile NHS reference cost was applied in the model and for adverse events, the upper quartile NHS reference cost was applied in the model, will also be provided separately. Table 26 provides original and revised unit costs as used in the economic model. Values for fatal events, 'no event' and the long term post non-fatal event state costs were retained at the values of the original submission owing to an absence of alignment within the NHS reference costs.

Table 26: List of resource use and associated costs in the economic model (original and revised)

Resource use	Value in CS	Value in revised base case	National Average Unit Cost, 2014/15 schedule	Lower Quartile Unit Cost, 2014/15 schedule	Upper Quartile Unit Cost, 2014/15 schedule	HRG code from NHS reference costs, 2014/15 schedule
Inpatient						
Non-fatal MI	£4,476.18	£4,593.13	£4,593.13	£3,520.53 (sensitivity)	£5,341.93	EB10A-E, ED22A-C, ED23A-C, ED26A-C, ED27A-C, ED28A, ED28C
Non-fatal stroke	£4,925.76	£3,239.44	£3,239.44	£2,223.49 (sensitivity)	£3,929.59	AA35A-F
Fatal events (CAD and non-CAD)	£2,497.83	£2,497.83	N/A			
'No event'	£2,497.83	£2,497.83	N/A			
Outpatient and maintenance						
Post non-fatal MI (0-3 months)	£639.45	£720.56	N/A			
Post non-fatal MI (3-6 months)	£639.45	£540.42	N/A			
Post non-fatal MI (6-9 months)	£319.73	£360.28	N/A			
Post non-fatal MI (9-12 months)	£319.73	£180.14	N/A			
Post non-fatal MI (12+ months, every cycle)	£160.31	£160.31	N/A			
Post non-fatal stroke (0-3 months)	£1,343.39	£2,000.77	N/A			
Post non-fatal stroke (3-6 months)	£1,119.49	£1,714.94	N/A			
Post non-fatal stroke (6-9 months)	£877.57	£1,143.40	N/A			
Post non-fatal stroke (9-12 months)	£689.71	£857.47	N/A			
Post non-fatal stroke (12+ months, every cycle)	£689.71	£689.71	N/A			

Resource use	Value in CS	Value in revised base case	National Average Unit Cost, 2014/15 schedule	Lower Quartile Unit Cost, 2014/15 schedule	Upper Quartile Unit Cost, 2014/15 schedule	HRG code from NHS reference costs, 2014/15 schedule
'No event' (every cycle)	£160.31	£160.31	N/A			
Adverse events						
Grade 3-4 Dyspnoea	£732.98	£732.98	£732.98	£518.68	£846.10 (sensitivity)	DZ19H, DZ19J-N
Major TIMI bleed	£2,206.87	£2,824.81	£2,824.81	£1,923.36	£3,285.13 (sensitivity)	FZ38G-H, FZ38J-L
Minor TIMI bleed	£122.48	£942.19	£942.19	£728.49	£1,049.82 (sensitivity)	FZ38M-N, FZ38P

B15. In table 112 (page 282) of the company submission(4), costs for dyspnoea grade 3-4 are provided and based on a weighted average of DZ 19 'Other Respiratory Disorders' from National Health Service (NHS) reference costs 14/15.

- Please justify why these reference costs were chosen for dyspnoea and are adequate for such a calculation.

As no cost for dyspnoea was identified from the literature, the ICD-10 code for dyspnoea (R060) was coded to the HRG group DZ19 using the Health & Social Care Information Centre HRG4 2014/15 Local Payment Group. (Available at: http://www.hscic.gov.uk/article/6103/HRG4-201516-Local-Payment-Grouper).

- Please provide details on how the weighted average was obtained (methods + results).

The weighted average calculation for dyspnoea can be found in the response to question B14.

- Please provide the standard error, the lower and the upper bounds of this estimate from table 112 (page 282) of the company submission(4).

Please see the weighted average calculation for dyspnoea in the response to question B14. Lower and upper quartile costs are presented.

B16. Please provide a description of the 'No event' health state.

This response to question B16 will be provided separately.

- Justify the assumption that 'No event' inpatient costs are equal to the inpatient costs for inpatient costs of a fatal events "*due to the potential range of 'no event' inpatient costs"*.(4)

- Provide an overview of which events produced inpatient costs in the 'No event' health state (events name + number of events)

B17. The costs of non-fatal MI and non-fatal stroke are spread on a one year period with respectively 70% and 55% of the costs being accounted for as inpatient costs ('event' costs) and the rest being accounted for as outpatient costs (divided across the following tunnel states).

- Please justify the rationale between these 70% and 55%.

- Please justify why this methodology has been adopted.

A new approach to the estimation of inpatient costs, based on NHS reference costs is now provided in response to question B14. This approach addresses the concern expressed here.

Results and sensitivity analyses

B18. The probabilistic sensitivity analyses are based on a single individual, this is methodologically incorrect, see for instance Halpern et al. how to represent both 1st and 2nd order uncertainty (using an inner and outer loop).(13)

- Please provide probabilistic sensitivity analyses based on the cohort analysis (i.e. the 'simple' analysis) for the base case.

A probabilistic analysis based on average characteristics from the cohort (i.e. 'simple') is provided ('Simple PSA'). It should be noted that this PSA does not capture the non-linearity in the model (particularly first order uncertainty), resulting in higher ICERs than those of the equivalent deterministic 'complete' analysis. An enhancement to the probabilistic analysis from the original submission is also provided, where the analysis is now based on eleven profiles in contrast to the single patient profile in the original submission. These eleven patient profiles are derived from the original single patient profile whose ICER most closely mirrors that of the cohort as a whole, and the five patient profiles that generate ICERs immediately above and below that ('Eleven typical ICER patients PSA').

- Please provide a summary of LY gained by health state using the format of table 115 from the company submission.(4)

A summary of life years gained by health state using the base case cost effectiveness model described in the original submission and in the format of table 115 is provided below:

Table 27: Summary of life years gained by health state (complete analysis)

Health state	Life years intervention (ticagrelor 60 mg BID + LD ASA)	Life years comparator (Low-dose ASA)	Increment	Absolute increment	Absolute increment (%)
No event	11.1186	10.9627	0.1559	0.1559	70.59%
First event					
Post non-fatal MI	0.0307	0.0321	-0.0014	0.0014	0.61%
Post non-fatal stroke	0.0098	0.0103	-0.0006	0.0006	0.25%
Subsequent events					
No event	1.1549	1.2167	-0.0618	0.0618	28.00%
Post non-fatal MI	0.0167	0.0175	-0.0009	0.0009	0.39%
Post non-fatal stroke	0.0056	0.0059	-0.0003	0.0003	0.15%
Adverse events					
Dyspnoea	-	-	-	-	-
TIMI Bleeds	-	-	-	-	-
Total	**12.3363**	**12.2453**	**0.0909**	**0.2208**	**100.00%**

- According to the NICE Methods Guide, probabilistic methods provide the best estimates of mean costs and outcomes in non-linear decision models. Please provide probabilistic sensitivity analyses based on the cohort analysis (i.e. the 'simple' analysis) for all scenario and subgroup analyses presented in the company submission.

Transparency and validity

B19. The company submission presents a description of the external and technical validation of the model in section 5.10.(4) However, other aspects of validity are not addressed in the company submission.

- Please describe which steps have been undertaken to assess the face validity of the cost-effectiveness model.

- Please provide a comparison of the observed and modelled TIMI minor bleeds events, and grade 1-2 dyspnoea as it is provided for the other events (Table 141, company submission(4)).

- Please provide a comparison regarding input parameters, model structure, assumptions and outcomes of the current assessment with previous studies identified in the systematic literature review of the company and relevant TA's (i.e. studies included in table 51, page 157 of the company submission and TA182, TA210, TA236, TA317, TA335).

- Please provide a comparison of the number of MI's, strokes, other CV events, and survival with an external, preferably UK, database (e.g. http://www.isdscotland.org/Health-Topics/, https://indicators.hscic.gov.uk/webview/, https://www.ucl.ac.uk/nicor/audits/minap).

- In figure 67 (page 193) of the company submission (4), the company compares the survival probabilities by age as modelled in the cost-effectiveness analysis with the survival probabilities according to UK life tables. Please provide the exact reference for the UK life tables (with an active web link).

The response to this question will be provided separately.

Section C: Textual clarifications and additional points

C1. Table 10 (page 44) of the company submission(4): Please confirm that the "mean, %" under "Percentage of professional time spent in direct patient care" for "England and Wales (n=85)" is 85.7.

We confirm that this should read 85.7.

Impact of ERG requests on base case analysis

As described above we have made a number of changes to the base case on account of ERG questions/requests, specifically:

- Inpatient costs based on NHS reference costs where possible
- Functional form for AEs selected by AIC
- Including gout as AE

Table 28 shows the stepwise impact of these changes on QALYs, life-years, costs and the ICER.

Table 28: Stepwise impact of all changes to the model adopted for (revised) base case

	QALYs	Life-Years	Costs
1. Original Submission Base Case			
Tica 60mg + ASA	9.27	12.34	£14,443
ASA monotherapy	9.20	12.25	£13,019
Incremental	0.0708	0.0909	£1,424
ICER	£20,098	£15,655	
2. ERG request – Inpatient costs based on NHS reference costs where possible			
Tica 60mg + ASA	9.27	12.34	£14,475
ASA monotherapy	9.20	12.25	£13,042
Incremental	0.0708	0.0909	£1,433
ICER	£20,233	£15,760	
3. ERG request - functional form for AEs selected by AIC (extending from #2)			
Tica 60mg + ASA	9.27	12.34	£14,463
ASA monotherapy	9.20	12.25	£13,036
Incremental	0.0706	0.0909	£1,427
ICER	£20,225	£15,692	
4. ERG request - including gout as an AE (extending from #3) = *(revised) base case*			
Tica 60mg + ASA	9.26	12.34	£14,518
ASA monotherapy	9.20	12.25	£13,086
Incremental	0.0694	0.0909	£1,432
ICER	£20,636	£15,749	

An updated results section follows, where we present deterministic and probabilistic analyses for base case and all subgroups. Results for all scenario analyses, i.e. those from the original submission (updated) and new scenario analyses as requested during the ERG clarification process will be provided separately.

Amended results

Base case results - deterministic

Base-case incremental cost effectiveness analysis results

The base case considers patients with MI <2 years ago.

Ticagrelor 60 mg BID + low-dose ASA accumulates total (discounted) costs of £14,518 and 9.2645 QALYs. Low-dose ASA accumulates total (discounted) costs of £13,086 and 9.1951 QALYs. This equates to ticagrelor 60 mg BID + low-dose ASA producing an additional 0.0694 QALYs at an incremental cost of £1,432 when compared to low-dose ASA. This generates a base-case ICER of £20,636. Table 114 below presents the base-case incremental cost-effectiveness results in det ail.

Table 114: Base-case results (complete analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) per inc QALY
Low-dose ASA	£13,086	12.2453	9.1951	-	-	-	-
Ticagrelor 60 mg BID + low-dose ASA	£14,518	12.3363	9.2645	£1,432	0.0909	0.0694	£20,636*

*The corresponding ‘simple analysis’ overestimates the ICER for this population by 22% (ICER of £25,180).

Sensitivity analyses

Base case results - probabilistic

The base-case PSA results are presented in Table 118. The scatter plot is presented in Figure 54. The CEAC is presented in Figure 55.

Table 118: Base-case PSA results (MI <2 years ago)

	Eleven typical ICER patients PSA	Simple PSA
Incremental costs	£1,393	£1,434
95% CI around incremental costs	£982 to £1,594	£1,383 to £1,480
Incremental QALYs	0.0676	0.0574
95% CI around incremental QALYs	0.0407 to 0.1114	0.0435 to 0.072
Change in costs (%)	-29.5 to 14.5	-3.5 to 3.2
Change in QALYs (%)	-39.7 to 64.8	-24.1 to 25.5
ICER	£20,604	£25,004*

*does not capture model non-linearity

Based on the 'Eleven typical ICER patients PSA', ticagrelor 60 mg BID + low-dose ASA has a 42.5% probability of being cost-effective at £20,000 per QALY gained, increasing to 88.5% at £30,000 per QALY gained. For the 'Simple PSA', which does not capture non-linearity in the model, the values are 2.4% and 90.5% respectively.

Figure 54: Base-case PSA scatterplot (MI <2 years ago), eleven typical ICER patients PSA

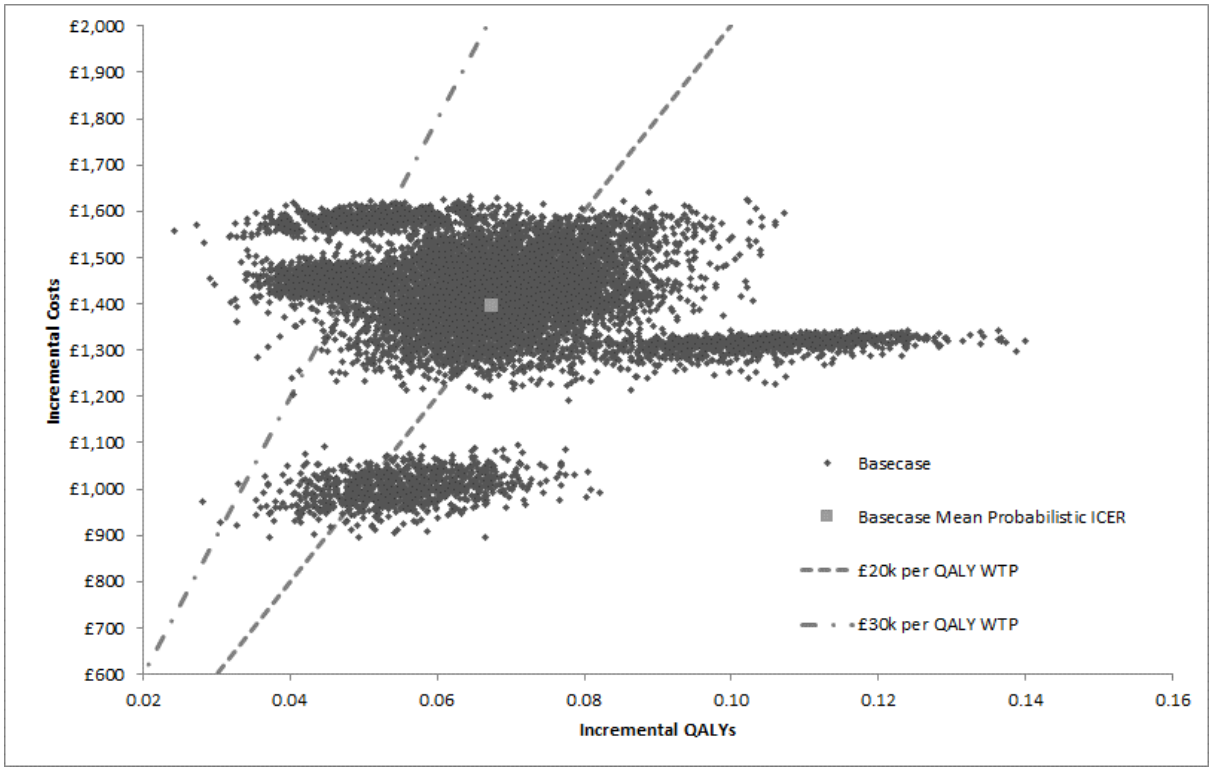
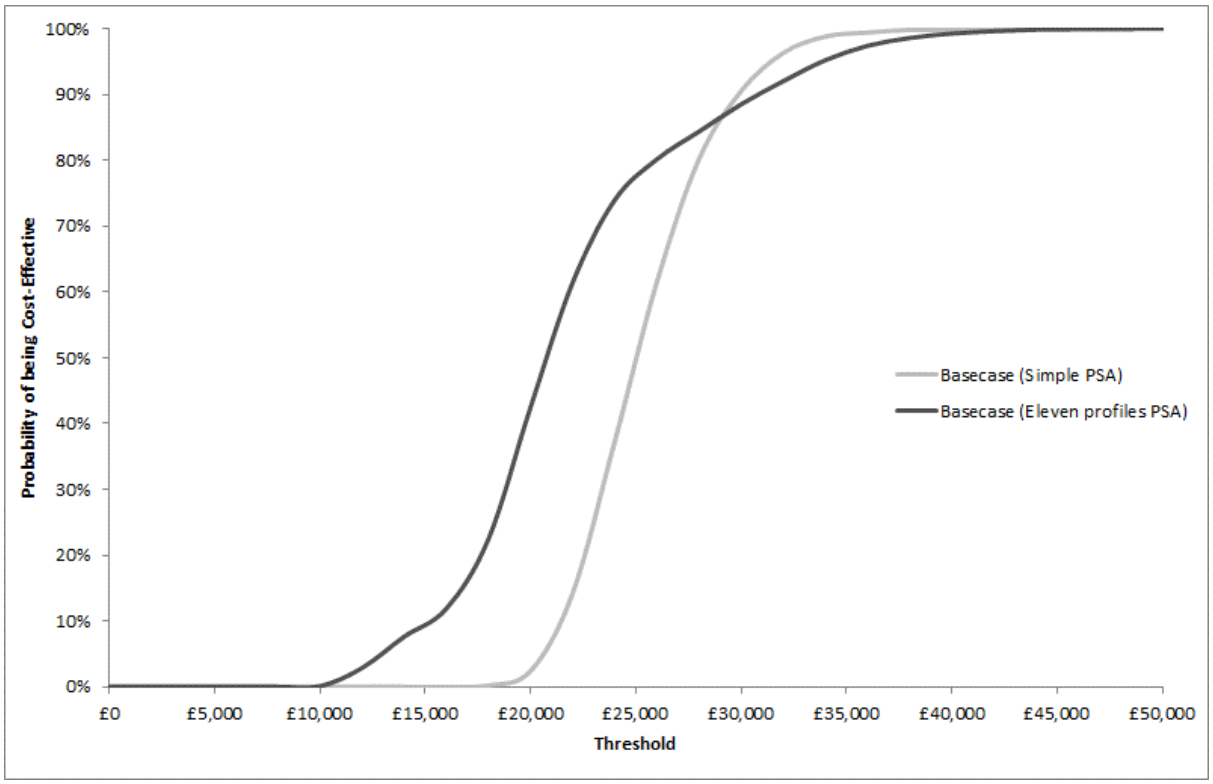


Figure 55: Base-case PSA CEAC (MI <2 years ago)



Subgroup analysis

Results

A. Continuation therapy

Within clinical practice it is expected that the majority of patients who start ticagrelor 60 mg BID + low-dose ASA will do so immediately after the cessation of their previous ADP inhibitor treatment. As such, we have analysed those patients within the base-case population who withdrew from their previous ADP inhibitor treatment less than 30 days before randomisation (N=3,602) as these patients are likely to be most representative of clinical practice.

Ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0663 QALYs at an incremental cost of £1,423, generating an ICER of £21,466 (Table 131).

Table 131: Continuation therapy (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£13,421	9.3693			
Ticagrelor 60 mg BID + low-dose ASA	£14,844	9.4356	£1,423	0.0663	£21,466

Results for the PSA are shown in Table 132, Figure 57 and Figure 58.

Table 132: Continuation therapy PSA results

	Eleven typical ICER patients PSA	Simple PSA
Incremental costs	£1,440	£1,428
95% CI around incremental costs	£1,204 to £1,699	£1,377 to £1,474
Incremental QALYs	0.0700	0.0550
95% CI around incremental QALYs	0.0458 to 0.1111	0.0422 to 0.0685
Change in costs (%)	-16.4 to 17.9	-3.6 to 3.2
Change in QALYs (%)	-34.5 to 58.7	-23.2 to 24.6
ICER	£20,585	£25,985*

*does not capture model non-linearity

Based on the 'Eleven typical ICER patients PSA', ticagrelor 60 mg BID + low-dose ASA has a 34.4% probability of being cost-effective at £20,000 per QALY gained, increasing to 95.3%

at £30,000 per QALY gained. For the 'Simple PSA', which does not capture non-linearity in the model, the values are 0.8% and 85.5% respectively.

Figure 57: Continuation therapy PSA scatterplot, eleven typical ICER patients PSA

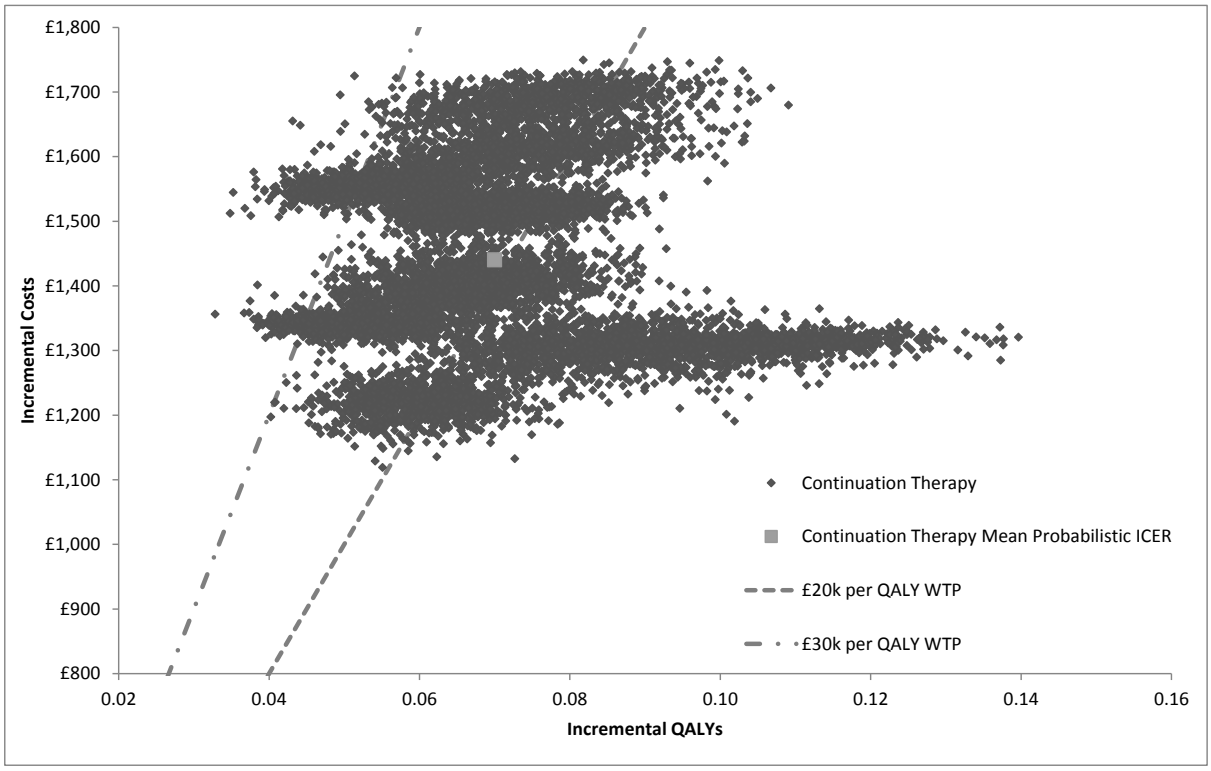
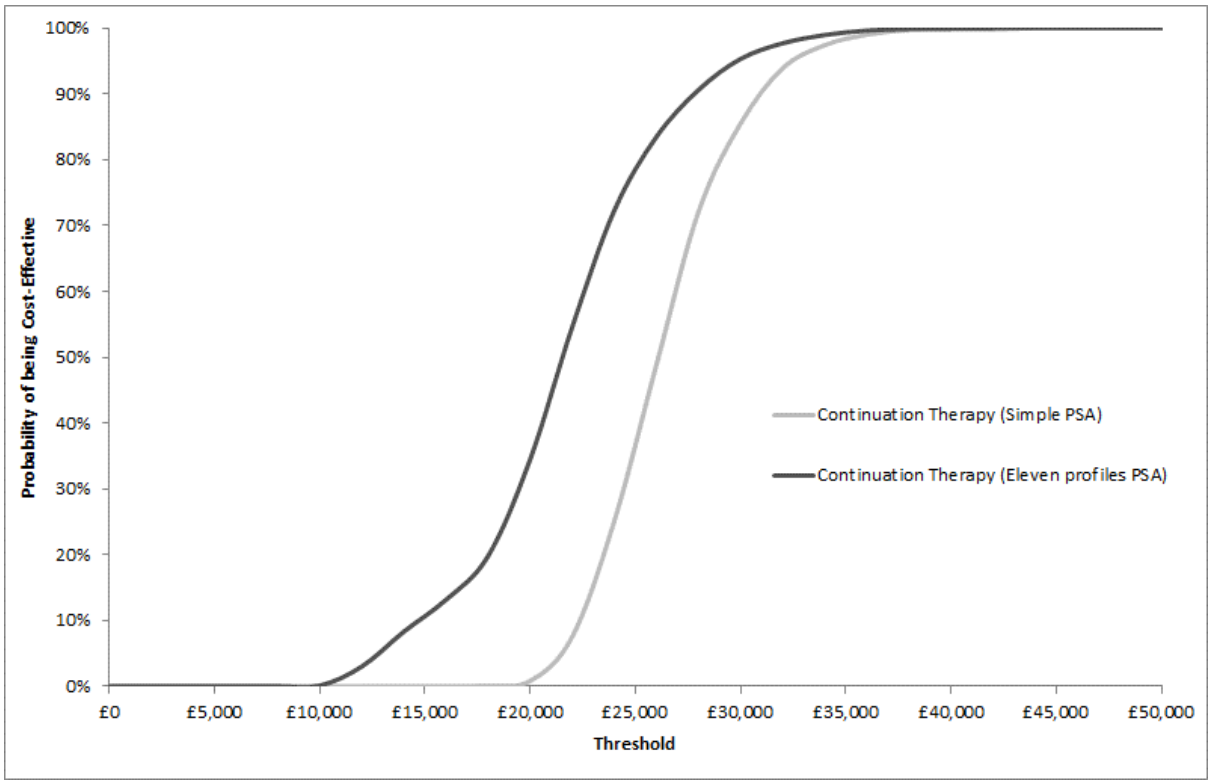


Figure 58: Continuation therapy CEAC



B. Diabetes

As per the NICE scope, we have analysed those patients with and without diabetes separately. Patients with diabetes are known to be at an increased risk (compared to the non-diabetic population) of cardiovascular comorbidities. Within the base-case population 2,741 patients had diabetes and 5,923 did not.

Patients with diabetes

For patients with diabetes, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0989 QALYs at an incremental cost of £1,437, generating an ICER of £14,535.

Table 133: Diabetes (Yes) (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£13,573	8.9723			
Ticagrelor 60 mg BID + low-dose ASA	£15,010	9.0712	£1,437	0.0989	£14,535

Results for the PSA are shown in Table 134, Figure 59 and Figure 60.

Table 134: Diabetes (Yes) PSA results

	Eleven typical ICER patients PSA	Simple PSA
Incremental costs	£1,309	£1,453
95% CI around incremental costs	£894 to £1,724	£1,392 to £1,504
Incremental QALYs	0.0951	0.0940
95% CI around incremental QALYs	0.0626 to 0.1569	0.0724 to 0.1166
Change in costs (%)	-31.7 to 31.7	-4.2 to 3.5
Change in QALYs (%)	-34.2 to 64.9	-23.0 to 23.9
ICER	£13,758	£15,453*

*does not capture model non-linearity

Based on the 'Eleven typical ICER patients PSA', ticagrelor 60 mg BID + low-dose ASA has a 97.0% probability of being cost-effective at £20,000 per QALY gained, increasing to 100.0% at £30,000 per QALY gained. For the 'Simple PSA', which does not capture non-linearity in the model, the values are 97.5% and 100.0% respectively.

Figure 59: Diabetes (Yes) PSA scatterplot, eleven typical ICER patients PSA

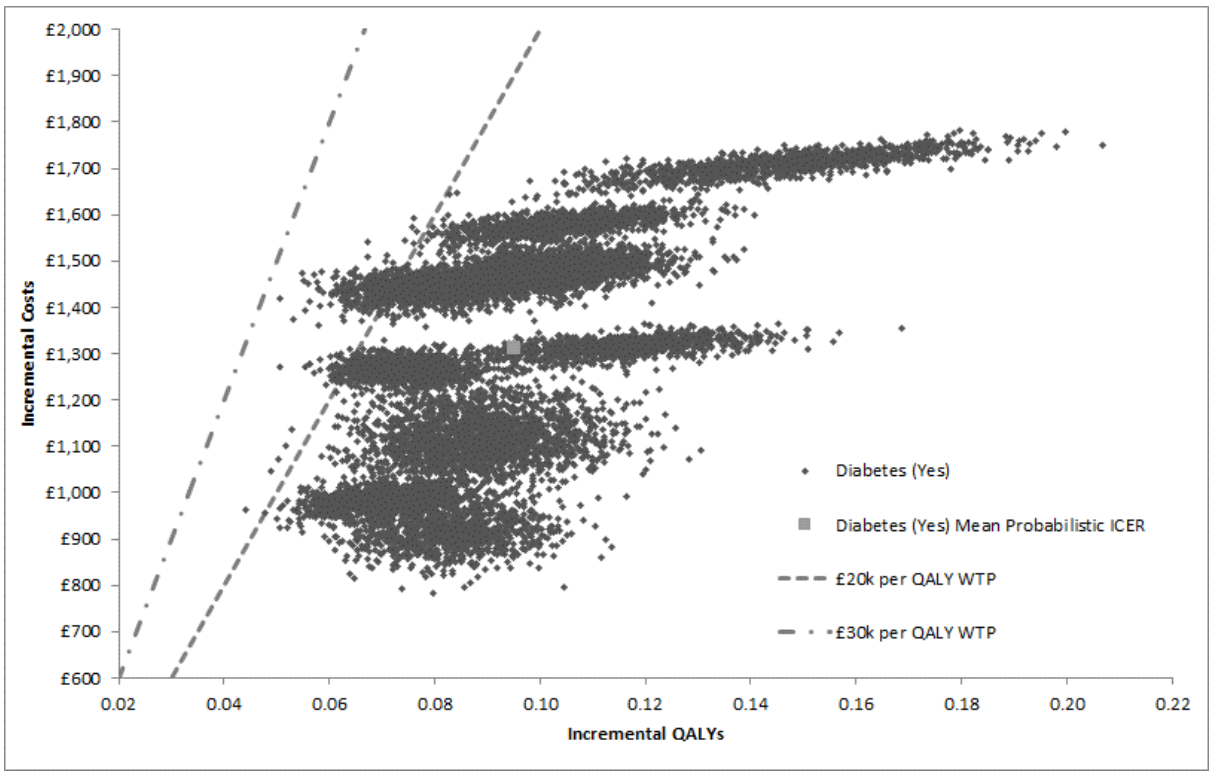
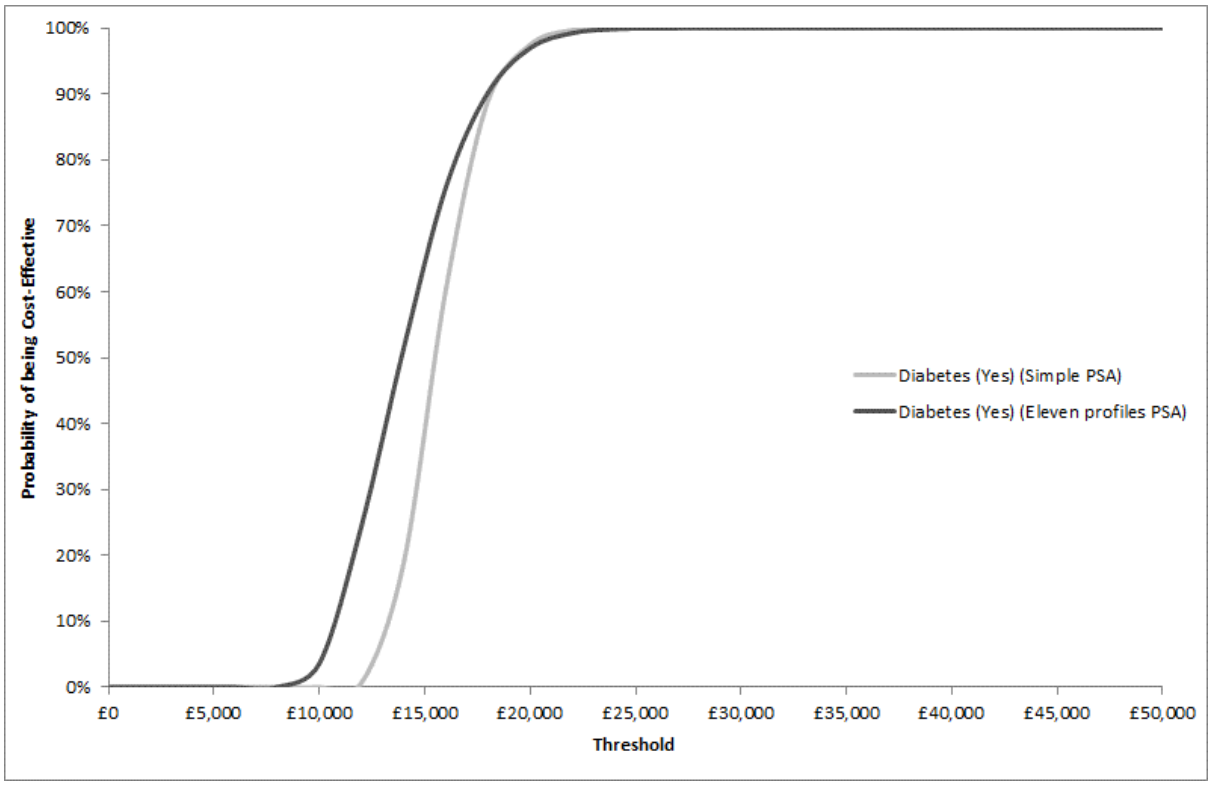


Figure 60: Diabetes (Yes) CEAC



Patients without diabetes

For patient without diabetes, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0558 QALYs at an incremental cost of £1,430, generating an ICER of £25,642.

Table 135: Diabetes (No) (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£12,861	9.2981			
Ticagrelor 60 mg BID + low-dose ASA	£14,291	9.3539	£1,430	0.0558	£25,642

Results for the PSA are shown in Table 136, Figure 61 and Figure 62.

Table 136: Diabetes (No) PSA results

	Eleven typical ICER patients PSA	Simple PSA
Incremental costs	£1,344	£1,436
95% CI around incremental costs	£894 to £1,724	£1,389 to £1,479
Incremental QALYs	0.0497	0.0454
95% CI around incremental QALYs	0.0312 to 0.0895	0.0342 to 0.0574
Change in costs (%)	-28.6 to 18.9	-3.3 to 3.0
Change in QALYs (%)	-37.1 to 80.1	-24.8 to 26.3
ICER	£27,051	£31,611*

*does not capture model non-linearity

Based on the 'Eleven typical ICER patients PSA', ticagrelor 60 mg BID + low-dose ASA has a 8.7% probability of being cost-effective at £20,000 per QALY gained, increasing to 66.5% at £30,000 per QALY gained. For the 'Simple PSA', which does not capture non-linearity in the model, the values are 0.0% and 33.5% respectively.

Figure 61: Diabetes (No) PSA scatterplot, eleven typical ICER patients PSA

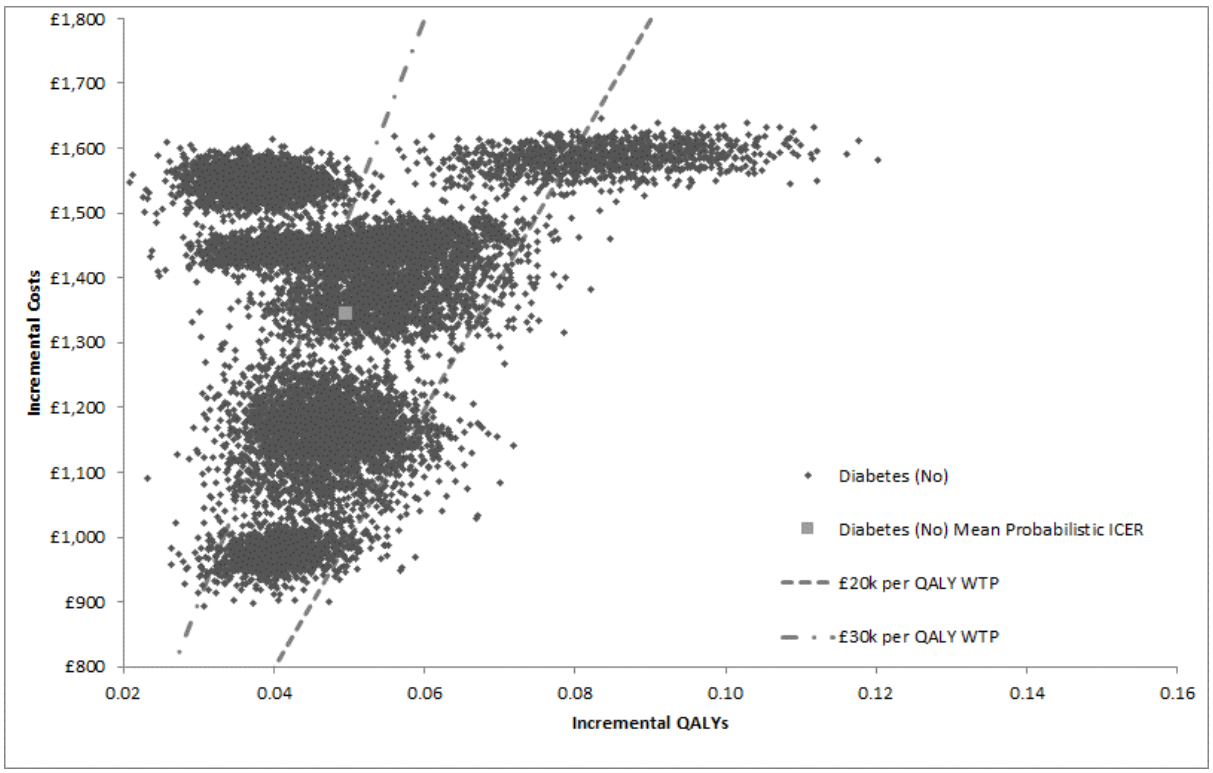
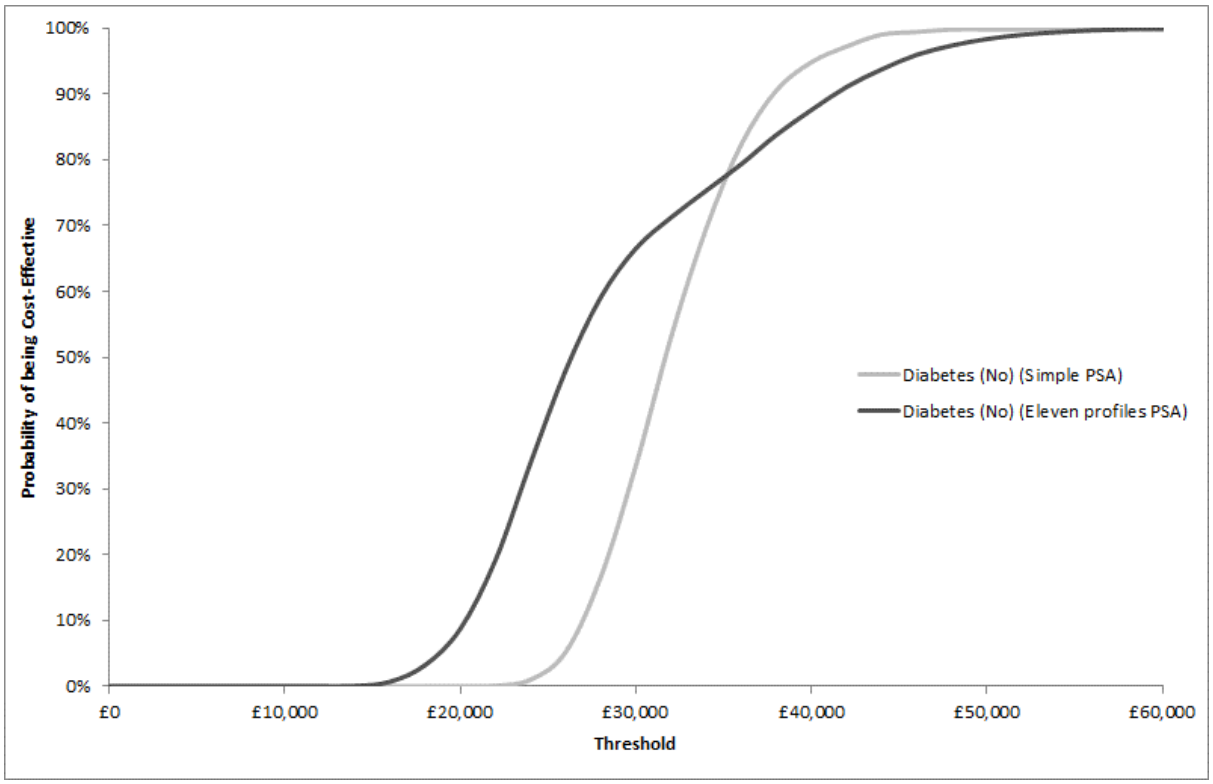


Figure 62: Diabetes (No) CEAC



C. History of PCI

The NICE scope requests stratification according to whether people have or have not had prior revascularisation. Since 'prior revascularisation' was not a prespecified subgroup of the trial, whereas 'history of PCI' was (the difference being history of coronary artery bypass grafting), we present analysis according to presence or absence of history of PCI. Within the base-case population 7,261 patients had a history of PCI whilst 1,401 did not. For two patients the status was unknown.

Patients with a history of PCI

For patients with a history of PCI, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0613 QALYs at an incremental cost of £1,428, generating an ICER of £23,279 (Table 137).

Table 137: History of PCI (Yes) (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental

					(QALYs)
Low-dose ASA	£13,381	9.4350			
Ticagrelor 60 mg BID + low-dose ASA	£14,809	9.4963	£1,428	0.0613	£23,279

Results for the PSA are shown in Table 138, Figure 63 and Figure 64.

Table 138: History of PCI (Yes) PSA results

	Eleven typical ICER patients PSA	**Simple PSA**
Incremental costs	£1,373	£1,432
95% CI around incremental costs	£1,002 to £1,670	£1,383 to £1,477
Incremental QALYs	0.0658	0.0515
95% CI around incremental QALYs	0.0380 to 0.1047	0.0395 to 0.0639
Change in costs (%)	-27.0 to 21.7	-3.5 to 3.1
Change in QALYs (%)	-42.2 to 59.1	-23.2 to 24.0
ICER	£20,864	£27,800*

*does not capture model non-linearity

Based on the 'Eleven typical ICER patients PSA', ticagrelor 60 mg BID + low-dose ASA has a 31.9% probability of being cost-effective at £20,000 per QALY gained, increasing to 95.1% at £30,000 per QALY gained. For the 'Simple PSA', which does not capture non-linearity in the model, the values are 0.1% and 72.5% respectively.

Figure 63: History of PCI (Yes) PSA scatterplot, eleven typical ICER patients PSA

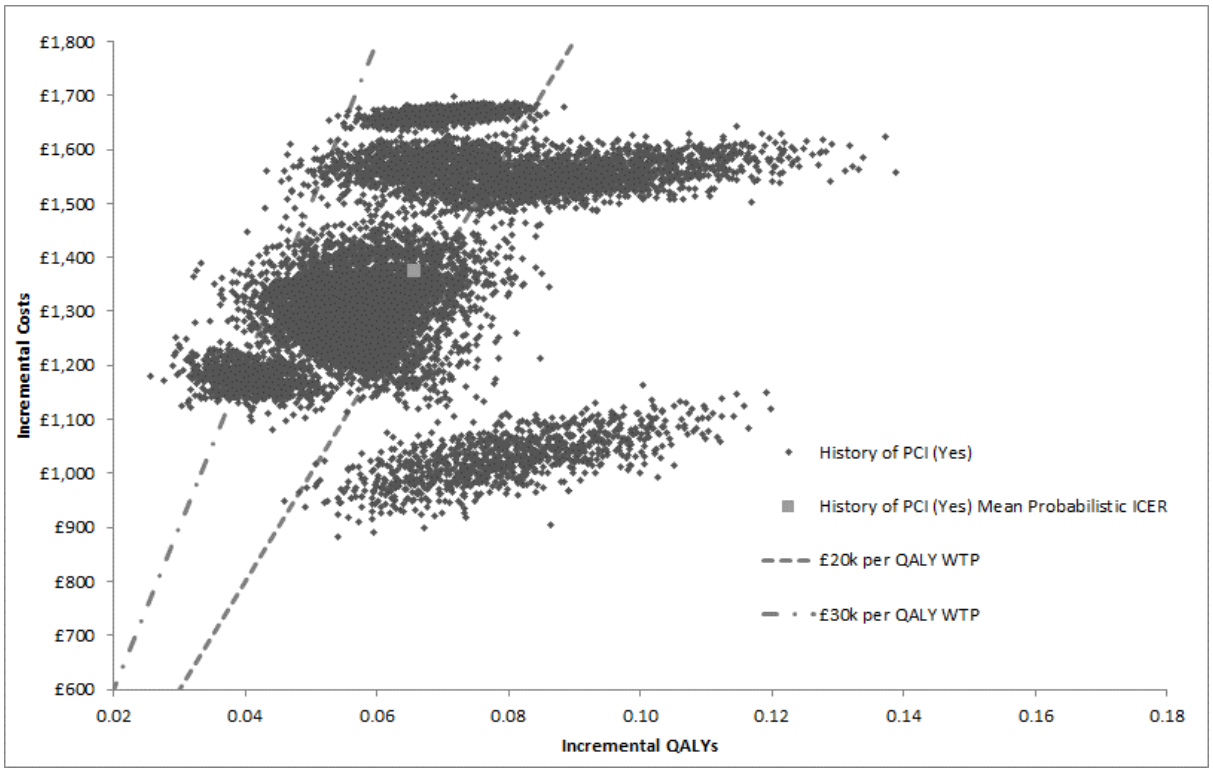
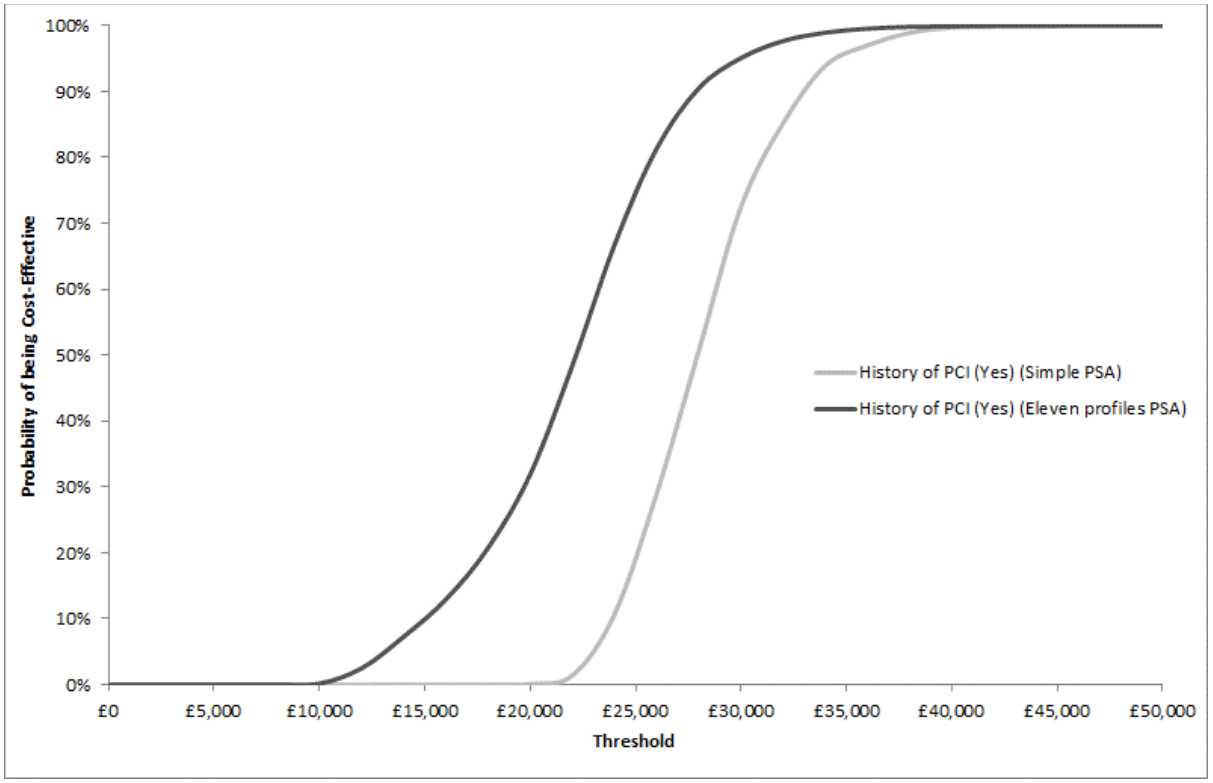


Figure 64: History of PCI (Yes) CEAC



Patients without a history of PCI

For patients without a history of PCI, ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.1111 QALYs at an incremental cost of £1,453, generating an ICER of £13,080.

Table 139: History of PCI (No) (complete analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Low-dose ASA	£11,561	7.9532			
Ticagrelor 60 mg BID + low-dose ASA	£13,014	8.0643	£1,453	0.1111	£13,080

Results for the PSA are shown in Table 140, Figure 65 and Figure 66.

Table 140: History of PCI (No) PSA results

	Eleven typical ICER patients PSA	Simple PSA
Incremental costs	£1,438	£1,468
95% CI around incremental costs	£1,108 to £1,733	£1,401 to £1,529
Incremental QALYs	0.1084	0.1071
95% CI around incremental QALYs	0.0676 to 0.1560	0.0767 to 0.1379
Change in costs (%)	-23.0 to 20.5	-4.6 to 4.1
Change in QALYs (%)	-37.7 to 43.8	-28.3 to 28.8
ICER	£13,264	£13,712*

*does not capture model non-linearity

Based on the 'Eleven typical ICER patients PSA', ticagrelor 60 mg BID + low-dose ASA has a 94.8% probability of being cost-effective at £20,000 per QALY gained, increasing to 100.0% at £30,000 per QALY gained. For the 'Simple PSA', which does not capture non-linearity in the model, the values are 100.0% and 100.0% respectively.

Figure 65: History of PCI (No) PSA scatterplot, eleven typical ICER patients PSA

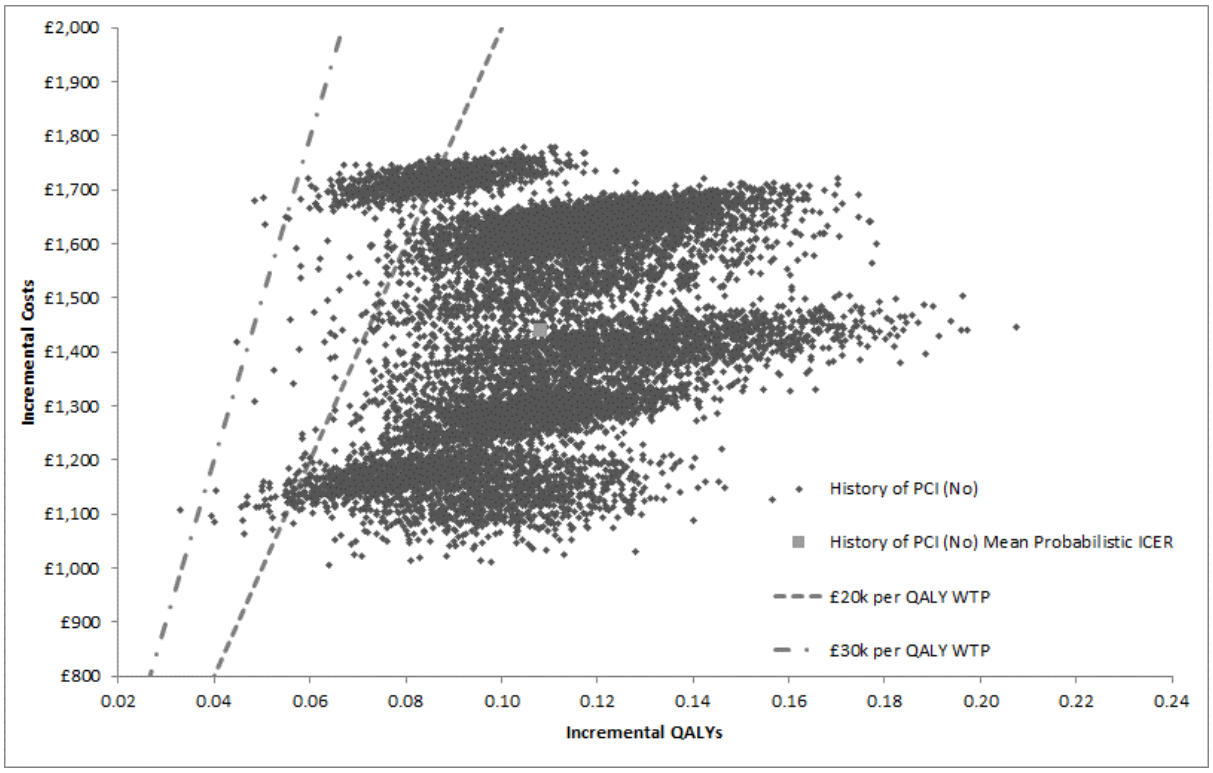
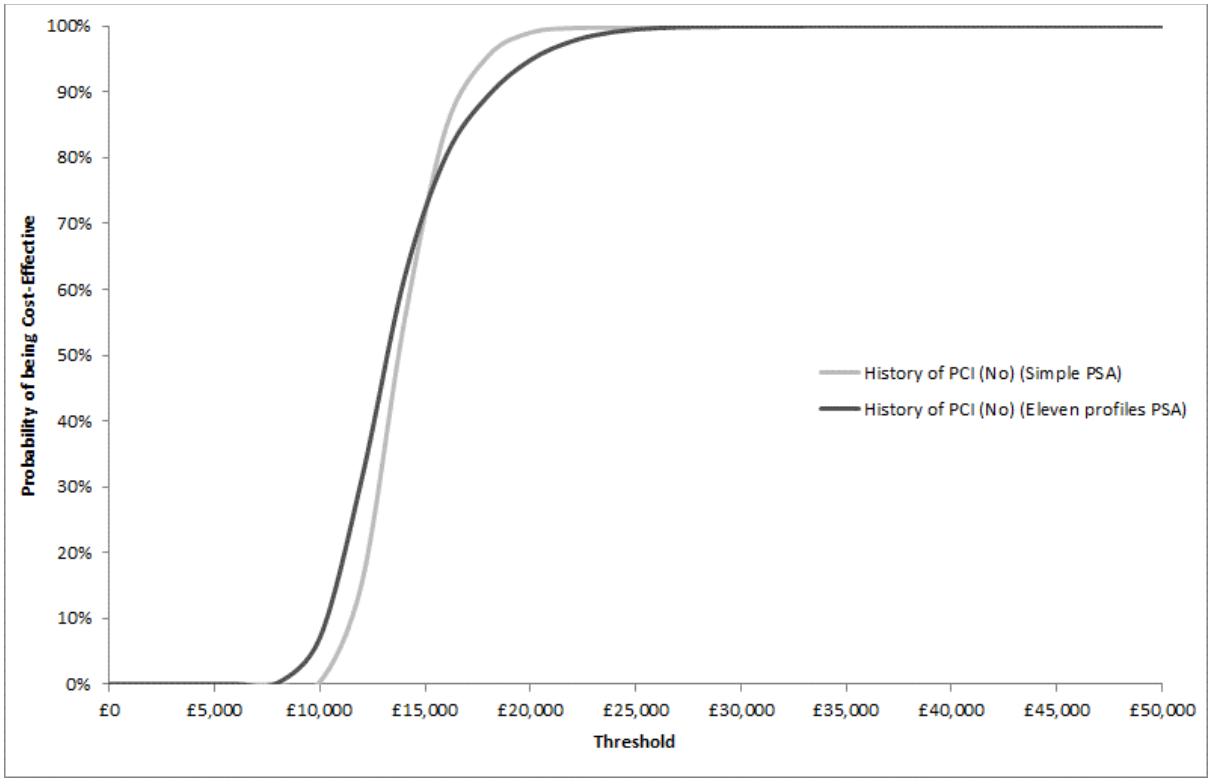


Figure 66: History of PCI (No) CEAC



References

1. National Institute for Health and Care Excellence. Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]. Final scope [Internet]. London: National Institute for Health and Care Excellence, 2016 [accessed 18.4.16].
2. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, et al. Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction. Journal of the American College of Cardiology. 2015;65(20):2211-21.
3. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. Journal of the American College of Cardiology. 2007;49(19):1982-8.
4. AstraZeneca. Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]: AstraZeneca evidence submission to National Institute of Health and Clinical Excellence. Single technology appraisal (STA). 2016.
5. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term use of ticagrelor in patients with prior myocardial infarction. New England Journal of Medicine. 2015;372(19):1791-800.
6. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Bmj. 1998;316(7133):736-41.
7. (NICE) NIfHaCE. TA317: Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes. 2014.
8. (NICE) NIfHaCE. TA210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events 2010. Available from: https://www.nice.org.uk/guidance/ta210.
9. (NICE) NIfHaCE. TA182: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. 2009.
10. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. PharmacoEconomics. 2003;21 Suppl 1:43-50.
11. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabetic medicine : a journal of the British Diabetic Association. 2003;20(6):442-50.
12. NHS reference costs 2014/15 [Internet]. 2015.
13. Halpern EF, Weinstein MC, Hunink MG, Gazelle GS. Representing both first- and second-order uncertainties by Monte Carlo simulation for groups of patients. Med Decis Making. 2000;20(3):314-22.

Response to Clarification Questions

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID813_Ticagrelor_ClarificationQuestions_AZResponse_Part 2	Final	Yes	

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Section B: Clarification on cost-effectiveness data

B4. Please add a scenario analysis incorporating treatment with ticagrelor 60 mg, starting 12 months after having experienced a subsequent MI (consistent with the response to question A11).

This scenario analysis is explored in the updated model and reported in Section H of the results section appended to this response.

B5. Please add a scenario analysis replacing clopidogrel treatment 1 to 12 months after experiencing a subsequent MI by treatment with tricagrelor 90 mg.

This scenario analysis is explored in the updated model and reported in Section I of the results section appended to this response.

Risk equations for first and subsequent event

B8. Treatment (Tic60/ pMI_Tic60 variable) was not included in the estimation of transition probabilities using the risk equations to estimate subsequent events and both first and for "fatal other" this was applicable to the estimation of the first events.

- Please clarify why the treatment variable was not included in these risk equations.
- Please examine the impact of not including the treatment variable for "non-fatal stroke" in a sensitivity analysis (by including the treatment variable in the risk equations).

This scenario analysis is explored in the updated model and reported in Section J of the results section appended to this response.

Health related quality of life

B12. **Priority request:** As explained by the company, the use of a linear random effect panel data analysis allowed for utility values > 1(Table 98, page 262, company submission(1)). Therefore, the company capped the utility value from the PEGASUS TIMI 54 to 1. However, utility decrements used in the model are still based on the same linear model. Naïvely capping the maximal utility value will presumably bias the utility decrements since the scale on which utility decrements are based is different than 0-1.

- Please justify why capping the maximal value is considered appropriate instead of using a model providing utility estimates between 0-1.
- Please justify why applying (multiple) utility decrements was considered more appropriate than calculating utility values for the different health states.
- Recalculate the utility values using a model providing utility values between 0-1 bounds (e.g. a probit model) and provide details on:

a. The number of events, patients and EQ-5D questionnaires used to calculate the utility estimates and utility decrements, if applicable.

b. The methodology used to determine utility estimates and utility decrements, e.g. variable selection and assumptions underlying the model.

c. The uncertainty around each utility estimate and each utility decrement (e.g. standard deviation, standard error, lower and upper bounds).

d. Include these new utility values in the cost-effectiveness model (provide the methods and results)

A scenario analysis where the cap associated with baseline utilities is included/removed is explored in the updated model and reported in Section K and L, respectively of the results section appended to this response.

A scenario analysis where baseline utilities are derived using a gamma model (using a log-link) is explored in the updated model and reported in Section M of the results section appended to this response.

Resource use and costs

B14. **Priority request:** The company submission states that the cost data from ERG review of TA317 inflated to 2015 values were adopted for the base case. However, TA317 used inflated values from TA182 and, as table 104 shows, TA182 used NHS reference costs. Therefore, please provide, for each cost estimate presented in table 103 of the company submission(1): the primary source, the NHS reference costs number(s) and name(s) as well as the uncertainty around the estimate from TA182. In addition, please provide the same information using the reference costs from the latest schedule i.e. 2014/15. Provide this information as in Table 1.

a. Please incorporate the reported costs in the cost-effectiveness model with their measures of uncertainty and describe the methods used to do so

b. Please provide the results of including these costs and their measures of uncertainty.

c. Please also explain why the latest NHS reference costs (2014/15) were not used.

Additional scenario analyses are used to explore the impact of these changes in the updated model and reported in the results section appended to this response.

- Section N: costs for the tunnel states are retained from the original submission document
- Section O: lower quartile costs applied for efficacy events and upper quartile NHS reference cost are applied for adverse events

B16. Please provide a description of the ‘No event’ health state.

- Justify the assumption that 'No event' inpatient costs are equal to the inpatient costs for inpatient costs of a fatal events "*due to the potential range of 'no event' inpatient costs"*.(1)

As shown in Table 1, a broad range of 'background' hospitalisations were recorded in the PEGASUS-TIMI 54 trial (which are 'no event' hospitalisations from the perspective of the model). Owing to the range of hospitalised events observed, for pragmatic purposes the inpatient cost applied for the 'no event' health state was assumed to be equal to the inpatient cost for fatal events. The model is highly insensitive to the choice of inpatient cost for the 'no event' health state.

- Provide an overview of which events produced inpatient costs in the 'No event' health state (events name + number of events)

The probability of hospitalisation in the 'no event' health state is 2.6% per cycle (Table 87, p211 of original submission). Table 1 provides an overview of hospitalisations in PEGASUS-TIMI 54 not associated with model events (i.e. excluding adjudicated MI, stroke, TIMI major or minor bleeding, death and serious dyspnoea).

Table 1: Hospitalization due to serious adverse events excluding adjudicated MI, stroke, TIMI major or minor bleeding, death and serious dyspnoea (full analysis set; patients with <2 years from qualifying MI)

	Number of patients (%)	
Final discharge diagnosis	**Ticagrelor 60mg BID (N=4331)**	**Placebo (N=4333)**
Coronary	[redacted]	[redacted]
Non-cardiac chest pain		
Stable angina		
Unstable angina		
NSTEMI		
STEMI		
Other		
Cardiac Arrythmia		
Atrial tachy-arrhythmia		
Ventricular arrythmia		
Brady-arrythmia		
Non-fatal cardiac arrest		
Congestive Heart Failure		
Cerebrovascular Event		
Primary Ischemic Stroke		
Primary intracranial hemorrhage		
Other Cardiovascular		
Aortic		
Pulmonary Embolism		
Other		
Non-ICH Bleeding		
Gastroenterological		
Genitourinary		
Hemoptysis		
Other bleeding		

Transparency and validity

B19. The company submission presents a description of the external and technical validation of the model in section 5.10.(1) However, other aspects of validity are not addressed in the company submission.

a. Please describe which steps have been undertaken to assess the face validity of the cost-effectiveness model.

In order to decide on an appropriate model structure, a targeted review of previous economic model structures was completed. From this, two broad approaches to modelling the separate events/health states that are part of a composite endpoint emerged. Firstly, a risk equation can be developed for the composite endpoint and then, conditional on having the endpoint the different components to the composite endpoint can be apportioned. A second approach is to model the risk of the components of the composite endpoints separately in a competing risks framework. This was the approach used for the current appraisal and has been used previously in the Scottish Cardiovascular Policy Model. The principal advantage of using a competing risks framework is that it allows for different coefficients for each separate endpoint. So, for example, SBP may be expected to be more important for cerebrovascular disease than for CHD outcomes, as was evident in the Scottish CVD Policy Model. Additionally, as the risk equation approach models events directly, as opposed to a composite event and assessing the probability of that event being of a certain type, far fewer assumptions need to be made.

Experts ([redacted]) with extensive experience in both HTA decision making, statistical methodology and model development were involved in the model selection process and agreed that the competing risks approach was preferable. This model selection has been demonstrated to be appropriate as the model accurately predicts to the observed events and includes health states congruent with the patient experience and clinical pathways from PEGASUS-TIMI 54.

b. Please provide a comparison of the observed and modelled TIMI minor bleeds events, and grade 1-2 dyspnoea as it is provided for the other events (Table 141, company submission(1)).

An expanded copy of Table 141 (p325) from the original submission is presented below and compares the observed events requested with those calculated by the complete analysis model.

Table 141: Comparison of the number of observed vs. modelled events, during a period of the PEGASUS-TIMI 54 ('Label' population, derived from complete analysis).

	Ticagrelor 60 mg BID + low-dose ASA		Low-dose ASA		Modelled vs. observed		Comments
	Observed	Modelled	Observed	Modelled	Ticagrelor 60 mg BID + LD ASA	Low-dose ASA	
First event							
Non-fatal MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Unchanged from original submission
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fatal CV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Composite outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Other fatal event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Subsequent event							
Non-fatal MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Unchanged from original submission
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fatal CV events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Other fatal events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Adverse event							
TIMI Major bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Unchanged from original submission Exponential
TIMI Minor bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Incorporated ERG request Log-Normal
Dyspnoea grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Modelled events derived using Weibull (Original submission used Exponential)
Dyspnoea grade 1-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Incorporated ERG request Log-Normal

c. Please provide a comparison regarding input parameters, model structure, assumptions and outcomes of the current assessment with previous studies identified in the systematic literature review of the company and relevant TA's (i.e. studies included in table 51, page 157 of the company submission and TA182, TA210, TA236, TA317, TA335).

Summaries, in the form of tables, for the five studies identified by the economic SLR and the five relevant TAs are provided for the following categories:

• Model structure (Table 2)

• Input parameters (Table 3)

• Model key assumptions (Table 4)

• Model outcomes (Table 5)

As demonstrated in Table 2 there is no consensus on modelling approach undertaken between the studies and previous TAs and no model structure could be adopted intact since indications modelled were different to the decision problem of this submission. Some consistency, as expected, was found in the use of tunnel and transient-event states to model acute and follow-on phases of specific events.

The relevance of costs and utilities used in these sources were considered in Table 3 and as described in the original submission (Sections 5.4 and 5.5) and the subsequent response to clarification questions provided separately.

The key assumptions for these studies and TAs are summarised in Table 4. No assumptions were adopted from other studies or appraisals for the current submission. Key assumptions of the economic evaluation were tailored to the needs of this decision problem.

The comparison of model outcomes provided in Table 5 should be interpreted with caution as model outcomes are dependent on a number of factors including all the inputs, structures and assumptions described in Table 2, Table 3 and Table 4.

Table 2. Model characteristics

Author, Year	Indication	Comparison	Type of analysis and model	Health states¤	Modelling of AEs	Perspective, discounting, time horizon, cycle length and prices used
Current submission [ID813]						
AstraZeneca, 2016	Secondary prevention of atherothrombotic events after MI.	TICA+ASA ASA	• CUA • Decision tree for short term events and Markov model for long term events.	**Events (transient event):** • Non-fatal MI • Non-fatal stroke • TIMI major bleed • TIMI minor bleed • Dyspnoea (grade 3–4) • Dyspnoea (grade 1–2) **Health states (permanent state)** • Post non-fatal MI • Post non-fatal stroke	Transient events alongside health states.	• Payer-NHS/PSS perspective. • 3.5% applied for both costs and QALYs. • Lifetime (40 yrs) time horizon. • 3-month cycles. • 2015 prices (GBP).
Economic studies (n=5)						
Banerjee S et al., 2012(2)	For the secondary prevention of vascular events in adults with ACS or PVD.	CLOPI ASA ASA+CLOPI	• CUA • Separate Markov models for ACS (6 health states) and PVD (7 health states), considers MI within and beyond 12 months.	**Separate models were developed for the ACS and PVD population groups.** **The ACS model consists of six health states:** • Qualifying MI or new MI • Post-new MI • New stroke • Post-new stroke • Vascular death • Non-vascular death	Not as a health state	• Payer-CADTH perspective. • The discount rate for costs and outcomes in the base case scenario was 5%, and in the sensitivity analyses it was 3% and 0%, as suggested in the CADTH guidelines for economic evaluations. • Lifetime (100 yrs of age) time horizon. • Annual cycles. • 2009 prices (CAD).
Begum N et al., 2016 (3)	Secondary Prevention of ACS.	Rivaroxaban +ST-APT ST-APT mono	• CEA • Markov model structure showing 16 health states.	• Bleeding (Major, minor, medical attention) • Revascularization (PCI, CABG) • First MI (+subsequent events) • First IS(+subsequent	Bleedings and revascularizations were considered as transient health states	• Swedish societal perspective. • Costs and benefits discounted by 3.0% • Lifetime (40 yrs) time horizon. • 12-weekly cycles in the first

Author, Year	Indication	Comparison	Type of analysis and model	Health states¤	Modelling of AEs	Perspective, discounting, time horizon, cycle length and prices used
				events) • First IS/ICH(+subsequent events) • Fatal MI • Fatal IS • Fatal HS/ICH • OCD (inc. fatal bleeding) • NCD		2 yrs (observation period) + 6-monthly cycles thereafter (extrapolation period). • 2013 prices and 2014 conversion (from SEK to Euros).
Chen J et al., 2009 (4)	Secondary Prevention of CV Events: Results from the CHARISMA Trial.	CLOPI+ASA ASA	• CEA • Trial-based analysis (based on CHARISMA trial).	**Clinical trial outcomes:** • CV death • MI • Stroke	As outcomes from trial, added to the total cost per arm	• Payer-US perspective. • Costs discounted at 3%. • Lifetime time horizon. • NR cycles. • 2007 prices (USD).
Chen J et al., 2011 (5)	Secondary Prevention of CV Events in Canada for Patients With Established CVD.	CLOPI+ASA ASA mono (+PBO)	• CEA • Trial-based analysis.	**Clinical trial outcomes:** • CV death • MI • Stroke	As outcomes from trial, added to the total cost per arm	• Payer-Canada perspective. • Costs and benefits discounted by 5%. • Lifetime time horizon. • NR cycles. • 2008 prices (CAD).
Gaspoz JM et al., 2002 (6)	Secondary prevention of CHD.	CLOPI ASA ASA+CLOPI	• CUA • Computer simulation model: CHD policy model.	• Reduction in rate of CHD events (angina, HF, both) • Reduction in rate of mortality from non-coronary causes • Reduction in rate of revascularization	As additional costs per treatment arm	• NR perspective. • Costs and benefits discounted by 3% • 25 yrs time horizon. • NR cycles. • 2000 prices (USD).
Past NICE submissions						

Author, Year	Indication	Comparison	Type of analysis and model	Health states[¤]	Modelling of AEs	Perspective, discounting, time horizon, cycle length and prices used
TA335, 2015 (7, 8)	For Preventing Atherothrombotic Events in People with ACS and Elevated Cardiac Biomarkers.	Rivaroxaban +ASA +/- CLOPI ASA +/- CLOPI	• CUA • Markov cohort model.	Acute care (1st 3 months) + Follow on care (2nd 3 months, 3rd and 4th 3 months, later 3 months): • MI • IS • HS/ICH • MI+MI • IS+IS • HS/ICH+HS/ICH • MI+IS • MI+HS/ICH 3 events	Bleedings and revascularisations are included in the model as transient health states	• Payer-NHS/PSS perspective. • 3.5% for costs and benefits. • Lifetime (40 yrs) time horizon. • 12-weekly cycles in the first 2 yrs (observation period) and 6-monthly cycles thereafter (extrapolation period). • 2013 prices (GBP).
TA210, 2010 (9, 10)	For the secondary prevention of OVEs: MI, IS, and vascular death.	CLOPI, MRD+ASA, ASA, MRD	• CUA • Markov model.	• Initial state • Death • History of MI • History of stroke • History of MI and stroke • TA80 state[¤].	As tunnel health states for 'other haemorrhagic events' and 'new or worsening CHF'.	• Payer-NHS perspective. • 3.5% for costs and benefits. • 35 yrs time horizon. • 3 month cycles. • 2007/08 prices (GBP).
TA182, 2009 (11, 12)	Acute coronary artery syndromes with PCI.	CLOPI, Prasugrel	• CUA • 2-phase model (the trial period and an extrapolation).	• MI • Stroke • CV Death • Other Death	Non-fatal bleeds incur temporary (2 weeks) HRQoL decrements and resource use consequences.	• Payer-NHS perspective. • Costs and benefits have been discounted at a rate of 3.5%. • Lifetime (40 yrs) time horizon. 1) opening 3 day period, 2) approx. 15 x 1 month cycles 3) 1 x approx. 9 months (Total time = 2 years) 4) 38 x yearly cycles. • 2006-2007 prices (GBP).
TA236, 2011 (13)	Patients with ACS (UA, NSTEMI, STEMI) including	TICA+ASA (TICA), CLOPI+ASA	• CEA • Two-part construct with a	• Non-Fatal MI • Non-Fatal Stroke • Death any cause	As health states	• Payer-NHS perspective. • 3.5% for costs and benefits • Lifetime (40 yrs) time horizon.

Author, Year	Indication	Comparison	Type of analysis and model	Health states¤	Modelling of AEs	Perspective, discounting, time horizon, cycle length and prices used
	patients MM and PCI or CABG	(CLOPI)	one-yr decision tree, based on data from the PLATO study, and a Markov model for long term extrapolation.	• No Event • Post MI • Post Stroke • Dead		• 1 yr cycles. • 2008-2009 prices (GBP).
TA317, 2014 (12)	Patients with ACS managed with PCI.	CLOPI, prasugrel	• CUA • A Markov model with 2 phases. The 1st equals TRITON-TIMI 38 trial and 2nd extrapolated to the time horizon.	• CV/Bleed death • Bleed endpoint event • Non-Fatal MI • Non-fatal stroke • All-cause mortality	Non-fatal bleeds incur temporary (2 weeks) HRQoL decrements and resource use consequences.	• Payer-NHS/PSS perspective. • 3.5% for costs and benefits • Lifetime (40 yrs) time horizon. • 1 yr cycles. • 2012 prices (GBP).

AE: Adverse events; ASA: Aspirin; CAD: Canadian dollars; CADTH: Canadian Agency for Drugs and Technologies in Health; GBP: Great Britain pounds; MI: Myocardial infarction; MM: Medically managed; NCD: Non-cardiovascular death; NHS/PSS: National health services/personal social services; OCD: Other cardiovascular death; PCI: Percutaneous coronary intervention; PVD: Peripheral vascular disease; QALY: Quality adjusted life years; SEK: Swedish Krona; ST-APT: Standard antiplatelet therapy; TICA: Ticagrelor; TIMI: TIMI: Thrombolysis In Myocardial Infarction; US: United states; USD: United states dollars; IS: Ischaemic stroke; IS/ICH:CABG: Coronary artery bypass graft; CV: Cardiovascular; NR: Not reported; PBO: Placebo; HF: Heart failure; CHD: Coronary heart disease; CVD: Cardiovascular disease; yrs: Years; MRD: Modified-release dipyridamole; NHS: National health service; OVEs: Occlusive vascular events; CHF: Coronary heart failure; HRQoL: Health related quality of life; UA: Unstable angina; STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; yr: Year; NICE: National Institute for Health and Clinical Excellence; AZ: Astrazeneca; CEA: Cost-effectiveness analysis; CUA: Cost-utility analysis; HS/ICH: HS/ICH: Haemorrhagic stroke/ Intracranial haemorrhage

¤Only those relevant to our decision model were extracted

ɒThis intermediate state relates to the TA80 guidance which recommends that treatment with CLOP+ASA should be continued for up to 12 months (4 cycles in the model) after the most recent acute episode of NSTEMI. In the model, after 4 cycles, patients go back to antiplatelet monotherapy.

Table 3. Model inputs of relevant sources

Author, year	Source of clinical evidence	Costs used in the analysis[§]	Utility Measure	Utilities used in analysis[¶]	Starting age
Current submission [ID813]					
AstraZeneca, 2016	The PEGASUS-TIMI 54	Non-fatal MI: £4,476.18	EQ-5D	Average at 1st visit: 0.8501	65.3 yrs
		Non-fatal stroke: £4,925.76			
		Fatal events (CAD and non-CAD): £2,497.83		Non-fatal MI: -0.0474	
		No event: £2,497.83			
		Post non-fatal MI (0-3 + 3-6 months): £639.45		Non-fatal stroke: -0.0934	
		Post non-fatal MI (6-9 + 9-12 months): £319.73		Post MI: -0.0342	
		Post non-fatal MI (12+ months, every cycle): £160.31		Post stroke: -0.0665	
		Post non-fatal stroke (0-3 months): £1,343.39			
		Post non-fatal stroke (3-6 months): £1,119.49		Dyspnoea (Grade 3-4): -0.0481	
		Post non-fatal stroke (6-9 months): £877.57			
		Post non-fatal stroke (9-12 + 12+ months): £689.71		Dyspnoea (Grade 1-2): -0.0154	
		No event (every cycle): £160.31		TIMI minor bleed: -0.0129	
		Grade 3-4 Dyspnoea: £732.98			
		Major TIMI bleed: £2,206.87		TIMI major bleed: -0.0466	
		Minor TIMI bleed: £122.48			
Economic studies (n=5)					
Banerjee S et al., 2012(2)	Literature	Non-fatal stroke, first yr: $20,823	EQ-5D	Non-fatal stroke, initial yr: 0.65	60 yrs
		Non-fatal stroke, subsequent yrs: $4,336		Non-fatal stroke, follow on yrs: 0.694	
		Non-fatal MI, first yr: $10,824			
		Non-fatal MI, subsequent yrs: $3,112		Non-fatal MI, initial yr: 0.704	

Author, year	Source of clinical evidence	Costs used in the analysis[§]	Utility Measure	Utilities used in analysis[¶]	Starting age
		Fatal stroke: $8,418			
		Fatal MI: $8,946		Non-fatal MI, follow on yrs: 0.725	
		Vascular death: $8,682[∞]			
Begum N et al., 2016 (3)	ATLAS ACS 2-TIMI 51 trial	Cost of MI (first 3 months, acute treatment): €8,789	Various sources of literature (NR)	No event (event-free): 0.842	62 yrs
		Cost of MI (second 3 months, follow-on care): €3,883		MI first 6 months: 0.779	
		Cost of MI (second 6 months, follow-on care): €7,767		MI second 6 months: 0.821	
		Cost of MI (second 12 months, follow-on care): €5,445		MI follow on 6 month cycles: 0.821	
		Cost of IS or HS/ICH (first 3 months, acute treatment): €12,517		IS or HS/ICH first 6 months: 0.703	
		Cost of IS or HS/ICH (second 3 months, follow-on care): €2,529		IS or HS/ICH second 6 months: 0.748	
		Cost of IS or HS/ICH (second 6 months, follow-on care): €5,138		IS or HS/ICH follow on 6 month cycles: 0.792	
		Cost of IS or HS/ICH (second 12 months, follow-on care): €5,815			
		Cost of fatal events (excluding NCD): €1,790		TIMI major bleeding: 0.750	
		Cost of NCD: €0		TIMI minor bleeding: 0.800	
		Cost of TIMI major bleeding :€4,044			
		Cost of TIMI minor bleeding: €337		TIMI bleed requiring medical attention: 0.8	
		Cost of TIMI minor bleeding requiring medical attention: €153			
Chen J et al., 2009 (4)	CHARISMA trial	Hospitalizations: CLOPI+ASA: $4,109, ASA alone: $4,266	NA	NA	45 yrs
		Inpatient physician costs: CLOPI+ASA: $1,329, ASA alone: $1,363			
		CLOPI: CLOPI+ASA: $3,062, ASA alone: $169			
		Other medications: CLOPI+ASA: $4,822, ASA alone: $4,837			

Author, year	Source of clinical evidence	Costs used in the analysis[§]	Utility Measure	Utilities used in analysis[¶]	Starting age
		Outpatient care: CLOPI+ASA: $421, ASA alone: $501			
		Total: CLOPI+ASA: $13,743, ASA alone:$11,136			
Chen J et al., 2011 (5)	CHARISMA trial	Hospitalizations: CLOPI+ASA: $2,939, ASA alone: $3,085	NA	NA	45 yrs
		CLOPI: CLOPI+ASA: $1,784, ASA alone: $89			
		Other medications: CLOPI+ASA: $2,013, ASA alone: $2,012			
		Outpatient care: CLOPI+ASA: $337, ASA alone: $401			
		Total: CLOPI+ASA: $7,075, ASA alone: $5,587			
Gaspoz JM et al., 2002 (6)	Literature and official health statistics and surveys.	Cost of non-CHD (35–44 yr): $1,994/yr	NR	NR	35-84 yrs
		Cost of non-CHD (45–64 yr): $3,794/yr			
		Cost of non-CHD (65–84 yr): $7,796/yr			
		Mean annual cost of CHD: $6,200			
Past NICE submissions					
TA335, 2015 (7, 8)	Primarily based on ATLAS-ACS 2-TIMI 51 study and findings form the literature	MI acute care (1st 3 months): £3,586	EQ-5D	MI (1st cycle): 0.779	18 yrs
		MI follow on care (2nd 3 months): £1,980		MI (2nd cycle): 0.821	
		MI cost (3rd and 4th 3 months): £1,440		MI (3rd cycle): 0.821	
		MI cost (later 3 months): £540		IS (1st cycle): 0.703	
		IS acute care (1st 3months): £7,756		IS (2nd cycle): 0.748	
		IS follow on care (2nd 3 months): £3,060		IS (3rd cycle): 0.792	
		Fatal MI: £1,500		TIMI Major Bleed (excluding ICH): 0.77 (0.19, 1.00)	
		Fatal IS: £4,500		TIMI Minor Bleed: 0.84	
		Fatal HS/ICH: £4,500		No further ACS event (All cycles): 0.842	

Author, year	Source of clinical evidence	Costs used in the analysis[§]	Utility Measure	Utilities used in analysis[¶]	Starting age
		Other CV Death: £3,000			
		No Further ACS Event: £0			
TA210, 2010 (9, 10)	Literature	Non-fatal MI: £5,761.88	EQ-5D for some	No event, LT, previous stroke: 0.61	65 yrs
				No event, LT, previous MI: 0.87	
		Non-fatal MI, annual continuing care cost: £577.6		No event LT, previous PAD: 0.8	
		Non-fatal IS (Rankin 0-2)[α]: £6,409.94		No event, LT, MVD patients: 0.61	
		Non-fatal IS (Rankin 3-5)[β]: £13,674.38		After stroke, LT, previous stroke; MI; PAD; MVD: 0.61	
		Non-fatal disabling stroke, annual continuing care cost: £5,175.44		After MI, LT, previous stroke; PAD; MVD: 0.61	
		Fatal MI: £2,218.39		After MI, LT, previous MI: 0.87	
		Other vascular death: £2,225		After stroke and MI, LT, previous stroke; MI; PAD; MVD: 0.61	
		Fatal HS/ICH (Rankin 3-5)[β]: £8,767.69		Stroke, ST decrements after event, Patients with previous stroke: -0.174	
		Other non-vascular death: £2,225		Stroke, ST decrements after event, Patients with previous MI: -0.248	
				Stroke, ST decrements after event, Patients with previous PAD: -0.228	
		Major bleeding event: £2,010.35		Stroke, ST decrements after event, MVD patients: -0.174	
		Minor bleeding event: £111.57		MI, ST decrements after event, Patients with previous stroke: -0.058	
		No Key events, annual continuing care cost: £0		MI, ST decrements after event, Patients with previous MI: -0.082	
TA182, 2009 (11, 12)	TRITON-TIMI 38 study and the literature	Non-fatal MI: • CLOPI: £1,492, Prasugrel: £1,492	EQ-5D	MI: 0.0524	NR
		Non-fatal Stroke: • CLOPI: £1,932, Prasugrel: £1,822		Stroke: 0.0524	
		Major bleed: • CLOPI: £1,155, Prasugrel: £1,155		Major bleed: 0.007	
		Minor bleed: • CLOPI: £1,382, Prasugrel: £1,604			

Author, year	Source of clinical evidence	Costs used in the analysis[§]	Utility Measure	Utilities used in analysis[¶]	Starting age
TA236, 2011 (13)	PLATO trial	Non-fatal MI: • TICA: £16,643, CLOPI: £16,362	EQ-5D	Non-fatal MI: • TICA: 0.786, CLOPI: 0.774, MM: 0.779	70 yrs
		Non-fatal Stroke: • TICA: £15,394, CLOPI: £17,483		No further event: • TICA: 0.840, CLOPI: 0.844, MM: 0.842	
		No event: • TICA: £8,544, CLOPI: ££8,633		Non-fatal stroke: • TICA: 0.709, CLOPI: 0.695, MM: 0.703	
TA317, 2014 (12)	TRITION-TIMI 38	Non-fatal MI: £6,165.21	EQ-5D	Non-fatal non disabling stroke: 0	35 yrs
		Non-fatal non-disabling stroke: £6,858.64		Non-fatal disabling stroke: 0	
		Non-fatal disabling stroke: £14,602.7		Non disabling stroke: • Male: 0.838, Female: 0.769	
		Non-disabling stroke: £1,804.06		Disabling stroke: • Male: 0.487, Female: 0.418	
		Disabling stroke: £5,537.72		Fatal MI: -0.100	
		Other vascular death: £2,407.5		Fatal stroke: -0.100	
		Fatal MI: £2,373.68		Other Vascular death: -0.100	
		Fatal Stroke: £9,381.43			
		Non-vascular death: £2,407.5		Non vascular death: -0.100	
		Event free/MI only: £618.03			
		Major TIMI bleed: £2,010.35		Event free/MI only: 0.874	
		Minor TIMI bleed: £111.57			

ACS: Acute coronary syndrome; ASA: Aspirin; AZ: AstraZeneca; CHD: Coronary heart disease; CLOP: Clopidogrel; CV: Cardiovascular; EQ-5D: European Quality of Life-5 Dimensions; HS/ICH: HS/ICH: Haemorrhagic stroke/ Intracranial haemorrhage; IS: Ischaemic stroke; LT: Long term; MI: Myocardial infarction; MM: Medically managed; MVD: Multivascular disease; NA: Not applicable; NCD: Non cardiovascular death; NICE: National Institute for Health and Clinical Excellence; NR: Not reported; PAD: Peripheral arterial disease; ST: Short term; TIMI: TIMI: Thrombolysis In Myocardial Infarction; yr: Year; yrs: Years

§ Information about drug cost were excluded as irrelevant for comparison and only drug categories relevant to the decision problem of this submission were extracted.

∞ Cost of vascular death is average of costs of fatal stroke and fatal MI.

α Not disabled, β Disabled

¶ Only utilities potentially relevant to the decision problem were extracted

Table 4. Key model assumptions of relevant economic evaluations

Author, year	Model key assumptions in bullet points[o]
Current submission [ID813]	
AstraZeneca, 2016	• It is assumed that it is appropriate to extrapolate the risk equations beyond the time frame of the clinical trial. This is a generally accepted assumption within economic modelling and a deterministic sensitivity analysis was undertaken to assess the impact of choosing different functional forms. No extrapolation of treatment effect is made beyond the trial. • Assumed that risk equations other than the time to first event are not impacted upon by whether the patient is included or is not included within the label population. There is no clinical rationale for there to be any difference between these risk equations for the label and the full PEGASUS-TIMI 54 trial population. If there is a difference, this should be accounted for by the patients underlying baseline characteristics. • It was appropriate to impute missing data in order to assist with the statistical analysis. • Risk of adverse events (dyspnoea and bleeding) is assumed only to occur whilst patients remain on active treatment. • Although patients can have multiple subsequent events, the risk of further subsequent events is constant and is independent of the number of subsequent events the patient has had. • Although permanent treatment discontinuation is taken into account we have assumed that all patients will remain 100% adherent to treatment until permanent treatment discontinuation occurs, for the purposes of drug costing. This represents a conservative approach for TICA 60mg BID. • Subsequent events have the same inpatient costs as first events. • Due to the potential range of 'no event' inpatient costs, we have assumed that the inpatient cost of 'no event' would be the same as the cost of fatal events. • It is assumed that all patients experiencing a non-fatal MI, non-fatal stroke or severe adverse event will be hospitalised. • Costs from TA317 are representative of the cost for the first 12 months from the event. We have assumed that 70% of the cost of the non-fatal MI is accrued as an inpatient whilst 55% of the cost of a non-fatal stroke (both disabling and non-disabling) is accrued as an inpatient. The remainder is accrued as an outpatient and maintenance cost, in order to arrive at the same cost in the yr following event as applied in the ERG models (after inflation and for the same mix of disabling and non-disabling strokes). • Given that higher costs are often experienced closest to the event we have assumed that the acute outpatient and maintenance costs will decrease over the first 12 months. • We have assumed that the long-term 'no event' cost is the same as the long-term non-fatal MI cost as all patients have at least one MI in their history (the qualifying MI for the trial). A 'no event' patient in the model is a patient with no events beyond the qualifying MI. The long term maintenance cost is expected to be the same, irrespective of the number of MIs in a patient's history. • There is no outpatient and maintenance cost for dyspnoea grade 1-2. • For base case it was assumed that the decision on whether or not TICA 60mg BID should be prescribed for history of MI will be taken by the cardiologist at the time the patient is discharged from hospital for the qualifying

Author, year	Model key assumptions in bullet points[◎]
	MI (via the letter of discharge recommendations to the GP). As such no incremental healthcare visit associated to the initiation of TICA 60mg BID is assumed for base case. Other scenarios are explored under sensitivity analysis. • It was assumed that the patient population under consideration within the model were unlikely to have a higher baseline utility than that of the UK general population.
Economic studies (n=5)	
Banerjee S et al., 2012(2)	• RR of non-vascular death for CLOPI was unavailable and was assumed to equal 1. • The cost of non-vascular death was assumed to be zero, as it is not a disease-related cost. • A mean starting age of 60 yrs for patients and a discount rate of 5% for costs and outcomes were assumed in the base case analysis. • Same efficacy across age groups, as is standard practice.
Begum N et al., 2016 (3)	• A half cycle correction was applied to reflect the continuous nature of the occurrence of transitions during each cycle by assuming that, on average, all transitions occurred halfway through any particular cycle. • The model assumed there was no treatment effect associated with rivaroxaban or CLOPI or ticlopidine after treatment discontinuation. In line with treatment guidelines, ASA monotherapy was assumed to be continued after discontinuation of all other treatment(s) for the remainder of the model. • As ticlopidine is not available in Sweden for the treatment of ACS patients, it was assumed that all patients who received ticlopidine in the ATLAS ACS 2-TIMI 51 clinical trial (<1% of patients) were subsequently treated with CLOP, without affecting the overall clinical outcomes. • Revascularization and non-ICH bleeding events were assumed to only occur during the observation period (in accordance with the specified length of treatment in each arm) as the rates would be considered equal after rivaroxaban and ST-APT discontinuation, and their impact on the incremental outcomes negligible after the observation period. • To capture long-term survival rates, transition probabilities on the effectiveness and safety of ASA were extrapolated assuming constant rates in time. • In the absence of specific, separate costs for IS and HS/ICH, the costs were assumed to be the same for the stroke types. • The lengths of disutility associated with bleeding and revascularization events were based on literature and expert opinion, and were assumed to be 30 days for TIMI major bleeding and PCI, 2 days for TIMI minor bleeding and TIMI bleeding requiring medical attention. • Conservative assumption that cost of non-CV death equals zero.
Chen J et al., 2009 (4)	• Actual duration of treatment was assumed to mirror that provided in the CHARISMA trial (a median of 28 months) as the precise effect of long-term therapy in the study population was unknown. • CLOPI treatment was assumed to be discontinued at the end of the trial, and therefore, the base case analysis also assumed no further differences between the two treatment groups in the rates of subsequent CV events beyond the end of the trial.

Author, year	Model key assumptions in bullet points[◎]
	• The analysis assumed no further treatment costs or benefit beyond the time frame of the trial.
Chen J et al., 2011 (5)	• Actual duration of treatment was assumed to mirror that provided in the CHARISMA trial (a median of 28 months) as the precise effect of long-term therapy in the study population was unknown. • CLOPI treatment was assumed to be discontinued at the end of the trial, and therefore, the base case analysis also assumed no further differences between the two treatment groups in the rates of subsequent CV events beyond the end of the trial.
Gaspoz JM et al., 2002 (6)	• Additional relative reductions were assumed for the rates of coronary events (8.7%) and deaths from non-coronary causes (5.0%) to model the effects of CLOP. • In the base case analysis, ASA was assumed to be used in 85% of patients with coronary heart disease in 2003; this is based on data on patients discharged after acute infarctions. • The model assumed that 94.3% of patients were eligible for treatment with ASA and 100% were eligible for treatment with CLOP. • The cost of the combination of ASA and CLOPI was assumed to be the sum of the two individual drug costs. • The incidence of stroke was assumed to be the incidence reported in pooled secondary statin trials.
Past NICE submissions	
TA335, 2015 (7, 8)	• Tunnel states are used to model the first six months, second six months and later periods after an event. This allows variable transitions, costs and – where relevant – utilities, dependent on the time since the event, allowing more accurate reflection of clinical reality. • In the extrapolation period 6 monthly cycles are applied which was supported by the clinical expert (KR). • The model does not differentiate event types once patients suffer 3 events or more. The clinical expert (KR) suggested the distinction should be made, however the low number of patients who suffer 3 events or more in the trial does not substantiate disentanglement of the ATLAS 2 trial data. • Discontinuation is only applied to the 'free of secondary events' health state, i.e. in any cycle the total number of patients experiencing discontinuation of treatment due to MI, IS or HS/ICH is subtracted from the total number of patients in the free of secondary events health state. This approach was supported by the clinical expert (KR). • The interruption bleeding events may have on antithrombotic or antiplatelet therapy is not modelled within the discontinuation as this only has short–term impact of 5-7 days after which the decision to re-initiate treatment is solely based on the physician's decision. • Bleeding events and revascularisations are considered transient health states. A cost and utility is applied but no long term impact of these events is considered in the model (benefits in terms of reduced event risks following a revascularisation procedure are already captured in the clinical trial data). This reflects evidence in the literature sourced in the systematic review of economic models, which suggests short-term impacts of bleeding events. (Greenhalgh 2009, (53;54;65;80;96)). • Intracranial haemorrhages and fatal bleeds are more severe and are expected to have a larger impact than all severities of TIMI bleeds. Therefore these are considered in other model health states. Intracranial haemorrhages are considered in the haemorrhagic stroke state, and fatal bleeds are considered in the other cardiovascular

Author, year	Model key assumptions in bullet points[o]
	death state and also supported by the clinical trial. The bleeding states considered in the model are TIMI major bleeds (excluding ICH and fatal bleeds), TIMI minor bleeds, and TIMI bleeds requiring medical attention. • Patients who suffer a non-fatal and fatal event in any given cycle of the model will be considered as a fatality in that cycle. • Transition probabilities for the extrapolation period are based on the last cycle from the observation period of the comparator arm to allow for estimation of transition probabilities when all patients are on ASA monotherapy, corrections for the difference in cycle length (because the cycle length in the observation period is 12 weeks and the cycle length in the extrapolation period is 6 months) and RRR associated with lifetime ASA monotherapy are applied. • The extrapolation period factors in increased risks of events due to ageing, the increased risk of case fatalities due to ageing, relative risks of suffering subsequent events and decreasing number of events observed over time in the ATLAS 2 trial. • The initial case fatalities estimate for MI is taken from the trial data and we use Hippisley-Cox et al (2004)(113) to derive initial case fatality estimates for stroke. • Data from Smolina et al (2012)(111;112) and Hippisley-Cox et al (2004) (113) are used to estimate the increased risk of suffering a non-fatal MI and non-fatal stroke respectively. • Data from Smolina et al (2012) (111;112) and Hippisley-Cox et al (2004) (113) are used to estimate the increased risk of suffering a fatal MI and fatal stroke respectively. • In the absence of suitable data to differentiate between the increased risk due to age of suffering a non-fatal stroke and the increased risk of suffering a fatal stroke, we apply the relative difference between the increased annual risk of a non-fatal MI and fatal MI to estimate the increased risk of suffering a fatal stroke relative to the risk of suffering a non-fatal stroke.
TA210, 2010 (9, 10)	• Non-vascular death was assumed to be the difference between ‘all-cause mortality’ and ‘death from vascular causes’. • When fatal and non-fatal vascular events were not reported separately, then the total of fatal and non-fatal events was used as an approximation for non-fatal events in the dataset. • In the absence of any evidence on non-vascular death having a dose-response relationship with ASA (in contrast to the vascular events and AEs), it was assumed that the risk of non-vascular death was equal for all ASA doses. • As the ESPRIT trial did not impose a specific ASA dose, but left the decision on dosing to the local investigators, the ASA arm of this trial was assumed to be a weighted average of the low, medium and high ASA dose arms, with weights equal to the proportion of patients observed on the different doses: 46%, 48% and 5%, respectively. • The ATTC data describing the efficacy of ASA versus no treatment reported only on the composite end-point of ‘serious vascular events’ but not on the separate components. Therefore the assumption was made that the relative efficacy of ASA versus no treatment was equal for all these separate end-points: MI, stroke and vascular death.

Author, year	Model key assumptions in bullet points[©]
TA182, 2009 (11, 12)	• **Minor bleeds:** Bleeds have no long-term prognostic impact beyond the clinical trial duration of 15 months, in terms of morbidity or mortality. The health effects of non-fatal bleeds do not last beyond the duration of the trial i.e. immediate effects are of limited duration and are not prognostic. This assumption was endorsed by clinical experts, on the basis that there is no robust or definitive evidence available on the prognostic impact of bleeds beyond the acute or medium term treatment phase. 15 months was considered a sufficiently long period to capture the impact of bleeds. • **Utilities:** At entry to the model all patients were allocated utilities that reflect UK population norms and existing ACS. Stroke carries a marginally increased decrement also applied to patients with MI. It has been assumed that major bleeds involved a temporary 14 day utility penalty equivalent to 25% of the population norm. The assumptions with regard to MI and stroke decrements are likely to be conservative as the cumulative effect of repeat events in terms further damage to the myocardium, or increased severity of disability associated with stroke may not fully be captured (and these events occur with less frequency in the prasugrel arm). The bleed utility assumption was based on previous assumptions adopted in earlier models where bleeds were potentially important outcomes. The impact of the acute utility decrement was varied in the sensitivity analysis. There is likely to be little or no impact upon the results. Clinical experts endorsed this assumption. The effect of greater impacts in terms of MI and stroke utility was also examined in sensitivity analysis. • Mortality after ACS event: Immediately upon entering TRITON TIMI 38 patients were re-vascularised, and the additional risk for mortality may have been reduced or attenuated as a consequence. Relative risks were applied for MI and stroke as prognostic events. MI and stroke are known to be associated with increased risks for all-cause mortality relative to the general population. MI and stroke are known to be associated with increased risks for all-cause mortality relative to the general population. These effects were applied to all patients to reflect initial ACS status in the model, however the impact of re-vascularisation should be acknowledged. Increases in risk due to in-trial events were based on published estimates for the impact of re-infarction and stroke. • **Treatment discontinuation:** It was assumed that patients were likely to discontinue CLOPI and prasugrel at the same rate. No discontinuations other than due to death are included within the model. The discontinuation rates within the clinical trial were the same for both arms at 17% (see clinical section 6.4). Therefore, this model assumption is conservative as the treatment effect is based upon 83% continuation of therapy but costs have been applied for 100% continuation. Inclusion of discontinuation would have increased the complexity of the model without any distinct change in the outcomes. Clinicians endorsed the assumption. • **Treatment efficacy, duration:** No treatment effects are modelled beyond the duration of the trial or modelled duration (e.g. 12 months).

Author, year	Model key assumptions in bullet points[◎]
	There was no evidence to support the impact of treatment effects beyond the duration of the trial. The duration of treatment is varied in the model and the effects related to duration were also varied in line with duration of treatment.
TA236, 2011 (13)	• Assumption relevant to the life-yrs calculation, that on average patients in both trial arms who die during the trial do so half-way through the trial. • The estimation of mean QALYs per patient depends on assumptions about the likely pattern of utility scores experienced by patients who died during the trial as well as the timing of death. • Assumption of a Weibull common function for both sets of data. • For the post stroke health state assume that HRQoL improves over time.
TA317, 2014 (12)	• **Long-term accumulating risks:** The main objective of the AG's model of prasugrel is to assess whether or not modelling the accumulation of risk-bearing disease events has the effect of causing the long-term experience of patients in both the comparator arms to converge. In this context the AG considered that this objective could be mainly served through the explicit incorporation of strokes, and their associated elevated event risks and larger on-going care costs, into the model. The AG also considered that some more marginal issues could be omitted so as to achieve modelling efficiency by generating rapid feedback of results to the user. • **Main source of parameter values:** The model employed in this appraisal is a simplified version of the individual patient simulation model developed for the NICE appraisal of CLOPI and modified release dipyridamole which resulted in NICE guidance TA210. The event risk and fatality risk parameters for that model have been preserved in the new formulation, and were sourced primarily from analyses of results from the CAPRIE trial which were kindly made available to the AG by the manufacturer of CLOP. The AG sought clinical advice as to the suitability of using the CAPRIE data. This advice indicated that the CAPRIE trial results were the most appropriate basis for estimating long-term risk probabilities in the follow-up of ACS patients treated with PCI in the UK. • **Annual cycles:** The AG's model involves annual cycles for 39 yrs beyond the index PCI event. This cycle length was adopted for convenience, recognizing that it risks some inaccuracy in the number events occurring each yr. In the TA210 model individual patients may suffer multiple events in any yr, and each contributes to modifying the future risk profile of the patient. By contrast, the AG's model assumes that such events occur to separate individuals, and the risk profile is only updated annually. The extent of any inaccuracy introduced as a result of this change is unclear, and could, in principle, either increase or decrease overall event rates. However, as the same risks apply to both prasugrel and CLOPI patients it is unlikely that incremental costs and outcomes will be affected. • **Time horizon:** The maximum time horizon (40 yrs) of the AG's model could be considered to be excessively long, since the duration of the primary trial (TRITON-TIMI 38) was no more than 15 months, and the CAPRIE trial, which was used for populating the risk parameters, had only 3 yrs of follow-up data. In particular, the stability of the risk

Author, year	Model key assumptions in bullet points[O]
	equations used for advancing age might be called into question. With this in mind, model results are reported at various time points from 5 yrs, which represents a more cautious extrapolation. Follow-up secondary prophylaxis is limited to low-dose ASA in the model, partly for convenience, but also to avoid the possibility of obscuring the primary comparison between prasugrel and CLOPI use for the primary PCI. Similarly, no attempt has been made to incorporate various other aspects of guidance relating to post-stroke and post-MI care (including surgery, and other medication options). • **Secondary prophylaxis:** No attempt has been made to incorporate the adverse effects of ASA therapy, or the possibility of non-adherence to continuing ASA treatment. In addition, the risk of bleeding events associated with long-term prophylaxis was not considered. For all these issues, patients in both arms will be similarly affected throughout follow-up, so that the net effect on incremental differences should be marginal. • **Stroke-related disability:** In line with the TA210 model, the representation of stroke-related disability has been limited to two categories based on the modified Rankin Scale. The available data to calibrate the model with greater precision are not available, and this approximation works well with a natural distinction between mild and severe dependency.

AE: Adverse event; AG: Assessment group; ASA: Aspirin; ATTC: Antithrombotic Trialists' Collaboration; BID: Twice per day; CLOP: Clopidogrel; CV: Cardiovascular; ERG: Evidence review group; GP: General practitioner; HRQoL: Health related quality of life; HS/ICH: HS/ICH: Haemorrhagic stroke/ Intracranial haemorrhage; ICH: Intracranial haemorrhage; IS: ischaemic stroke; MI: Myocardial infarction; NICE: National Institute for Health and Clinical Excellence; PCI: Percutaneous coronary intervention; RR: Relative risk; RRR: Relative risk reduction; ST-APT: Standard antiplatelet therapy; TICA: Ticagrelor; TIMI: Thrombolysis In Myocardial Infarction; UK: United Kingdom; yr: year; yrs: Years

[O] Only assumptions potential relevant to our decision area were extracted

Table 5. Outcomes tables of relevant economic evaluations

Author, year	QALYs (LYG)	Costs	ICER
Current submission [ID813]			
AstraZeneca, 2016	• Low-dose ASA: 9.2034 • TICA 60 mg BID + low-dose ASA: 9.2742 • Incremental: 0.0708 (0.0909)	• Low-dose ASA: £13,019 • TICA 60 mg BID + low-dose ASA: £14,443 • Incremental cost: £1,434	£20,098[¥]
Economic studies (n=5)			
Banerjee S et al., 2012(2)	**ACS:** • ASA: 6.070 • CLOPI: 6.032 • CLOPI + ASA: 6.095	**ACS:** • ASA: $36,498 • CLOPI: $37,153 • CLOPI + ASA: $37,230	**ACS:** **CLOP, dominated by ASA:** • CLOPI + ASA vs ASA, $29,604
Begum N et al., 2016 (3)	• Rivaroxaban + ST-APT: 10.86 • ST-APT alone: 10.72	• Rivaroxaban + ST-APT: €63,562 • ST-APT alone: €64,433	€8,045
Chen J et al., 2009 (4)	**Additional LYG with CLOPI:** • Overall population: 0.072 • Patients with prior MI: 0.130	**Mean total cost per patient (overall):** • CLOPI + ASA, $13,743 • ASA monotherapy, $11,136 **Cost difference:** • Overall population, $2,607 • Patients with prior MI, $2,662	**ICER/LYG:** • Overall population, $36,343 • Patients with prior MI, $20,413
Chen J et al., 2011 (5)	**Additional QALYs with CLOPI:** • Overall population: 0.07 (0.057)[a] • Patients with prior MI: NR (0.106)	**Mean total cost per patient (overall):** • CLOPI + ASA: $7,075 • ASA monotherapy: $5,587 **Cost difference:** • Overall population: $1,488 • Patients with prior MI: $1,297	**ICER/LYG:** • Overall population: $25,969 • Patients with prior MI: $12,265 **ICER/QALY gained:** • Overall population: $21,549 • Patients with prior MI: NR
Gaspoz JM et al., 2002 (6)	**QALYs gained from 2003 to 2027:** • Scenario of zero utilization (A): 115,535,000 • Scenario under current use of ASA (85%) (B): 121,768,000 • Scenario of ASA being given to all eligible patients (C): 122,450,000	Total cost from 2003 to 2027: • Scenario of zero utilization (A): $1,797,000 • Scenario under current use of ASA (85%) (B): $1,867,000 • Scenario of ASA being given to all eligible patients (C): $1,874,000	**ICER/QALY**: • B vs A, $11,000 • C vs B, $11,000 • D vs C, $31,000 • E vs D, $250,000 • F vs D, $130,000

Author, year	QALYs (LYG)	Costs	ICER
	• Scenario of ASA for all eligible patients and CLOPI for the remaining (5.7%) (D): 122,906,000 • Scenario of CLOPI for all patients (E): 123,538,000 • Scenario of combination of CLOPI for all patients plus ASA for eligible patients (F): 124,343,000	• Scenario of ASA for all eligible patients and CLOPI for the remaining (5.7%) (D): $1,888,000 • Scenario of CLOPI for all patients (E): $2,045,000 • Scenario of combination of CLOPI for all patients + ASA for eligible patients (F): $2,071,000	
Past NICE submissions			
TA335, 2015 (7, 8)	• Rivaroxaban plus ASA with or without CLOPI: 9.56 • ASA with or without CLOPI: 9.44 **LYG:** • Rivaroxaban plus ASA with or without CLOPI: 11.48 • ASA with or without CLOPI: 11.34	• Rivaroxaban+ASA with or without CLOPI: £14,768 • ASA with or without CLOPI: £14,004	£6,203
TA210, 2010 (9, 10)	**History of MI:** • ASA: 6.7 (7.55) • CLOPI: 6.83 (7.7)	**History of MI:** • ASA: £6,349 • CLOPI: £8,992	**History of MI:** £20,662
TA182, 2009 (11, 12)	• CLOPI: 12.701 (16.365) • Prasugrel: 12.728 (16.400)	• CLOPI: £6,299 • Prasugrel: £6,468	£6,382
TA236, 2011 (13)	**LYG:** • CLOPI: 7.602 • TICA: 7.736	• CLOPI: £13,737 • TICA: £14,135	£3,075
TA317, 2014 (12)	• CLOPI: 10.97 (14.14) • Prasugrel: 11.02 (14.20)	• CLOPI: £5,867 • Prasugrel: £6,463	£11,796

ACS: Acute coronary syndrome; ASA: Aspirin; BID: Twice a day; CLOPI: Clopidogrel; ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; Lys: Life years; mg: Milligramm; MI: Myocardial infarction; NICE: National Institute of Health and Clinical Excellence; NR: Not reported; ST-APT: Standard antiplatelet therapy; TICA: Ticagrelor

[¥] The corresponding 'simple analysis' overestimates the ICER for this population by 21% (ICER of £24,378).

[a] These results were extracted as reported by the article although most commonly QALYs do not exceed life years gained.

d. Please provide a comparison of the number of MI's, strokes, other CV events, and survival with an external, preferably UK, database (e.g. http://www.isdscotland.org/Health-Topics/, https://indicators.hscic.gov.uk/webview/, https://www.ucl.ac.uk/nicor/audits/minap).

We thank the ERG for providing the links to potential data sources to answer this question. However the publically available data in each registry is not appropriate in this instance as it is necessary to use event rates in a very specific population equating to the base case cohort (i.e. patients who had an MI <2 years ago and at high risk of further atherothrombotic events). Although it is possible to make a bespoke request for data from these sources, any results would not normally be available in the timeframe required by the NICE process (i.e. 10 working days from receipt of clarification questions). Furthermore, the endpoints recorded in these sources are not aligned to all the endpoints requested (e.g. CV death unless associated with a hospitalisation).

e. In figure 67 (page 193) of the company submission (1), the company compares the survival probabilities by age as modelled in the cost-effectiveness analysis with the survival probabilities according to UK life tables. Please provide the exact reference for the UK life tables (with an active web link).

Life Expectancy at Birth and at Age 65 by Local Areas in England and Wales. Office of National Statistics, London (2015). Available at: http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/lifeexpectancyatbirthandatage65bylocalareasinenglandandwalesreferencetable1

Scenario analysis

An overview of the scenario analyses that follow is provided in Table 6.

Table 6: Overview of scenario analyses

Scenario Analysis	Comments
Scenarios included in the original submission	
A. inclusion of an initiation cost	Scenarios conducted within the original submission, re-run here in the context of having revised the base case in the following areas: • Inpatient costs based on NHS reference costs where possible • Functional form for AEs selected by AIC • Including gout as AE
B. using costs and utilities from the rivaroxaban technology appraisal	
C. using utilities derived from the systematic review of HRQoL	
D. using PEGASUS-TIMI 54 trial mortality	
E. including subsequent treatment effects	
F. a two-way analysis assessing the 'no event' maintenance cost	
G. a one-way analysis assessing the impact of starting age	
New scenarios responding to calrification questions	
H. ticagrelor 60mg treatment, starting 12 months after a subsequent MI	Described in clarification question B4.
I. ticagrelor 90mg treatment, 1-12 months after a subsequent MI	Described in clarification question B5.
J. impact of not including the treatment effect variable for "non-fatal stroke"	Described in clarification question B8.
K. Baseline utilities informed by PEGASUS-TIMI 54 – capped at 1	Described in clarification question B12.
L. Baseline utilities informed by PEGASUS-TIMI 54 – uncapped	Described in clarification question B12.
M. Baseline utilities informed by PEGASUS-TIMI 54 – gamma model (using a log-link)	Described in clarification question B12.
N. Tunnel state costs as per original submission	Described in clarification question B14.
O. Inpatient costing - lower quartile NHS ref cost for efficacy events, upper quartile for AEs	Described in clarification question B14.

Probabilistic analyses were provided for base case and all subgroups within the response to the clarification questions, for pragmatic purposes given the number of scenarios requested, we provide deterministic analyses only using complete analysis in nearly all cases.

Results of structural sensitivity analysis

A. Initiation cost

For methods, please see original submission document pages 303-304. Key input parameter values and results of the analysis are presented in Table 7.

Table 7: Initiation cost scenario analyses (complete analysis)

Scenario	Initiation by GP (%)		Initiation by cardiologist (%)		Incremental costs	ICER*
	ASA	Tica 60mg BID + ASA	ASA	Tica 60mg BID + ASA		
1	15	15	0	0	£1,432	£20,636
2	15	100	0	0	£1,469	£21,168
3	15	15	0	85	£1,535	£22,122
4	0	0	0	100	£1,554	£22,384

*incremental QALY in all analyses remained 0.0694

As shown, even if all patients were initiated to ticagrelor 60mg BID did so via a cardiologist, with no initation cost associated to the comparator, the ICER would still be within the cost-effectiveness threshold defined by NICE.

B. Rivaroxaban technology appraisal

For methods, please see original submission document pages 304-306. Results of the analysis are presented in Table 8.

Table 8: Rivaroxaban TA cost and utilities scenario analyses (complete analysis)

Scenario	Costs	Utilities	Incremental costs	Incremental QALYs	ICER
1	X	-	£1,509	0.0694	£21,742
2	-	X	£1,432	0.0685	£20,904
3	X	X	£1,509	0.0685	£22,024

All ICERs are within the range deemed acceptable by NICE, illustrating that ticagrelor 60 mg BID + low-dose ASA is cost-effective with a different set of assumptions for costs and utilities.

C. HRQoL systematic review data

For methods, please see original submission document pages 307-308. Results of the analysis are presented in Table 9.

Table 9: HRQL systematic review data scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,432	0.0701	£20,418

This demonstrates that even though the disutility for these events was increased compared to the base case, the impact on the ICER was minimal.

D. PEGASUS-TIMI 54 trial mortality

For methods, please see original submission document page 308. Results of the analysis are presented in Table 10.

Table 10: PEGASUS-TIMI 54 trial mortality scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,476	0.0990	£14,917

As demonstrated, using this approach decreases the ICER to £14,917. However, the 'simple analysis' (chosen in order to view the Markov trace) shows that in this case over 35% of patients are still alive at 100 years of age (in both arms). This demonstrates that the base-case assumption, using the UK life tables, was the more appropriate.

E. Subsequent events treatment effects

For methods, please see original submission document page 309. Results of the analysis are presented in Table 11.

Table 11: Subsequent events treatment effects scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,451	0.0752	£19,292

In this analysis ticagrelor 60 mg BID + low-dose ASA accrues an additional 0.0752 QALY at an incremental cost of £1,451, generating an ICER of £19,292. This demonstrates that the base case approach of not applying a treatment effect for subsequent events, was the more conservative.

F. 'No event' maintenance cost

For methods, please see original submission document page 309. Results of the analysis are presented in Table 12. It should be noted that this analysis was undertaken using the

‘simple analysis’ which overstates the ICER by approximately 22%. Assuming this overstatement would apply to all the analyses here, if this analysis had been undertaken using the ‘complete analysis’ the ICERs would have ranged from approximately £17,289 to £23,011, indicating cost-effectiveness over plausible combinations of no event and long term post non-fatal MI outpatient and maintenance cost per cycle.

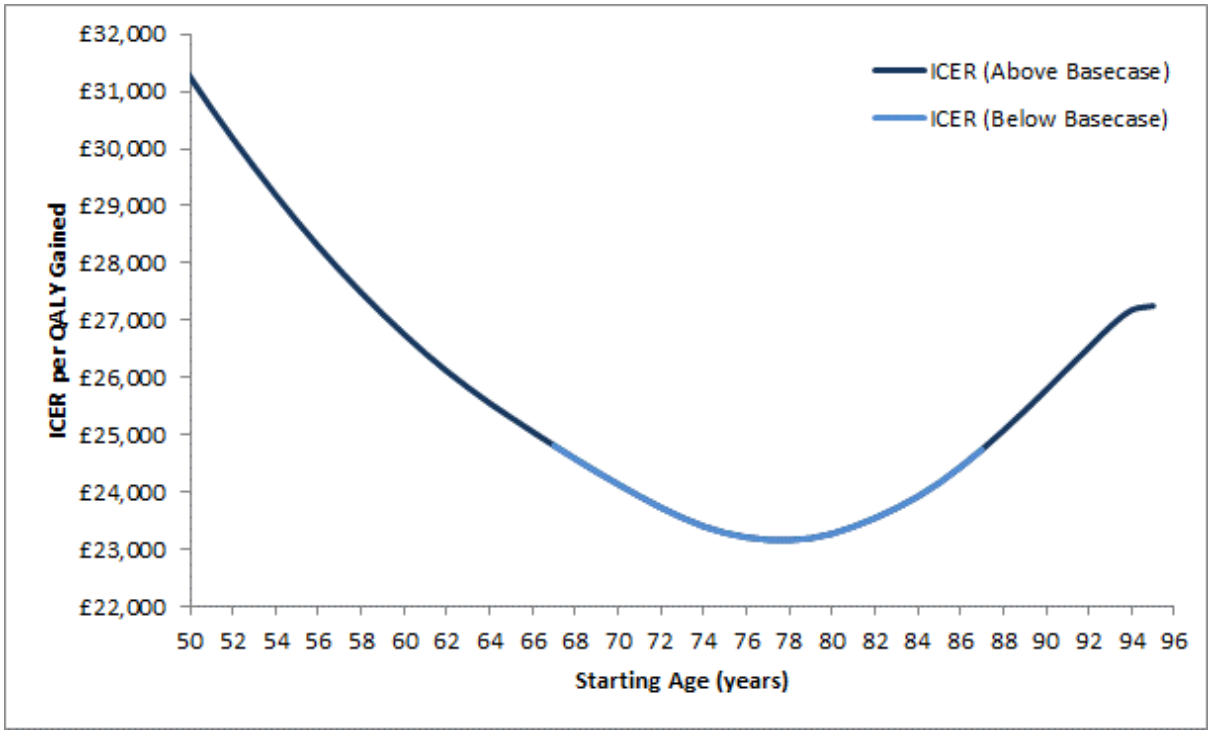
Table 12: No event and non-fatal MI outpatient and maintenance cost scenario analyses (simple analysis)

		Outpatient and maintenance cost per patient: no event					
		£0	**£100**	**£200**	**£300**	**£400**	**£500**
Outpatient and maintenance cost per patient: non-fatal MI (Stable phase, 12+ months)	**£0**	£24,014	£25,111	£26,209	£27,306	£28,403	£29,501
	£100	£23,644	£24,741	£25,839	£26,936	£28,034	£29,131
	£200	£23,274	£24,372	£25,469	£26,566	£27,664	£28,761
	£300	£22,905	£24,002	£25,099	£26,197	£27,294	£28,392
	£400	£22,535	£23,632	£24,730	£25,827	£26,924	£28,022
	£500	£22,165	£23,263	£24,360	£25,457	£26,555	£27,652

G. Impact of starting age

The mean age of patients with MI <2 years ago entering the PEGASUS-TIMI 54 trial was 65.3 years. The 'real world' patient in England may be some years older. The mean age of patients within the observational study as presented at section 4.11 of the original submission was 77.0. Therefore, using the 'simple analysis' methodology, we assessed the impact on starting age on the ICER, with findings presented in Figure 1.

Figure 1: Impact of starting age on ICER (simple analysis)



* This analysis considers patients of 50 years or older (as per the inclusion criteria specified in the PEGASUS TIMI-54 trial). There was one patient included in the analysis aged 49 years, and this starting age generated an ICER of £31,821, using the 'simple analysis'.

Patients aged 50-52 years yield ICERs >£30,000, however these are generated using the 'simple analysis', which for base case overstated the ICER by 22%. Assuming this overstatement would apply to all analyses here, if this analysis had been undertaken using the 'complete analysis' the ICER for a 50 year old patient would be approximately £24,376.

Those aged between 66 and 88 years had an ICER below that of the base-case ICER, generated with an average cohort age of 65.3 years. The ICER for a patient with starting age 77.0 years is approximately £2,000 less than that of the base case.

H. Ticagrelor 60mg treatment, starting 12 months after a subsequent MI

This scenario analysis relates to clarification question B4.

As described within the response to B4, directly addressing the request would bring significant structural implications for the model, which was not feasible in the time available. To illustrate the direction of change, the scenario analysis presented here is based upon increasing the cost associated to the post non-fatal MI (12+ months) health state by £178.06 per cycle (the cost of ticagrelor 60mg BID per 3 months). This is similar to assuming ticagrelor 60mg BID is given for remaining lifetime from 12 months following an MI event. As such, this scenario analysis overstates the impact on the ICER opposite the requested analysis but is illustrative of directional impact. Results are provided in Table 13.

Table 13: Ticagrelor 60mg treatment, starting 12 months after a subsequent MI scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,402	0.0694	£20,202

This analysis serves to illustrate that employing the cost of ticagrelor 60mg in the model, in years 2-4 following the occurrence of a non-fatal MI, would reduce the ICER by a small amount vs. base case.

I. Ticagrelor 90mg treatment, 1-12 months after a subsequent MI

This scenario analysis relates to clarification question B5.

In this scenario, the cost of ticagrelor 90mg, rather than clopidogrel, was applied for the 12 months following the occurrence of a non-fatal MI in the model. Results are provided in Table 14.

Table 14: Ticagrelor 90mg treatment, 1-12 months after a subsequent MI scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,429	0.0694	£20,585

This analysis shows that employing the cost of ticagrelor 90mg in the model, for the 12 months following a non-fatal MI, reduces the ICER marginally vs. base case.

J. Not including the treatment effect variable for "non-fatal stroke"

This scenario analysis relates to clarification question B8.

As requested an additional sensitivity analysis has been undertaken to assess the removal of the treatment effect for first non-fatal stroke, by setting the coefficient for ticagrelor 60mg to zero in the first non-fatal stroke risk equation. Results are provided in Table 15.

Table 15: Not including the treatment effect variable for "non-fatal stroke" scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,487	0.0606	£24,533

It should be noted that a consequence of the removal of the treatment effect for first non-fatal stroke is to underestimate the treatment effect for the composite primary endpoint. Thus, AstraZeneca believes that it is not appropriate to remove the treatment effect for first non-fatal stroke in the base case.

K. Baseline utilities informed by PEGASUS-TIMI 54 – capped at 1

This scenario analysis relates to clarification question B12.

Baseline utilities for the base case reflect UK population norms. The model also includes PEGASUS-TIMI 54 derived baseline utilities (for derivation methods, please see original submission document pages 263-265), for the purposes of scenario analysis. Results are provided in Table 16.

Table 16: Baseline utilities informed by PEGASUS-TIMI 54 – capped at 1 scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,432	0.0744	£19,253

Using PEGASUS-TIMI 54 derived baseline utilities, capped at 1, reduces the ICER vs. base case by approximately £1,400.

L. Baseline utilities informed by PEGASUS-TIMI 54 – uncapped

This scenario analysis relates to clarification question B12.

This analysis mirrors scenario K. expect that baseline utilities are allowed to exceed 1. This impacted only 37 patients (0.43%) within the MI <2 years ago population. Results are provided in Table 17.

Table 17: Baseline utilities informed by PEGASUS-TIMI 54 – uncapped scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,432	0.0744	£19,253

The results are the same as those for scenario K. on account of the small number of patients impacted.

M. Baseline utilities informed by PEGASUS-TIMI 54 – gamma model (using a log-link)

This scenario analysis relates to clarification question B12.

Methods for this scenario analysis are described with the response to clarification question B12. Results are provided in Table 18.

Table 18: Baseline utilities informed by PEGASUS-TIMI 54 – gamma model (using a log-link) scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,432	0.0725	£19,749

The use of a gamma model (using a log-link) to inform PEGASUS-TIMI 54-derived baseline utilities resulted in a slightly higher ICER than those for scenarios K. and L. (and an ICER slightly lower than base case, where baseline utilities are informed by UK population norms).

N. Tunnel state costs as per original submission

This scenario analysis relates to clarification question B14.

With the introduction of NHS reference costs to inform inpatient costs in the revised base case, costs associated to post non-fatal MI and post non-fatal stroke tunnel states were adjusted, in order to arrive at the same first year post-event costs as in the original base case (and correspond with the first year post-event costs for the ERG-derived model in TA317, after inflation). In this scenario, the adjustment made to tunnel state costs is removed, such that they reflect the original base case. Results can be seen in Table 19.

Table 19: Tunnel state costs as per original submission scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,435	0.0694	£20,680

Removing the adjustment made to tunnel state costs increased the ICER marginally.

O. Inpatient costing - lower quartile NHS ref cost for efficacy events, upper quartile for AEs

This scenario analysis relates to clarification question B14.

This analysis can be thought of as representing a 'worst case' for ticagrelor 60mg BID + ASA with respect to NHS reference costs for inpatient events. Lower quartile costs are used for efficacy events and upper quartile costs for adverse events. Methods regarding the derivation of lower and upper quartile costs can be found within the response to clarification question B14. The resultant cost inputs can be seen in Table 20.

Table 20: Cost inputs for Scenario O.

Resource use	Value in revised base case	Value in Scenario O.	Comments
Inpatient			
Non-fatal MI	£4,593.13	£3,520.53	NHS reference costs lower quartile value
Non-fatal stroke	£3,239.44	£2,223.49	NHS reference costs lower quartile value
Fatal events (CAD and non-CAD)	£2,497.83	£2,497.83	Unchanged
'No event'	£2,497.83	£2,497.83	
Outpatient and maintenance			
Post non-fatal MI (0-3 months)	£720.56	£720.56	Unchanged
Post non-fatal MI (3-6 months)	£540.42	£540.42	
Post non-fatal MI (6-9 months)	£360.28	£360.28	
Post non-fatal MI (9-12 months)	£180.14	£180.14	
Post non-fatal MI (12+ months, every cycle)	£160.31	£160.31	
Post non-fatal stroke (0-3 months)	£2,000.77	£2,000.77	
Post non-fatal stroke (3-6 months)	£1,714.94	£1,714.94	
Post non-fatal stroke (6-9 months)	£1,143.40	£1,143.40	

Post non-fatal stroke (9-12 months)	£857.47	£857.47	
Post non-fatal stroke (12+ months, every cycle)	£689.71	£689.71	
'No event' (every cycle)	£160.31	£160.31	
Adverse Events			
Grade 3-4 Dyspnoea	£732.98	£846.10	NHS reference costs upper quartile value
Major TIMI bleed	£2,824.81	£3,285.13	NHS reference costs upper quartile value
Minor TIMI bleed	£942.19	£1,049.82	NHS reference costs upper quartile value

Results for the scenario analysis are provided in Table 21.

Table 21: Inpatient costing - lower quartile NHS ref cost for efficacy events, upper quartile for AEs scenario analysis (complete analysis)

Incremental costs	Incremental QALYs	ICER
£1,448	0.0694	£20,860

Using lower quartile NHS reference costs for efficacy events and upper quartile costs for adverse events increased the ICER but only marginally.

References

1. AstraZeneca. Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]: AstraZeneca evidence submission to National Institute of Health and Clinical Excellence. Single technology appraisal (STA). 2016.
2. Banerjee S, Brown A, McGahan L, Asakawa K, Hutton B, Clark M, et al. Clopidogrel versus Other Antiplatelet Agents for Secondary Prevention of Vascular Events in Adults with Acute Coronary Syndrome or Peripheral Vascular Disease: Clinical and Cost-Effectiveness Analyses. CADTH technology overviews. 2012;2(1):e2102.
3. Begum N, Stephens S, Schoeman O, Fraschke A, Kirsch B, Briere JB, et al. Cost-effectiveness Analysis of Rivaroxaban in the Secondary Prevention of Acute Coronary Syndromes in Sweden. Cardiology and therapy. 2015;4(2):131-53.
4. Chen J, Bhatt DL, Dunn ES, Shi C, Caro JJ, Mahoney EM, et al. Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone for secondary prevention of cardiovascular events: results from the CHARISMA trial. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2009;12(6):872-9.
5. Chen J, Shi C, Mahoney EM, Dunn ES, Rinfret S, Caro JJ, et al. Economic evaluation of clopidogrel plus aspirin for secondary prevention of cardiovascular events in Canada for patients with established cardiovascular disease: Results from the CHARISMA trial. The Canadian journal of cardiology. 2011;27(2):222-31.
6. Gaspoz JM, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink MG, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. The New England journal of medicine. 2002;346(23):1800-6.
7. (NICE) NIfHaCE. TA335: Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. 2015.
8. Pandor A, Pollard D, Chico T, Henderson R, Stevenson M. Rivaroxaban for Preventing Atherothrombotic Events in People with Acute Coronary Syndrome and Elevated Cardiac Biomarkers: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. PharmacoEconomics. 2015.
9. (NICE) NIfHaCE. TA210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events 2010. Available from: https://www.nice.org.uk/guidance/ta210.
10. Greenhalgh J, Bagust A, Boland A, Martin Saborido C, Oyee J, Blundell M, et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis. Health technology assessment (Winchester, England). 2011;15(31):1-178.
11. (NICE) NIfHaCE. TA182: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. 2009.
12. Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Fleeman N, et al. Prasugrel (Efient(R)) with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182): systematic review and economic analysis. Health technology assessment (Winchester, England). 2015;19(29):1-130.
13. (NICE) NIfHaCE. TA236: Ticagrelor for the treatment of acute coronary syndromes. Manufacturer's submission 2011. Available from: https://www.nice.org.uk/guidance/ta236/chapter/3-the-manufacturers-submission.

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Single technology appraisal

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Dear Astrazeneca

The appraisal lead team and the technical team at NICE have looked at the submission received on 11 April 2016 from Astrazeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The lead team and the technical team at NICE will be addressing these issues at the appraisal meeting. .

Please provide your written response to the clarification questions by **5pm** on Tuesday 5 July 2016. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Wendy Gidman, Technical Lead wendy.gidman@nice.org.uk. Any procedural questions should be addressed to Stephanie Yates, Project Manager stephanie.yates@nice.org.uk.

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Analysis

A1. Priority request: Please can you clarify the naming and flow of analysed populations and subpopulations used throughout all sections of the company submission. Currently populations are inconsistently defined and it is unclear which patient populations are included in effectiveness and cost effectiveness analyses. Specifically clarity is required in relation to the terms full analysis, 'label' population, base case, intention to treat analysis and on treatment analysis. Flow diagrams and supporting tables defining populations and justifying inclusion in analyses would be helpful.

Section B: Clarification on cost-effectiveness data

Analysis

A2. Priority request: Please can you clarify the difference between the EMA indicated 'label population' (n=10,779) and the MI <2 years ago (n=8,664). Furthermore can you explain which population was included in economic models and justify this decision. On page 325 of the company submission it states that,"It is expected that the predictive accuracy of modelled events compared to observed events is comparable in patients with a qualifying naming and flow of analysed populations and subpopulations". Please can you expand on this comment and justify this decision.

- Please can you clarify the naming and flow of analysed populations and subpopulations used throughout all sections of the company submission. Currently populations are inconsistently defined and it is unclear which patient populations are included in effectiveness and cost effectiveness analyses. Specifically clarity is required in relation to the terms full analysis, 'label' population, base case, intention to treat analysis and on treatment analysis. Flow diagrams and supporting tables defining populations and justifying inclusion in analyses would be helpful.

A table summarising the 3 main population types and 2 main types of analyses is provided.

Term	Definition	First reference	Use
Population type			
full analysis (or study) population	All patients who were randomised to study drug were included irrespective of their protocol adherence and continued participation in the study. All patients had experienced an MI 1-3 years prior to study entry	P 19 Also see CONSORT diagram in Fig 6.	Clinical effectiveness
'label' population	Post-hoc subgroup of patients within PEGASUS-TIMI 54 who conform to the population defined in the license from EMA: i.e. experienced an MI <2 years previously or within 1 year of previous ADP inhibitor treatment	P 177	Cost effectiveness
base case	Patients within the PEGASUS-TIMI 54 study who experienced an MI <2 years previously. These patients are: • pre-specified and stratified subgroup of the full analysis population and • within the limits of the label population.	P 21	Clinical effectiveness & Cost effectiveness
Analysis type			
intention to treat analysis	Patients analysed according to their randomised study drug irrespective of whether the event occurred before or following discontinuation	P 92	primary analysis of efficacy endpoints
on treatment analysis	defined as on or after the date of first dose and up to and including 7 days following the date of last dose of study drug	P92	primary analysis of safety endpoints

- Please can you clarify the difference between the EMA indicated 'label population' (n=10,779) and the MI <2 years ago (n=8,664). Furthermore can you explain which population was included in economic models and justify this decision? On page 325 of the company submission it states, It is expected that the predictive accuracy of modelled events compared to observed events is comparable in patients with a qualifying naming and flow of analysed populations and subpopulations". Please can you expand on this comment and justify this decision

The 'label population' (n=10,779), consists of patients with MI <2 years ago or previous ADP inhibitor therapy <1 year ago. Of these patients, n=2,115 had ADP inhibitor therapy <1 year ago but MI ≥2 years ago. These patients are not considered representative of UK clinical practice, where ADP inhibitor therapy tends to be

stopped at 1 year following MI. For this reason the company's base case is focussed on patients with MI <2 years ago (n=8,664).

Regarding the economic model, for the 'individual profile-based' cohort simulation (complete analysis, deterministic), all 10,779 patient profiles from the label population go through the model individually. Thereafter the model reports results (costs, QALYs, ICER etc.) corresponding to the population of interest as selected by the user, which for the company's base case is the MI <2 years ago population (Figure 1). This approach produces exactly the same results as if only patients with MI <2 years ago been run through the model.

On page 325 of the company submission it is stated that "The modelled events compared to the observed events are shown for patients included in the EMA indicated 'label population' (n=10,779). It is expected that the predictive accuracy of modelled events compared to observed events is comparable in patients with a qualifying MI <2 years ago (n=8,664)." This statement is based upon the fact that ~80% of the label population is patients with MI <2 years ago.

Within the company's submission document, the validation of modelled vs. observed events was conducted in the label population, rather than the base case MI <2 years ago population, due to availability of data at the time of the original submission.

We are now in a position to provide the validation of modelled vs. observed events in the MI <2 years ago population. Modelled events have been derived using the ERG's adapted model and base case assumptions (i.e. those stated on page 141 of the ERG's report). Table 1 reports results of the validation based on both

- the company's preferred approach
    - where modelled events are derived using the deterministic 'individual profile-based' cohort simulation (complete analysis)
- the ERG's preferred approach,
    - where modelled events are derived using the probabilistic average profile-based' cohort simulation (simple analysis)

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Figure 1: Simplified schematic diagram of the 2 approaches in the cost effectiveness model.

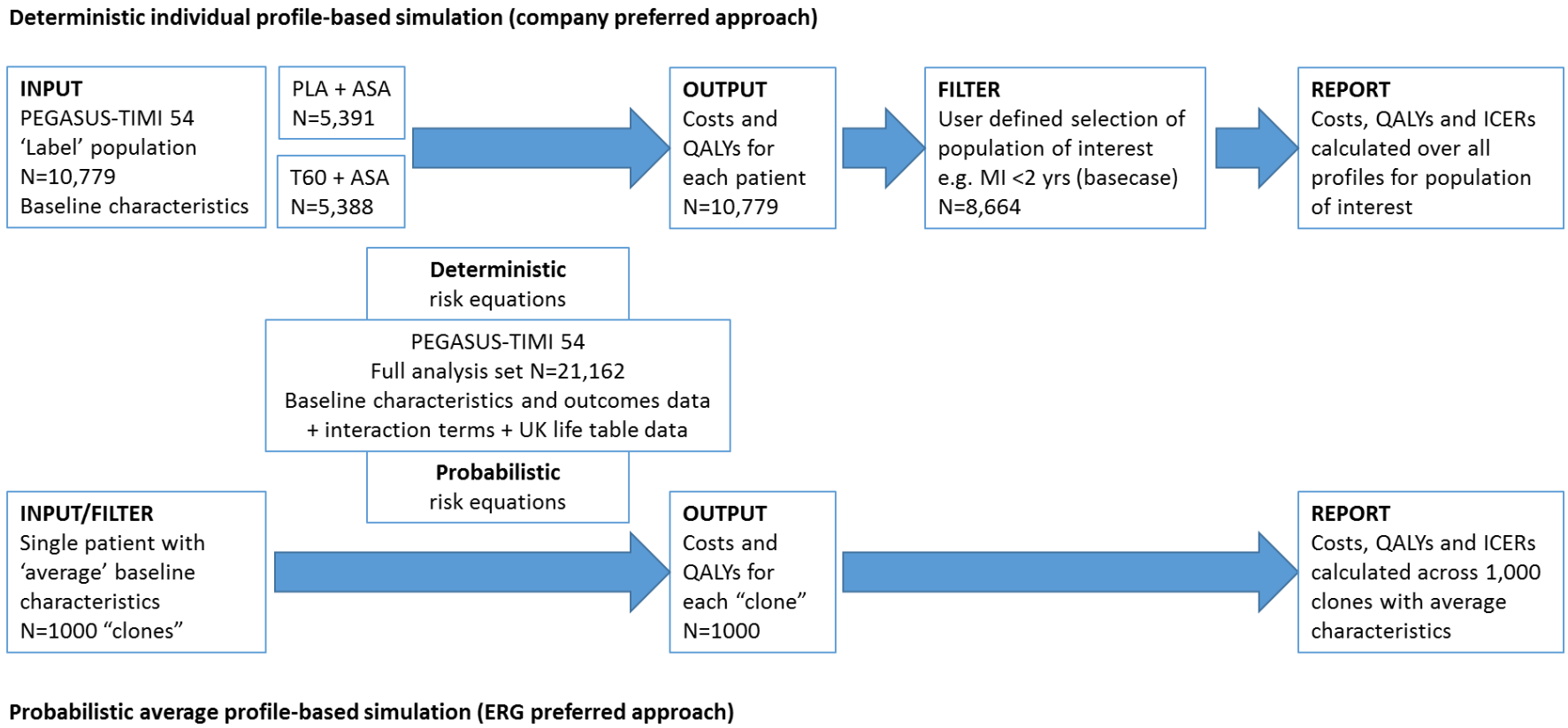

Table 1: Comparison of the number of observed vs. modelled events, during a period of the PEGASUS-TIMI 54 (MI<2 years ago population)

	Ticagrelor 60 mg BID + low-dose ASA	Low-dose ASA	Modelled vs. observed	Modelled vs. observed (%)

	Observed	Modelled – Company's preferred	Modelled - ERG's preferred	Observed	Modelled – Company's preferred	Modelled - ERG's preferred	Ticagrelor 60 mg ASA- Company's preferred	Ticagrelor 60 mg ASA - ERG's preferred	Low-dose ASA - Company's preferred	Low-dose ASA - ERG's preferred	Ticagrelor 60 mg ASA- Company's preferred	Ticagrelor 60 mg ASA - ERG's preferred	Low-dose ASA - Company's preferred	Low-dose ASA - ERG's preferred
First event														
Non-fatal MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-4	-29	-8	-36	-2%	-17%	-4%	-18%
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+3	-5	-2	-12	+7%	-12%	-3%	-20%
Fatal CV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+1	-27	-1	-38	+1%	-32%	-1%	-34%
Composite outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	-61	-11	-86	0%	-21%	-3%	-23%
Other fatal event*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-7	-19	-3	-16	-11%	-31%	-5%	-27%
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-7	-80	-14	-102	-2%	-23%	-3%	-24%
Subsequent event														
Non-fatal MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-6	-19	+2	-13	-18%	-58%	+6%	-42%
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	-3	-2	-6	0%	-43%	-18%	-55%
Fatal CV events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+7	-4	-4	-18	+70%	-40%	-15%	-69%
Other fatal events*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+2	-5	+4	-4	+20%	-50%	+36%	-36%
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+3	-31	0	-41	+5%	-52%	0%	-52%
Adverse event														
TIMI Major bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+5	-5	+2	-2	+9%	-9%	+8%	-8%
TIMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2	-10	-2	-4	-6%	-29%	-15%	-31%

	Ticagrelor 60 mg BID + low-dose ASA			Low-dose ASA			Modelled vs. observed				Modelled vs. observed (%)			
	Observed	Modelled – Company's preferred	Modelled - ERG's preferred	Observed	Modelled – Company's preferred	Modelled - ERG's preferred	Ticagrelor 60 mg ASA- Company's preferred	Ticagrelor 60 mg ASA - ERG's preferred	Low-dose ASA - Company's preferred	Low-dose ASA - ERG's preferred	Ticagrelor 60 mg ASA- Company's preferred	Ticagrelor 60 mg ASA - ERG's preferred	Low-dose ASA - Company's preferred	Low-dose ASA - ERG's preferred
Minor bleeds														
Dyspnoea grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-4	-8	-1	-2	-25%	-50%	-25%	-50%
Dyspnoea grade 1-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	+69	+55	-21	-38	+11%	+9%	-8%	-15%

Footnotes:

Company's preferred: Deterministic 'individual profile-based' cohort simulation (complete analysis)

ERG's preferred: Probabilistic 'average profile-based' cohort simulation (simple analysis)

*Info for other fatal events greyed out as this only applies in the case of the "PEGASUS-TIMI 54 trial mortality" scenario. Base case informed by cause eliminated life tables

ASA = acetylsalicylic acid; BID = twice daily; CV = cardiovascular; ERG = Evidence Review Group; mg = milligram; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction

Table 1 illustrates that:

1. The company's preferred approach leads to a significantly more accurate prediction of observed trial events than the ERG's preferred approach
2. The bias in the model against ticagrelor is more pronounced in the case of the ERG's preferred approach, as compared with the company's preferred approach, leading to further bias in (i.e. overstatement of) the ICER

To illustrate point 2., we focus on fatal CV events, which play a pivotal role in the accrual of QALYs and therefore in determining the ICER: Under the company's preferred approach, the model under predicts the treatment effect of ticagrelor by 2 first events (+1 minus -1) and 11 subsequent events (+7 minus -4), the latter stemming from the base case assuming no subsequent treatment effects. Thus the total under prediction of treatment effect is 13 events. Under the ERG's preferred approach, the model under predicts ticagrelor treatment effect by 11 first events (-27 minus -38) and 14 subsequent events (-4 minus -18), a total under prediction of treatment effect of 25 events.

Thus we reiterate the company's position that the most appropriate method of calculating the ICER is via the deterministic 'individual profile-based' cohort simulation, since this captures the non-linearity in the model associated to heterogeneity in patient baseline characteristics. Below we provide an amended version of table 5.37 as presented within the ERG's report (page 142), so as to accurately reflect the company base-case position. In table 5.37 below, the company base-case has been derived using the ERG's adapted model and the ERG's base case assumptions (those on page 141 of the ERG's report) but using the deterministic 'individual profile-based' cohort simulation.

Table 5.37: Deterministic company base-case ('individual profile-based' cohort simulation) and probabilistic ERG base-case ('average profile-based' cohort simulation)

	Ticagrelor 60 mg BID + low-dose ASA		**Low dose ASA**				
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔQALY**	**ΔCosts**	**ICER**
Company base-case	9.148	£12,985	9.078	£11,554	0.069	£1,431	£20,675
ERG base-case	9.768	£14,113	9.709	£12,674	0.058	£1,439	£24,711

ASA= acetylsalicylic acid; BID= twice per day; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

Erratum to Manufacturer's Submission for Ticagrelor for Secondary Prevention of Atherothrombotic Events after Myocardial Infarction

We have identified errors in the reporting of some coefficients used within the risk equations for the cost utility analysis model (and their corresponding p-values). Please note that the coefficients used in the model itself are correct (both deterministic and probabilistic applications). The errors lie in the way that some coefficients used in the model have been reported within the main submission and appendix documents. Please accept our apologies for these errors.

Here we provide corrected versions of the affected tables, with highlighting to show where values have been corrected. The ERG's report includes tables which reproduce the coefficients for the time to event risk equations, so we also include corrected versions of these tables (where affected).

Main Submission

Table 65: Time to first event: fatal CV

	Log–logistic	
Variable	**Coef.**	**p-value**
offlabel	0.3194	0.0417
Tic60	0.2032	0.0629
Tic90	0.2092	0.0548
t60offlabel	-0.4924	<0.0001
t90offlabel	-0.3977	<0.0001
sex	-0.3831	<0.0001
age	-0.0255	0.0088
weight	0.0115	0.0311
bmi	-0.0447	<0.0001
dmtype	-0.4135	<0.0001
MI_HIST	-0.4003	0.0020
cadmult	-0.2248	0.0072
smk_his2	-0.2262	<0.0001
stentany1	0.8067	0.0001
MEDTDDOS_n	-0.0044	0.0231
hyp	-0.3269	0.0683
chf	-0.6490	0.0938
SthAmerica	-0.4157	0.0373
histPAD	-0.6528	<0.0001
creatinine_cl	0.4503	0.0218
_cons	12.6182	<0.0001
shape	-0.2010	<0.0001

Shape variables take the following form: Log–Logistic – ln(gamma);

Table 74: Time to subsequent event (acute phase) – fatal other

	Weibull	
Variable	**Coef.**	**p-value**
smk_his1	0.1349	0.6480
sbpsup	0.0256	0.0040
dbpsup	-0.0418	0.0070
chf	0.7478	0.0150
NthAmerica	0.9957	0.0010
creatinine~l	-0.6756	0.0160
_cons	-7.1523	<0.001
shape	-0.5148	<0.001

Shape variables take the following form: Weibull – ln(p)

Table 79: Exponential hazard function: minor TIMI bleeds

Variable	Coef.	p-value	Lower 95% CI	Upper 95% CI
Tic90	1.3364	<0.0001	0.7684	1.9055
Tic60	1.1610	<0.0001	0.5878	1.7343
age	0.0520	<0.0001	0.0273	0.0767
weight	0.0110	0.0750	-0.0011	0.0230
cadmult	0.4700	0.0180	0.0802	0.8603
qev2rnd	0.0007	0.1080	-0.0002	0.0016
hyp	0.8027	0.0080	0.2059	1.4004
spbleed	1.2177	0.0080	0.3184	2.1168
creatinine_cl	-0.5819	0.0150	-1.0511	-0.1119
_cons	-17.2793	<0.0001	-19.6709	-14.8905

Table 81: Exponential hazard function: dyspnoea (grade 3–4)

Variable	Coef.	p-value	Lower 95% CI	Upper 95% CI
Tic90	1.3752	0.0070	0.3829	2.3674
Tic60	1.3742	0.0060	0.3852	2.3632
age	0.0632	0.0030	0.0220	0.1044
bmi	0.0634	0.0140	0.0129	0.1138
dmtype	0.8623	0.0120	0.1899	1.5347
smk_his1	0.7518	0.0250	0.0963	1.4072
anpect	0.5713	0.0720	-0.0507	1.1934
stroke	3.0161	0.0050	0.9174	5.1148
_cons	-21.0550	<0.0001	-24.4954	-17.6146

Table 83: Exponential hazard function: dyspnoea (grade 1–2)

Variable	Coef.	p-value	Lower 95% CI	Upper 95% CI
Tic90	0.8133	<0.0001	0.6673	0.9592
Tic60	0.6160	<0.0001	0.4661	0.7661
age	0.0123	<0.0001	0.0057	0.0190
bmi	0.0209	<0.0001	0.0099	0.0320
dmtype	-0.1007	0.1090	-0.2241	0.0229
smk_his1	0.1172	0.0370	0.0071	0.2276
stentany1	0.3551	<0.0001	0.1730	0.5373
qev2rnd	0.0001	0.7100	-0.0002	0.0003
MEDTDDOS_n	-0.0035	0.2200	-0.0092	0.0020
dbpsup	-0.0063	0.0330	-0.0120	-0.0005
cohdhist	0.1824	0.0030	0.0641	0.3010
Asia_Australia	0.3175	0.0010	0.1215	0.5142
NthAmerica	0.5953	<0.0001	0.4520	0.7381
SthAmerica	0.0297	0.7760	-0.1742	0.2340
tADP_30d12m	0.5305	<0.0001	0.3322	0.7286
tADP_12mplus	0.4399	<0.0001	0.2132	0.6664
tClop_7dplus	-0.2984	0.0030	-0.4952	-0.1017
_cons	-11.2638	<0.0001	-12.2245	-10.3067

Appendix 16

Table 44. Time to first event: fatal CV

	Exponential		Weibull		Gompertz		Log-normal		Log-logistic	
Variable	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value
offlabel	-0.3637	0.0490	-0.3760	0.0420	-0.3801	0.0400	0.3326	0.0580	0.3194	0.0420
Tic60	-0.2389	0.0650	-0.2421	0.0630	-0.2424	0.0620	0.2106	0.0810	0.2032	0.0630
Tic90	-0.2414	0.0610	-0.2444	0.0590	-0.2449	0.0580	0.2238	0.0630	0.2092	0.0550
t60offlabel	0.5696	0.0250	0.5727	0.0240	0.5725	0.0250	-0.5397	0.0260	-0.4924	0.0230
t90offlabel	0.4424	0.0850	0.4489	0.0810	0.4508	0.0800	-0.4081	0.0900	-0.3977	0.0680
sex	0.3848	0.0010	0.3921	0.0010	0.3941	0.0010	-0.4544	<0.001	-0.3831	0.0020
age	0.0304	0.0000	0.0305	<0.001	0.0304	<0.001	-0.0264	<0.001	-0.0255	<0.001
weight	-0.0091	0.0630	-0.0095	0.0540	-0.0096	0.0510	0.0145	0.0230	0.0115	0.0940
bmi	0.0371	0.0020	0.0383	0.0010	0.0387	0.0010	-0.0586	0.0030	-0.0447	0.0370
dmtype	0.4922	0.0000	0.4948	<0.001	0.4946	<0.001	-0.4426	<0.001	-0.4135	<0.001
MI_HIST	0.4572	<0.001	0.4618	<0.001	0.4621	<0.001	-0.4422	<0.001	-0.4003	<0.001
cadmult	0.2606	0.0100	0.2660	0.0090	0.2680	0.0080	-0.2662	0.0050	-0.2248	0.0090
smk_his2	0.2639	0.0330	0.2681	0.0310	0.2694	0.0310	-0.2458	0.0340	-0.2262	0.0310
stentany1	-0.9484	<0.001	-0.9497	<0.001	-0.9509	<0.001	0.9461	<0.001	0.8067	<0.001
MEDTDDOS_n	0.0053	0.0140	0.0053	0.0160	0.0053	0.0160	-0.0050	0.0280	-0.0044	0.0220
hyp	0.3901	0.0070	0.3916	0.0070	0.3926	0.0070	-0.4000	0.0010	-0.3269	0.0070
chf	0.7663	<0.001	0.7700	<0.001	0.7721	<0.001	-0.7345	<0.001	-0.6490	<0.001
SthAmerica	0.5036	<0.001	0.5118	<0.001	0.5195	<0.001	-0.4520	<0.001	-0.4157	<0.001
histPAD	0.7516	<0.001	0.7569	<0.001	0.7564	<0.001	-0.7529	<0.001	-0.6528	<0.001
creatinine_cl	-0.5280	<0.001	-0.5335	<0.001	-0.5351	<0.001	0.5008	<0.001	0.4503	<0.001
_cons	-13.7022	<0.001	-15.1248	<0.001	-14.0538	<0.001	14.0690	<0.001	12.6182	<0.001
shape			0.1857	0.0010	0.0006	<0.001	0.7541	<0.001	-0.2010	<0.001

Shape variables take the following form: Weibull – ln(p); Gompertz – gamma; Log Normal – ln(sigma); Log Logistic – ln(gamma)

Table 60. Time to subsequent event (acute phase) – fatal other

	Exponential		Weibull		Gompertz		Log–normal		Log–logistic	
Variable	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value
smk_his1	0.1503	0.6200	0.1349	0.6480	0.1380	0.6440	-0.2082	0.7020	-0.1820	0.7190
sbpsup	0.0252	0.0060	0.0256	0.0040	0.0255	0.0040	-0.0501	0.0030	-0.0454	0.0080
dbpsup	-0.0436	0.0070	-0.0418	0.0070	-0.0420	0.0080	0.0779	0.0080	0.0747	0.0090
chf	0.7710	0.0150	0.7478	0.0150	0.7623	0.0140	-1.3307	0.0210	-1.2731	0.0280
NthAmerica	0.9954	0.0010	0.9957	0.0010	0.9991	0.0010	-1.8920	0.0020	-1.7248	0.0030
creatinine~l	-0.6887	0.0170	-0.6756	0.0160	-0.6774	0.0160	1.2473	0.0170	1.1666	0.0230
_cons	-9.4901	<0.001	-7.1523	<0.001	-9.1748	<0.001	13.5536	<0.001	11.7323	<0.001
shape			-0.5148	<0.001	-0.0017	0.0310	1.3386	<0.001	0.4851	<0.001

Shape variables take the following form: Weibull, ln(p); Gompertz, gamma; Log–normal, ln(sigma); Log–logistic, ln(gamma)

Table 5.10: Overview of parametric time-to-event models for time to first event

First event	Non-fatal MI	Non-fatal stroke	Fatal CV	Fatal other
Distribution	Log-logistic	Log-logistic	Log-logistic	Log-logistic
Variable[a]	**Coefficient**	**Coefficient**	**Coefficient**	**Coefficient**
Offlabel	0.2771		0.3194	
Tic60	0.2057	0.2674	0.2032	
Tic90	0.1860	0.1647	0.2092	-0.2276
Tic60 * offlabel			-0.4924	
Tic90 * offlabel			-0.3977	
Age	-0.0130	-0.0355	-0.0255	-0.0468
Angina pectoris	-0.3164			0.1800
ASA dose			-0.0044	
Asia/ Australia	0.3051			
BMI			-0.0447	0.0462
CABG history	-0.8230			
Congestive heart failure		-0.5899	-0.6490	-0.1838
Creatinine clearance rate ≥60 ml/min	0.2789	0.5293	0.4503	0.3555
Diabetes	-0.4085	-0.3982	-0.4135	-0.3006
Hypercholesterolaemia		-0.4511		
Hypertension			-0.3269	
MI history	-0.7613		-0.4003	
Multivessel coronary artery disease	-0.3111		-0.2248	
North America	-0.4164			0.2294
Peripheral arterial disease history	-0.2420	-0.6216	-0.6528	-0.3635
Qualifying event was STEMI	-0.1945			
Sex		-0.3845	-0.3831	
Smoker current	-0.5086	-0.3579	-0.2262	-0.6724
Smoker former	-0.2321			-0.2456

First event	Non-fatal MI	Non-fatal stroke	Fatal CV	Fatal other
Distribution	Log-logistic	Log-logistic	Log-logistic	Log-logistic
Variable[a]	**Coefficient**	**Coefficient**	**Coefficient**	**Coefficient**
South America		-0.3865	-0.4157	
Stent (ever received)			0.8067	
Stroke history		-1.0763		
Supine SBP (mm Hg)	-0.0102	-0.0114		
Time since last ADP blocker > 12 months		0.3879		
Transient ischaemic attack history		-1.0498		
Weight			0.0115	-0.0136
_cons	13.1700	16.2000	12.6182	12.9254
Shape[b]	0.0728	0.1054	-0.2010	-0.3480

Source: Based on Tables 58, 60, 62, 65 and 67 of the CS[1]

Footnotes: [a] Baseline characteristics unless stated otherwise see Table 58 of the CS for more detailed variable descriptions; [b] Shape variables take the following form: Log Logistic – ln(gamma)

ADP = Adenosine diphosphate; ASA = acetylsalicylic acid; BMI = body mass index; CABG = coronary artery bypass graft; CV = cardiovascular; Hg = mercury; MI = myocardial infarction; mm = millimetre; SBP = systolic blood pressure; STEMI = *ST segment elevation myocardial infarction*

Table 5.12: Overview of parametric time-to-event models for time to subsequent event less than one year after the first event (i.e. 'acute phase')

Subsequent event	**Non-fatal MI**	**Non-fatal stroke**	**Fatal CV**	**Fatal other**
First event dependent[a]	Independent	Dependent	Independent	Independent
Distribution	Log-logistic	Weibull	Log-normal	Weibull
Variable[b]	**Coefficient**	**Coefficient**	**Coefficient**	**Coefficient**
Tic60 * MI as first event[c]	-0.3394		0.3329	
Tic90 * MI as first event[c]	-0.1234		0.2025	
Age		-0.0372	-0.0843	
Angina pectoris	0.4770			
BMI	-0.1395			
CABG history	-0.6892			
Congestive heart failure			-1.1951	0.7478
Creatinine clearance rate ≥60 ml/min				-0.6756
Diabetes			-1.5140	
Family history of premature coronary heart disease		0.6390		
MI history			-0.6498	
North America	-0.8491			0.9957
Peripheral arterial disease history	-0.7820	0.9746		
Qualifying event was STEMI	-0.7776		0.7976	
Smoker current		1.2319	-0.6152	
Smoker former	-0.5257	1.5596		0.1349
South America		0.7490		
Stent (ever received)			0.7044	
Stroke as first event		1.6432		
Supine DBP (mm Hg)	0.0473			-0.0418

Supine SBP (mm Hg)	-0.0250			0.0256
Transient ischaemic attack history		1.2766	-1.4353	
Weight	0.0350			
_cons	10.3937	-7.8999	15.3756	-7.1523
Shape[d]	0.1828	-0.3010	0.6877	-0.5148

Source: Based on Tables 68, 70, 72 and 74 of the CS[1]

Footnotes: [a] If dependent, a different probability is calculated for patients with MI and stroke as first event in the economic model; [b] Baseline characteristics unless stated otherwise see Table 58 of the CS for more detailed variable descriptions; [c] This parameter is not used in the economic model; [d] Shape variables take the following form: Log Logistic – ln(gamma); Weibull – ln(p); Log Normal – ln(sigma)

BMI = body mass index; CABG = coronary artery bypass graft; CV = cardiovascular; DBP = diastolic blood pressure; Hg = mercury; MI = myocardial infarction; ml = millilitre; mm = millimetre; SBP = systolic blood pressure; STEMI = *ST segment elevation myocardial infarction*

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], [redacted] and [redacted]

Name of your organisation: United Kingdom Clinical Pharmacy Association (UKCPA) – Cardiac Group

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ☑
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ☑
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? ☑
- other? (please specify)

The United Kingdom Clinical Pharmacy Association (UKCPA) was established in 1981 with the aim of supporting and encouraging the emergence of clinical pharmacy. It brings together like-minded pharmacists from difference practice areas to share knowledge, research and experiences. We provide a forum for pharmacists and technicians in all settings, notably community and hospital, to discuss and resolve current Clinical issues. The Association's mission statement is – "The UKCPA promotes expert practice in medicines management for the benefit of patients, the public and members by establishing standards, workforce development and advancing innovation in all health care settings. The UKCPA encourages Excellence, Leadership and Partnership".

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Initiation of therapy will occur in secondary care and the duration of treatment will be specified by the cardiologist during the admission.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
There is significant variation in the uptake of the newer generation P2Y12 inhibitors and application of NICE TAGs in clinical practice. The decision to prescribe one agent over another will be driven by the type of centre (e.g PCI capable) and individual clinical preferences.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
Dual antiplatelet therapy (aspirin + P2Y12 inhibitor) is the current standard of care for patients who present following an acute coronary syndrome and are treated either conservatively (medical management) or with mechanical reperfusion (percutaneous coronary intervention).

For those patients in whom medical management is the chosen treatment strategy, clopidogrel or ticagrelor may be prescribed in addition to aspirin. For those who undergo percutaneous coronary intervention (PCI), clopidogrel, prasugrel or ticagrelor may be prescribed in addition to aspirin.

Recently, low dose Rivaroxaban, an anticoagulant (direct thrombin inhibitor) has also been approved for use in ACS patients in combination with either aspirin or aspirin plus clopidogrel. Activation of the coagulation system occurs during the acute phase of an ACS event; thrombin plays a key role in the coagulation cascade, leading to clot formation. Clot-bound thrombin remains activated and causes progression of the thrombus; this process can persist beyond the acute phase and can occur in patients up to 6 months following unstable angina or a MI. Thereby providing some rationale as to why patients experience recurrent MACCE despite being treated with DAPT.

Despite such a robust clinical evidence base, the use of clopidogrel in practice is limited by its slow onset of action, significant inter-individual variability in response and its irreversibility. Newer more potent agents such as prasugrel and ticagrelor address these shortcomings by being far quicker in terms of their onset of action. In addition, both prasugrel and ticagrelor are able to provide greater and more consistent levels of inhibition of platelet activity (IPA). Which is particularly desirable in the context of ST elevation myocardial infarction (STEMI) where the narrow time frame from symptom onset to reperfusion necessitates the administration of antiplatelet agents that are rapid in terms of their onset.

The majority of PPCI centres will prescribe either prasugrel or ticagrelor in all STEMI patients with clopidogrel as a second line alternative in patients who are unable to take prasugrel/ticagrelor based on contraindications/cautions (risk of major bleeding) or a concomitant need for anticoagulation.

In terms of recommendations, NICE last updated their guidelines relating to the secondary prevention of patients who present following a myocardial infarction in 2014 and therefore the content will not be reflective of recent advances in evidence base. Both NICE and ESC (STEMI guidelines) recommend lifelong treatment with aspirin and up to 12 months of treatment with a P2Y12 inhibitor following PCI in elective cases or presentation after an ACS event.
More recently, however, the ESC NSTEMI guidelines acknowledge the findings of recently published clinical trials in which the safety and efficacy of both short term and extended durations of P2Y12 inhibition plus aspirin have been investigated. The guideline does not make a definitive recommendation but summarises that treatment duration can be shortened (3-6 months) or extended (up to 30 months) in selected patients if required.

The advantages and disadvantages of the technology
NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
Ticagrelor is a direct acting, reversible P2Y12 inhibitor, which like clopidogrel can be prescribed across the spectrum of ACS conditions irrespective of the management strategy adopted. In comparison to clopidogrel, it displays an improved drug handling profile in terms of onset of action and degree of platelet inhibition, which translates into improved clinical outcomes.

Prasugrel, a direct competitor to ticagrelor is limited by its restriction for use in patients who undergo PCI only. Furthermore only certain patient groups are eligible for treatment; those over the age of 75 years, under 60kg and those who have not experienced a previous cerebrovascular event. The use of either agent (prasugrel or ticagrelor) in combination with an anticoagulant is not recommended due to an associated increase in major bleeding.

Extended duration P2Y12 inhibition in addition to aspirin (DAPT and PEGASUS) has demonstrated a significant reduction in MACCE compared with aspirin alone. The risk of major bleeding however is increased for both treatment groups. These results do not differ between subgroups irrespective of age, sex, DAPT regime (prasugrel or ticagrelor), history of PCI, previous MI/stroke or chronic kidney disease.

An issue with regards to implementation will relate to how best we define "stabilised high risk patients" and in particular those with a continued low risk of bleeding who are most likely to benefit from extended duration DAPT.
The risk factors quoted in study for inclusion are, prior MI, diabetes, older age and patients with established atherosclerosis. Patients were excluded based on; concomitant long term anticoagulation, recent major surgery, ICH, recent active bleed or bleeding diathesis. Therefore, the inclusion and exclusion criteria specified is not entirely reflective of "all-comers"/general population who may present with an ACS.

In clinical practice, a decision to extend the duration of treatment with a P2Y12 inhibitor may be made on an individual case-by-case basis if there are concerns over stent thrombosis or following stent deployment in the left main stem. Exclusion of patients at a higher risk of bleeding e.g. with a previous stroke, GI bleed or need for anticoagulation may not occur in real world practice; should these patients present with an index or further ischaemic event they would still require treatment. However, consideration would be given to whether long term administration of a P2Y12 inhibitor would provide any additional benefits or whether these benefits would be offset by the increase in bleeding risk that would inevitably be introduced.

Evidence Base
The recent advances in stent technologies allow for shorter durations of DAPT following coronary artery stent implantation. Newer generation stents have improved biocompatibility and reduced thrombogenicity, thereby reducing the need for prolonged treatment with a P2Y12 inhibitor to minimise an individuals bleeding risk.

However, deployment of a stent does not prevent atherosclerosis or protect against atherosclerosis or its progression in the non-infarct related arteries (so called residual disease). Patients who present following an ACS compared to those with stable CAD are at increased risk of further ischaemic events. This is largely due to the increased inflammatory state that occurs during an ACS and the presence of a higher vulnerable plaque burden that is prone to rupture.

The administration of DAPT (aspirin + P2Y12 inhibitor) allows for:
- plaque stabilisation (through its anti-inflammatory effects),
- prevention of further atherothrombosis at the site of endovascular injury
- prevention of stent thrombosis following coronary artery stent implantation
- reduction in/prevention of further adverse cardiac events unrelated to previous PCI

All of which should be achieved whilst balancing the ischaemic benefit of treatment against bleeding risk in patients with ACS.

The standard 12 month duration of treatment is derived from studies in which clopidogrel was the P2Y12 inhibitor of choice. For example, in the CURE trial patients received 12 months of DAPT irrespective of the treatment modality e.g. PCI, surgical revascularisation or medical management. Our current guideline recommendations are derived from the clinical trials, which provide the evidence base that underpins the place in therapy of clopidogrel. They advise 12 months of DAPT irrespective of revascularisation strategy or stent type. Prolongation/extended duration of treatment with DAPT may be of benefit in patients who are deemed to be high risk because of co-morbidities or past medical history e.g, diabetes, previous MI.

PEGASUS is one of two extended duration dual antiplatelet therapy trials recently published. It is a randomised, double blind placebo-controlled trial designed to evaluate the safety and efficacy of ticagrelor plus aspirin for the prevention of MACCE in patients with a history of MI and risk factors.
Over 20,000 patients who had experienced a myocardial infarction within the last 1-3 years were randomly assigned to treatment with aspirin plus either ticagrelor 90mg bd, ticagrelor 60mg bd or placebo.
The primary efficacy end point was a composite of cardiovascular death, MI or stroke. The primary safety end point was TIMI major bleeding.
Although the results of the results of the study indicate statistically significant reduction in mortality at 3 years, this was at the expense of significantly higher rates of TIMI major bleeding for both strengths of ticagrelor compared with placebo ($p < 0.001$). (The mortality benefit of ticagrelor in the context of acute MI was also apparent following completion of PLATO).

The inclusion criteria stipulate recruitment of patients who experienced a spontaneous MI 1-3 years prior to enrolment and are at least 50 years of age. PEGASUS is not reflective of current UK practice, since we do not actively seek out patients post-event to restart or redefine treatment durations.

The other factors specified in the inclusion criteria could be used to define “high risk” patients; $\geq$ 65 years, diabetes requiring medication, second prior spontaneous MI, multivessel disease and chronic renal dysfunction.

However, in view of an increasingly aging population (who are increased risk of bleeding) and with co-morbidities that may warrant treatment with anticoagulation, the results of PEGASUS may not be applicable to the general "real world" population that present with an ACS.

While PEGASUS provides some insight into the benefits associated with extended duration DAPT, it does not address the issue of whether patients remain at increased risk because of incomplete endothelialisation or because of the presence of vulnerable plaques secondary to coronary artery disease progression.

The actual cost effectiveness benefits are not apparent based on the outcomes of PEGASUS since there was no overall reduction in all cause mortality and no reductions in the rates of hospital admissions for UA. In addition, the reduction in ischaemic events (1%) is at least partially offset by an increase in TIMI major bleeding (1.64%). The results of PEGASUS also demonstrate a significant difference between both strengths of ticagrelor and placebo in terms of discontinuation rates ($p < 0.001$). The majority of premature discontinuations were due to adverse events, principally dyspnoea and gout.

The design of PEGASUS is such that patients were retrospectively selected and assigned to a treatment arm. Of note, although all patients had experienced a prior MI, they were randomised to treatment after an interruption in therapy. This is not reflective of current UK practice, since treatment with a P2Y12 inhibitor would not be restarted unless the patient presents with another event. The decision to continue lifelong/prolonged treatment is usually made during the inpatient episode, particularly in patients who receive several stents, may be at increased risk of stent thrombosis or have significant left main stem disease that has/has not been stented. As such, the decision for standard or extended duration therapy would be made at the point of angiography.

The average duration of time from the index MI to the point of randomisation was 1.7 years in PEGASUS. The benefits of initiating extended duration DAPT may not be as great for those patients in whom a prolonged period of time has elapsed since their index event.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The DAPT study (extended duration treatment with aspirin plus either clopidogrel or prasugrel), although different in terms of patients groups, set up and outcome measures reported should also be given consideration when deciding on the choice of agent. The outcomes of DAPT indicate that extended duration thienopyridine therapy in stented patients leads to a reduction in stent thrombosis and further

adverse cardiac events. The findings of study don't differentiate between agents – but report that a greater proportion of patients were treated with clopidogrel 65% compared with 35% prasugrel. Based on the outcomes of DAPT, there may be an argument to switch patients over to extended duration therapy with clopidogrel after 12 months of treatment with a higher intensity antiplatelet agent. Thereby, providing a more cost effective, yet clinically comparable treatment option, that may be associated with a lower bleeding risk. Such a strategy is further supported by the outcomes of the AMI subset of the CHARISMA study; after 28 months of treatment with aspirin plus clopidogrel in patients with a prior MI, stroke or PAD, a significant reduction in CV death, non-fatal MI or non-fatal stroke was observed, albeit at the expense of increased bleeding risk.

An exit strategy/instructions for discontinuation should be specified, for example, co-prescribing with an oral anticoagulant in those patients who develop an indication for OAC e.g. atrial fibrillation. There should also be clear guidance regarding cessation of treatment ahead of a planned surgical intervention; current advice is to defer all non-urgent procedures until the course of DAPT is complete. The possibility of rebound hypercoagulability of platelets should also be borne in mind.

Rules for discontinuation may include, (1) develop an indication for OAC, (2) bleeding episode while on treatment and (3) need for surgical intervention.
Long-term adherence to secondary prevention strategies is variable and some studies have demonstrated that up to 50% of patients discontinue all medications after approximately six months (ref: Nunes V et al. (2009). Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners).

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

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Single Technology Appraisal (STA)

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

One in five patients who present with an ACS will suffer a recurrent cardiac event secondary to residual disease after their index admission. The use of extended duration DAPT will therefore be of benefit in higher risk patient groups to mitigate against further MACCE and stent thrombosis.

Using stroke prevention in atrial fibrillation as an example, the implementation of validated risk stratification tools to assess thrombotic risk and balance this against bleeding risk has helped to significantly improve and standardise the pharmacological management of patients who require anticoagulation.

The development and adaption of currently available tools to assess ischaemic and bleeding risk would be helpful to appropriately risk stratify patients and identify those who would be suitable for/benefit most from extended duration DAPT (whether that be with ticagrelor or clopidogrel). The use of such tools would provide clinical justification and rationale for such a strategy to the patients – for example GRACE for ischaemic risk which is recommended within NICE UA/NSTEMI guidelines and CRUSADE which is a validated tool for the assessment of major bleeding are considerations and are known to be used in current practice e.g. Barts Heart Centre.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No equality issues

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Single Technology Appraisal (STA)

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Robert Storey

Name of your organisation
University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
None

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
Currently acute coronary syndromes (ACS) are treated in the NHS with (1) revascularisation, when indicated and feasible following coronary angiography, (2) long-term pharmacological therapy with aspirin, statins and other secondary prevention medication (ACE inhibitors, beta-blockers etc), and (3) most commonly 12 months treatment with a platelet $P2Y_{12}$ receptor antagonist (ticagrelor, prasugrel or clopidogrel). The European Society of Cardiology 2011 and 2015 guidelines for the management of non-ST-elevation ACS and 2012 guidelines for the management of ST-elevation MI have set out clear guidance for the use of $P2Y_{12}$ receptor antagonists. Ticagrelor 90mg twice-daily is recommended in preference to clopidogrel for up to 12 months in patients with myocardial infarction or moderate-to-high risk unstable angina, regardless of management strategy, unless there are contraindications, intolerance of ticagrelor or requirement for co-administration of oral anticoagulant therapy. This is supported by the NICE TA for ticagrelor. Ticagrelor is usually given within 24 hours of diagnosis and before coronary angiography is performed. Prasugrel is an alternative to ticagrelor in patients who are planned for PCI, either those with ST-elevation myocardial infarction (STEMI) who are planned for primary PCI or those with non-ST-elevation ACS who have had coronary angiography and are proceeding to PCI.

Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? If the technology is already available, is there variation in how it is being used in the NHS?
Most UK centres have adopted ticagrelor as first-line management in non-ST-elevation ACS in preference to the previous standard therapy of clopidogrel, although there are geographical variations in the selection of patients and duration of therapy that are mostly based on individual perceptions of cost effectiveness rather than efficacy and safety. Most UK centres also use either ticagrelor or prasugrel as first-line therapy for primary PCI, which is the usual strategy for management of STEMI. The majority of centres recommend 12 months of $P2Y_{12}$ receptor antagonist following ACS in addition to long-term aspirin. The duration of therapy may be attenuated in those who are at high risk of fatal bleeding.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Ticagrelor is belongs to the class cyclo-pentyl-triazolopyrimidine which is distinct in pharmacological properties from the thienopyridine class to which clopidogrel and prasugrel belong. However, both ticagrelor and the thienopyridines target the same receptor on platelets, the $P2Y_{12}$ receptor. Ticagrelor has an additional mechanism of action through inhibiting cellular adenosine uptake and thereby increasing local adenosine levels although it is

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currently uncertain as to whether this explains some of its benefits as well as some of its adverse effects such as dyspnoea.
Clopidogrel is available as generic preparations and is therefore much cheaper than ticagrelor or prasugrel but has numerous limitations including (1) poor antiplatelet effect in about 30% of individuals which increases the ischaemic risk, (2) slower onset of action compared to ticagrelor and prasugrel, which may limit efficacy during the first hours of therapy when risk may be highest, (3) variable and slower offset of effect compared to ticagrelor which may increase risk in patients proceeding to open-heart surgery, and (4) limited or no effect on long-term CV mortality in clinical trials compared with placebo, in distinction to the evidence for CV mortality reduction with ticagrelor compared to clopidogrel. Prasugrel shares the last two of these important limitations with clopidogrel i.e. slower recovery of platelet reactivity after cessation of therapy and lack of evidence for long-term CV mortality reduction.

Is the technology always used within its licensed indications? If not, under what circumstances does this occur?
Ticagrelor 90mg bd is mostly used for its licensed indication of 1 year treatment post-ACS. For occasional patients, longer term treatment may be recommended because of high ischaemic risk. In addition, ticagrelor 90mg bd is sometimes used on an ad hoc basis in stable patients undergoing high-risk PCI because of concerns about insufficient efficacy of clopidogrel. Ticagrelor 60mg has not been available for sufficient time to determine off-label usage.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
Despite effective secondary prevention therapy, there is a high rate of recurrent ACS in addition to stroke and CV death. The HELICON registry determined that event rates are approximately 18% in the first year after ACS. For those patients who survive for 1 year following ACS without MI or stroke, the UK CALIBER registry showed that approximately 18% will suffer an MI or stroke or die in the following 3 years. Consequently there is a large unmet need for improved secondary prevention therapy, particularly in those at higher risk of recurrent ischaemic events and CV death.
The PEGASUS-TIMI 54 study sought to address this unmet need by assessing the efficacy and safety of long-term ticagrelor treatment in patients with a history of MI between 1 and 3 years previously. This study design was necessary because, at the time of the study initiation, very few patients had received one year's treatment with ticagrelor following MI and so it would not have been feasible to conduct the study as a continuation study of ticagrelor at 1 year post-MI. In order to obtain a sufficient number of events to power the study, patients enrolled in PEGASUS-TIMI 54 had to have additional atherothrombotic risk factors beyond a history of prior MI. Consequently the minimum age was 50 years and 1 further risk factor was required in addition (age 65 years or more, diabetes mellitus requiring medication, a history of 2 or more prior MIs, multivessel coronary artery disease, or chronic kidney disease not requiring dialysis). A decision was made early in the trial to exclude patients with prior ischaemic stroke due to their increased risk of intracranial

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haemorrhage although such patients had overall benefitted from ticagrelor in the PLATO study and this was based primarily on results of trials with different classes of antiplatelet drug. Two doses of ticagrelor were studied in comparison to placebo: ticagrelor 90mg bd, which is the licensed dose for treatment of ACS during the first year, and ticagrelor 60mg bd, which had not been studied previously (and is the subject of this technology appraisal). Both doses of ticagrelor significantly and similarly reduced the risk of recurrent MI, stroke or CV death and there were numerical trends favouring better tolerability of the 60mg dose. A platelet function substudy showed that ticagrelor 60mg bd achieves similar platelet inhibition to the 90mg bd dose with no significant interindividual variation in response in adherent patients. The reductions in MI and stroke were clinically relevant, such as with significant reductions in ST-elevation MI rates. There was consistency of benefit of both doses of ticagrelor across numerous subgroups such that higher risk patients tended to have greater absolute risk reduction. Pooled analysis of the ticagrelor doses showed a non-significant trend towards CV mortality reduction and a subanalysis of patients with diabetes provided evidence of CV mortality reduction in this higher risk subgroup. These findings were consistent with the results of the PLATO study. The disadvantages of treatment with ticagrelor were predominantly increased risks of bleeding and dyspnoea but there was no significant effect of ticagrelor at either dose on rates of either intracranial haemorrhage or fatal bleeding (thus explaining the trends towards reduced CV death). These adverse effects led to increased rates of discontinuation with ticagrelor, which seemed to weaken the treatment effect, but it should be acknowledged that most of the discontinuation occurred in the first year of treatment and so tolerability in clinical practice would be expected to be much greater in those who have already completed one year of therapy with ticagrelor 90mg bd, particularly considering the reduction in dose to 60mg bd at this stage, as per the license for long-term treatment.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The European Society of Cardiology 2015 guidelines for the management of non-ST-elevation MI have provided the following recommendation for long-term dual antiplatelet therapy, predominantly based on the findings of the PEGASUS-TIMI 54 study and meta-analysis including this study: "$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient." The strength of this recommendation (IIb) was decided before many of the results of subanalyses of the study were available. These guidelines are written by a Task Force consisting predominantly of cardiologists who are experts in fields relevant to ACS (e.g. pharmacology, biomarkers, imaging, epidemiology) and are generally involved in clinical research studies that underpin the guidelines. The guidelines incorporate evidence both from individual clinical trials and from meta-analyses and weight the evidence in terms of strength and relevance to contemporary cardiological practice. Recommendations are then made, some of which are based on expert opinion.

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In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

I envisage that ticagrelor 60mg bd will be an option for long-term treatment of patients meeting the inclusion and exclusion criteria for the PEGASUS-TIMI 54 study. This will allow cardiologists to adapt their advice for duration of treatment with ticagrelor at hospital discharge following MI: instead of recommending one year of treatment with ticagrelor 90mg bd following MI, patients with higher ischaemic risk, including increased risk of death related to coronary artery disease, will receive a recommendation for long-term treatment with ticagrelor, including down-titration from 90mg bd to 60mg bd at one year. Most eligible patients will undergo coronary angiography during their hospital admission for MI and patients can easily be identified at this stage, particularly since the investigation will identify those with multivessel disease and other inclusion criteria for PEGASUS-TIMI 54 will generally have been identified by this stage. Discharge advice regarding long-term treatment and reduction in dose at 1 year will need to be followed in primary care and bleeding and other adverse effects will need to be jointly managed by primary and secondary care as per usual practice. Specialist nurses, such as cardiac rehabilitation nurses, may play a role in some centres e.g. in coordinating down-titration at 1 year post MI). However, since efficacy, safety and (currently) cost are not substantially different between the 90mg and 60mg twice-daily dose regimens of ticagrelor, the failure to immediately down-titrate at 1 year does not seem to constitute a relevant clinical or financial risk.

Since there was no evidence of attenuation of either ischaemic risk or the benefit of ticagrelor at more than 4 years post-MI, I envisage that treatment is continued until such time as it is not tolerated (e.g. because of major bleeding) or a contraindication emerges and consequently the long-term management of ticagrelor would be similar to its management in the first year following MI. This is analogous to the use of novel oral anticoagulants for prevention of stroke in patients with atrial fibrillation. It is hoped that this strategy will reduce the long-term burden of ischaemic events in this population and extend life expectancy.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The advantages and disadvantages of ticagrelor 60mg bd for long-term treatment post MI are mostly outlined above. It is much more expensive than generic clopidogrel for long-term treatment but the evidence of benefit is much stronger. For example, the DAPT study assessed long-term treatment with

clopidogrel or prasugrel and showed reduced rates of MI, increased rates of bleeding but no significant effect on CV mortality. In fact, in the DAPT study and in meta-analyses there has been a trend to worse overall mortality with prolonged thienopyridine therapy. The evidence for a CV mortality benefit of ticagrelor is much stronger and it is uncertain whether this represents chance or whether the different mechanisms of action of ticagrelor underpin its apparently superior effects.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Ticagrelor 60mg bd would be continued after patients have completed a 1-year course of ticagrelor 90mg bd following MI. Subanalysis of the PEGASUS-TIMI 54 data suggested attenuated or absent benefit of ticagrelor in patients who had been stable off $P2Y_{12}$ inhibitor for more than 1 month and conversely enhanced benefit when ticagrelor was given to patients who had discontinued their previous $P2Y_{12}$ inhibitor within 1 month. Consequently there is a lack of evidence to support searching for post-MI patients who have been stable on aspirin monotherapy. This approach is supported by the observation of enhanced rates of MI, stroke and CV death in the 3-4 months following discontinuation of $P2Y_{12}$ inhibitor in both PEGASUS-TIMI 54 and DAPT studies which emphasises the importance of continuing dual antiplatelet therapy without a break in patients at high ischaemic risk.

Tolerability of ticagrelor after 1 year of treatment is generally good with the main reason for discontinuation being spontaneous bleeding. This inevitably leads to temporary suspension of therapy but is not necessarily a reason to permanently cease therapy since there is a higher risk of subsequent ischaemic events following major bleeding. Consequently the decision on whether to permanently stop or restart ticagrelor after bleeding must be individualised according to the nature of the bleeding and the individual risk of ischaemic events.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

My site was the second highest recruiter to PEGASUS-TIMI 54 internationally so I have local insights into this as well as being involved in the trial design and results interpretation. In my view, the patient population in the study was representative of patients at high long-term risk of ischaemic events following MI who currently receive 1 year of treatment with ticagrelor 90mg bd. The trial

did not study continuation of ticagrelor beyond 1 year and so the results must be extrapolated to a setting where ticagrelor is continued without a break at 1 year. However, the available data suggest that a greater treatment effect with lower discontinuation rates would be seen when ticagrelor is continued at 1 year at the lower dose of 60mg bd rather than started *de novo*.
PEGASUS-TIMI 54 narrowly failed to show a significant effect of ticagrelor on CV death alone but the relative risk reduction was consistent with that seen in the PLATO study in which the reduction in CV death with ticagrelor was highly significant. Furthermore, MI and stroke are accepted surrogate measures of CV death risk, which is supported by the observation that large MIs were reduced by ticagrelor in PEGASUS-TIMI 54. Sudden death and coronary artery disease-related death appeared to be reduced by ticagrelor in PEGASUS-TIMI 54, which reinforces similar data from PLATO.
Major bleeding was increased with ticagrelor and it is recognised that this is associated with higher rates of ischaemic events, particularly in the first month. However, rates of ICH and fatal bleeding were not increased with ticagrelor, which is surprising and may even indicate a protective effect of ticagrelor in the setting of major bleeding, particularly since fatal bleeding was also not increased by ticagrelor in PLATO.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
Dyspnoea is one of the limiting side effects of ticagrelor but tends to occur within the first week or so of treatment. Discontinuation of ticagrelor due to dyspnoea is extremely uncommon in patients who have tolerated ticagrelor for 1 year and so would be unlikely to be of relevance when ticagrelor is continued at 1 year with down-titration to 60mg bd. The main long-term adverse effect of ticagrelor relates to its effects on haemostasis. Bruising and minor bleeding such as nose bleeds are common with ticagrelor but mostly only reassurance and occasionally temporary cessation are required since this relates to its mechanism of action for preventing thrombotic events. Major bleeding related to ticagrelor is most likely to occur during the first year of treatment but there is a small annual excess beyond one year which constitutes the main limitation of long-term treatment with ticagrelor. There is a very small excess of gout with long-term ticagrelor related to its effects on blood uric acid levels but this is not sufficient to impact on treatment policy. Increased frequency of sinoatrial pauses occur particularly during early treatment with ticagrelor but this does not seem to be associated with clinical sequelae.
Despite use of ticagrelor as first-line treatment of ACS patients in my region since 2012, I am not aware of any issues with ticagrelor in clinical practice that have not been described in the clinical trials and our experience has generally been very positive with documented reduction in stent thrombosis rates and trend towards lower 1-year mortality.

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
I don't believe this appraisal will exclude any people protected by the equality legislation

- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
I don't believe this appraisal will have a different impact in this way

- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities
Patients with a prior history of disabling stroke may not be recommended for this technology as they were excluded from the PEGASUS-TIMI 54 trial in view of concerns of potential increased risk of intracranial haemorrhage with dual antiplatelet therapy

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts
The PEGASUS-TIMI 54 study design paper (Bonaca MP et al. Am Heart J 2014;167:437-444.e5.) details the rationale for excluding patients with prior history of ischaemic stroke in addition to those with prior history of intracranial haemorrhage.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

There have been recent publications of analyses of the PEGASUS-TIMI 54 data including the latest one:
Bonaca MP, Bhatt DL, Oude Ophuis T, et al. Long-term tolerability of ticagrelor for the secondary prevention of major adverse cardiovascular events: a secondary analysis of the PEGASUS-TIMI 54 trial [published online June 15, 2016]. *JAMA Cardiol*. doi:10.1001/jamacardio.2016.1017.

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Other recent publications are currently listed on PubMed.

Implementation issues

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If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The lower dose of ticagrelor, 60 mg tablets, will be available in sufficient quantity for any NICE recommendations supporting its use to be implemented. Consultant cardiologists managing patients for myocardial infarction will be able to modify their guidance with regard to duration of treatment with ticagrelor i.e. instead of recommending 12 months treatment they will be able to recommend downtitration from ticagrelor 90mg to 60mg twice-daily after 12 months for long-term treatment. NHS staff will need education about which patients are recommended to receive long-term ticagrelor and it is expected that this will be provided through the usual channels of medical education. No additional facilities or equipment will be required.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Nick Hartshorne-Evans
Name of your nominating organisation: Pumping Marvellous Organisation
Do you know if your nominating organisation has submitted a statement?

☐ Yes x No

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes x No

- a carer of a patient with the condition?

☐ Yes x No

- a patient organisation employee or volunteer?

x Yes ☐ No

Do you have experience of the treatment being appraised?

x Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NO

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I am the CEO of the UK's heart failure patient group and a lot of our members have had MI's and have been started or have experience of therapies for the prevention of secondary atherothrombotic events.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

The treatment outcomes that are important are ones that don't have adverse side effects, don't effect the QOL, are easy to take, sit well within a regime of other therapies and the main outcome is that it works.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

This is, in this case, a very open ended question and in my experience the easier the administration of the therapy, the more effective it is and the less likely the patient has of experiencing adverse effects the better the therapy. I don't think I am qualified to comment on comparators.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

The benefit that a patient would expect to gain from this treatment is a reduced risk of an atherothrombotic event.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

I am not aware other than clinical evidence presented that this treatment has any benefits over other NHS treatments in England

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I have not heard of or know of any differences of opinion between patients and or carers about the benefits of the treatment.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in

England.

Disadvantages of the treatment include increased risk of bleeding and history of intracranial bleed. I believe it has to be taken twice a day compared to clopidogrel that needs to be taken once a day therefore this may effect compliance and therefore therapeutic effectiveness.

Please list any concerns you have about the treatment being appraised.

No concerns

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Nil

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

I am not aware of any patient that would benefit or be disadvantaged over and above others.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

My understanding is this is a broad treatment for people who have had a previous MI therefore I am not aware of patients that might benefit less.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐x No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the

treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

No equality issues

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes x No

If yes, please explain what makes it significantly different from other treatments for the condition.

Is there anything else that you would like the Appraisal Committee to consider?

I believe this type of therapy is very difficult to assess when the desired outcome is clear cut which is preventative eg reduce risk of a atherothrombotic event.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Reduced risk of atherothrombotic event

- It should be easy to take in tablet format
- If the clinical evidence suggests better outcomes than existing treatment this is favourable as long as it is cost effective
- The appraisal should not underestimate the increased bleeding risk and if the patient is aware of this then it does have a psychological effect and may effect the patients and carers QOL

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Xavier Pouwels, Anoukh van Giessen and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Richard Birnie and Shona Lang acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

15D	15 dimensions
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse Events
AHA	American Heart Association
AiC	Academic in confidence
AIC	Akaike information criterion
ANZCTR	Australian New Zealand Trials Registry
AQoL	Assessment of Quality of Life
ARB	Angiotensin II receptor blocker
ASA	Acetylsalicylic acid
BID	Twice daily
BMI	Body mass index
BMS	Bare metal stent
CABG	Coronary artery bypass graft
CAD	Canadian dollar
CAD	Coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	Care Assessment Platform
CCC	Clinical Classification Categories
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence interval
CiC	Commercial in confidence
CNS	Central nervous system
CONSORT	Consolidated Standards Of Reporting Trials
CS	Company submission
CSR	Clinical study report
CUA	Cost utility analysis
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CYP3A	Cytochrome P450
DAPT	Dual antiplatelet therapy
DARE	Database of Abstracts of Reviews of Effects
DBP	Diastolic blood pressure

DES	Drug-eluting stent
DET	Data extraction table
dl	Decilitre
DM	Diabetes mellitus
DSA	Deterministic sensitivity analysis
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
ESC	European Society for Cardiology
EU	European Union
EUR	Erasmus University Rotterdam
FDA	US Food and Drug Administration
FFR	Fractional flow reserve
GI	Gastrointestinal
GP	General Practitioner
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
Hg	Mercury
HR	Hazard ratio
HRG	Health care resource group
HRQoL	Health-related Quality of Life
HS	Haemorrhagic stroke
HSE	Health Survey for England
HSUV	Health state utility value
HTA	Health Technology Assessment
HTA	Health Technology Assessment Database
HUI2/3	Health Utilities Index 2/3
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
ICH	Intracranial haemorrhage
ICTRP	International Clinical Trials Registry Platform
IHD	Ischaemic heart disease
Inc	Incremental
IQR	Interquartile range
IS	Ischaemic stroke
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention to treat
kg	Kilogram
KHNASES	Korean National Health and Nutrition Examination Survey
KM	Kaplan–Meier (estimate)
KSR	Kleijnen Systematic Reviews
LD	Low dose
LYG	Life years gained
MACCE	Major adverse cardiac and cerebrovascular event

MEPS	Medical Expenditure Panel Survey
MeSH	Medical Subject Headings
mg	Milligram
MI	Myocardial infarction
ml	Millilitre
mm	Millimetre
NA	Not applicable
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
NSTE-ACS	Non-ST-elevation acute coronary syndromes
NSTEMI	Non-ST segment elevation myocardial infarction
OAP	Oral antiplatelet
OD	Once Daily
OT	On-treatment
PAD	Peripheral arterial disease
PBAC	Pharmaceutical Benefits Advisory Committee
PCI	Percutaneous coronary intervention
PLATO	Platelet Inhibition and Patient Outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PVD	Peripheral vascular disease
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
QWB	Quality of well being
RCT	Randomised Controlled Trial
RIKS-HIA	The Register of Information and Knowledge about Swedish Heart Intensive Care Administrations
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SEK	Swedish Krona
SPHIA	Secondary Prevention after Heart Intensive Care Admission
SF-6D	Short form-6 dimensions
SG	Standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of product characteristics
ST-APT	Standard anti-platelet therapy
STA	Single Technology Appraisal
STEMI	ST segment elevation myocardial infarction
TIA	Transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TTO	Time trade off
UA	Unstable angina
UMC	University Medical Center
UK	United Kingdom

UKCPA	UK Clinical Pharmacy association
US(A)	United States (of America)
USD	United States dollar
WHF	World Heart Federation
WHO	World Health Organisation
WTP	Willingness-to-pay

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1 Summary

1.1 Critique of the decision problem in the company's submission

The patient population described in the final scope issued by the National Institute for Health and Care Excellence (NICE) is *"Adults who have had a myocardial infarction and are at increased risk of atherothrombotic events"*. The definition of the patient population addressed in the company submission (CS) is *"Adults who have had a myocardial infarction between 1 and 2 years ago and are at increased risk of atherothrombotic events"* which is based on the only study on ticagrelor identified as relevant for the CS, PEGASUS-TIMI 54. The patient population addressed in the CS is a subpopulation of the overall study population who had experienced a prior myocardial infarction (MI) between one and two years ago who also had ≥1 additional atherothrombotic risk factor. The Evidence Review Group (ERG) agrees with the company that the subgroup specified is the CS represents the most relevant available evidence for the population requested in the final scope.

The intervention in the CS is "*ticagrelor 60 mg BID [*twice daily] *co-administered with aspirin for up to 3 years*". This is in line with the scope which specified "*ticagrelor co-administered with aspirin*". The stipulation that treatment is for up to three years reflects the fact that the PEGASUS-TIMI 54 study treated patients for up to three years.

The comparators defined in the final scope were aspirin monotherapy or clopidogrel in combination with aspirin while the CS only included aspirin monotherapy as a comparator. The company argued that clopidogrel in combination with aspirin does not have a licensed indication in the population of interest, is not established as clinical practice in the NHS and that there is no evidence to support the comparison of ticagrelor plus aspirin versus clopidogrel plus aspirin as there is no head to head trial comparing these treatments and an indirect comparison was not possible. The ERG agrees with the company that the differences in terms of design and characteristics of included patients between trials of ticagrelor plus aspirin versus placebo plus aspirin and trials of clopidogrel plus aspirin versus placebo plus aspirin were such that any indirect comparison would have been very difficult to interpret due to substantial heterogeneity between studies.

The outcomes considered in the CS are in line with the final scope issued by NICE and include non-fatal myocardial infarction (STEMI and NSTEMI), non-fatal stroke, urgent coronary revascularisation, bleeding events, mortality, adverse effects of treatment, and health-related quality of life (HRQoL).

1.2 Summary of clinical effectiveness evidence submitted by the company

According to the CS, "*a systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy, tolerability and safety of prolonged DAPT (ticagrelor, clopidogrel, prasugrel, vorapaxar in combination with aspirin) including rivaroxaban in adult patients with a history of MI in September 2014. This review was updated in January 2015 and again in December 2015*".

The systematic review reported in the CS identified only one study directly comparing ticagrelor plus aspirin to any of the included comparators, PEGASUS-TIMI 54. Therefore, no formal meta-analysis was possible. The company assessed the similarity of the three studies identified by the systematic review for potential inclusion in a network meta-analysis but concluded that the studies were not comparable.

The PEGASUS-TIMI 54 trial randomised patients to ticagrelor 90 mg BID + acetylsalicylic acid (ASA) versus ticagrelor 60 mg BID + ASA versus placebo + ASA. In line with the application for an extension of the marketing authorisation submitted to the European Medicines Agency (EMA), data on ticagrelor 90 mg BID + ASA were not considered by the ERG. Quality assessment of the trial showed a low risk of bias.

The two arms of the PEGASUS-TIMI 54 trial relevant to the CS included 7,045 patients in the ticagrelor 60 mg BID + ASA arm and 7,067 patients in the placebo + ASA arm. The majority of patients came from Europe and South Africa (n=4,146 and n=4,154, respectively) with other participants recruited in Asia and Australia (n=788 each), North America (n=1,297 and n=1,303, respectively), and South America (n=814 and n=822, respectively). The relevant subgroup (MI <2 years ago) included 4,331 patients (ticagrelor 60 mg BID + ASA arm) and 4,333 patients (placebo + ASA arm). In line with the final scope, the CS provided details on certain subgroups, namely patients who had an MI <2 years ago with (n=1,419 and n=1,322, respectively) or without diabetes (n=2,912 and n=3,011, respectively) as well as patients who had an MI <2 years ago with (n=3,638 and n=3,623, respectively) or without history of percutaneous intervention (PCI; n=692 and n=709, respectively).

The results for the outcomes and populations defined in the final scope are presented in Table I. Details on HRQoL are presented in Section 1.4.

The CS estimates the annual number of incident continuation therapy ticagrelor 60 mg-eligible patients in England to be 27,887.

Table I: Outcomes from PEGASUS-TIMI 54

Population	Ticagrelor 60 mg BID	Placebo	Ticagrelor 60 mg BID vs. placebo
	Patient with events; n/N (%)		HR (95% CI)
Myocardial infarction			
Full Analysis Set	285/7,045 (4.0)	338/7,067 (4.8)	0.84 (0.72 to 0.98)
Patients with MI <2 years ago	[redacted]	[redacted]	[redacted]
Patients with MI <2 years ago, with diabetes	79/1,419 (5.6)	76/1,322 (5.7)	0.96 (0.70 to 1.32)
Patients with MI <2 years ago, without diabetes	101/2,912 (3.5)	145/3,011 (4.8)	0.72 (0.55 to 0.92)
Patients with MI <2 years ago, history of PCI	148/3,638 (4.1)	182/3,623 (5.0)	0.81 (0.65 to 1.00)
Patients with MI <2 years ago, no history of PCI	32/692 (4.6)	39/709 (5.5)	0.82 (0.51 to 1.31)
STEMI			
Full Analysis Set[#]	NR	NR	0.62 (0.45 to 0.86)
NSTEMI			
Full Analysis Set[#]	224/7,045 (3.1)	246/7,067 (3.5)	0.91 (0.76 to 1.09)
Stroke			
Full Analysis Set	91/7,045 (1.3)	122/7,067 (1.7)	0.75 (0.57 to 0.98)
Patients with MI <2 years ago	[redacted]	[redacted]	[redacted]
Patients with MI <2 years ago, with diabetes	21/1,419 (1.5)	33/1,332 (2.5)	0.59 (0.34 to 1.02)
Patients with MI <2 years ago, without diabetes	36/2,912 (1.2)	46/3,011 (1.5)	0.81 (0.52 to 1.25)
Patients with MI <2 years ago, history of PCI	44/3,638 (1.2)	54/3,623 (1.5)	0.81 (0.55 to 1.21)
Patients with MI <2 years ago, no history of PCI	13/692 (1.9)	25/709 (3.5)	0.51 (0.26 to 1.00)
Urgent coronary revascularisation			
Full Analysis Set[#]	[redacted]	[redacted]	[redacted]

Population	Ticagrelor 60 mg BID	Placebo	Ticagrelor 60 mg BID vs. placebo
	Patient with events; n/N (%)		HR (95% CI)
Bleeding events			
TIMI Major bleeding			
Full Analysis Set	138/7,045 (2.0%)	78/7,067 (1.1%)	1.78 (1.35 to 2.35)
Patients with MI <2 years ago	82/4,331 (1.9%)	55/4,333 (1.3%)	1.50 (1.06 to 2.11)
Patients with MI <2 years ago, with diabetes	27/1,402 (1.9)	8/1,310 (0.6)	3.32 (1.51 to 7.31)
Patients with MI <2 years ago, without diabetes	45/2,877 (1.6)	30/2,977 (1.0)	1.69 (1.07 to 2.68)
Patients with MI <2 years ago, history of PCI	62/3595 (1.7)	31/2585 (0.9)	2.17 (1.41 to 3.34)
Patients with MI <2 years ago, no history of PCI	10/684 (1.5)	7/701 (1.0)	1.55 (0.59 to 4.06)
Fatal bleeding events			
Full Analysis Set	13/7,045 (0.2%)	15/7,067 (0.2%)	0.87 (0.41 to 1.82)
Patients with MI <2 years ago[§]	10/4,331 (0.2%)	10/4,333 (0.2%)	1.00 (0.42 to 2.40)
Intracranial Haemorrhage			
Full Analysis Set	35/7,045 (0.5%)	33/7,067 (0.5%)	1.06 (0.66 to 1.71)
Patients with MI <2 years ago[§]	20/4,331 (0.5%)	22/4,333 (0.5%)	0.91 (0.50 to 1.67)
Other Major			
Full Analysis Set	98/7,045 (1.4%)	39/7,067 (0.6%)	2.53 (1.74 to 3.66)
Patients with MI <2 years ago[§]	59/4,331 (1.4%)	27/4,333 (0.6%)	2.19 (1.39 to 3.46)
TIMI Major or Minor bleeding			
Full Analysis Set	201/7,045 (2.9%)	106/7,067 (1.5%)	1.91 (1.51 to 2.42)
Patients with MI <2 years ago[§]	129/4,331 (3.0%)	75/4,333 (1.7%)	1.73 (1.30 to 2.30)
Mortality			
Cardiovascular death			
Full Analysis Set	174 (2.5)	210 (3.0)	0.83 (0.68 to 1.01)
Patients with MI <2 years ago	[redacted]	[redacted]	[redacted]

Population	Ticagrelor 60 mg BID	Placebo	Ticagrelor 60 mg BID vs. placebo
	Patient with events; n/N (%)		HR (95% CI)
Patients with MI <2 years ago, with diabetes	47/1,419 (3.3)	64/1,332 (4.8)	0.68 (0.47 to 0.99)
Patients with MI <2 years ago, without diabetes	47/2,912 (1.6)	73/3,011 (2.4)	0.66 (0.46 to 0.96)
Patients with MI <2 years ago, history of PCI	51/3,638 (1.4)	81/3,623 (2.2)	0.63 (0.44 to 0.89)
Patients with MI <2 years ago, no history of PCI	43/692 (6.2)	56/709 (7.9)	0.77 (0.52 to 1.14)
All-cause mortality			
Full Analysis Set	289 (4.1%)	326 (4.6%)	0.89 (0.76 to 1.04)
Patients with MI <2 years ago[§]	NR	NR	[redacted]
Adverse events			
Patients with any adverse event			
Full Analysis Set	5,342/7,045 (75.8%)	4,941/7,067 (69.9%)	NR
Patients with MI <2 years ago[§]	3,261/4,331 (75.3%)	3,022/4,333 (69.7%)	NR
Patients with any serious adverse event			
Full Analysis Set	27/7,045 (0.4)	13/7,067 (0.2)	2.08 (1.07 to 4.02)
Patients with MI <2 years ago[§]	19/4,331 (0.4)	7/4,333 (0.2)	2.71 (1.14 to 6.46)
Event leading to study drug discontinuation			
Full Analysis Set	297/7,045 (4.2)	51/7,067 (0.7)	5.95 (4.42 to 8.01)
Patients with MI <2 years ago[§]	176/4,331 (4.1)	29/4,333 (0.7)	6.18 (4.17 to 9.15)

Source: Based on Tables 25, 26, 35, 36, 41, 43, 44, 48 and 49 as well as Figure 15 of the CS and Tables 33, 41b, 43b and 44b as well as Figure 1 of the response to request for clarification

Footnotes: [*] Calculated by the ERG; [#] No results for any of the subgroups were reported; [§] No results for any other subgroups were reported

BID = twice daily; CI = confidence interval; CS = company submission; HR = Hazard ratio; mg = milligram; MI = myocardial infarction; NR = not reported; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST segment elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and additional searches of clinical trials registers and conference proceedings were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal.

The number of reviewers who assessed studies for inclusion in the review was unclear. The text of the CS implies that one reviewer assessed titles and abstracts in the first pass and that studies identified for inclusion at the second pass were checked by a second reviewer. The use of only one reviewer for screening of titles and abstracts would not be considered best practice and increases the risk of relevant studies being missed. Furthermore, if only the included studies were checked in the second pass by a second reviewer then relevant studies could have been excluded by a single reviewer. Similarly, details on how data extraction and quality assessment were conducted are lacking. The ERG agrees with the CS that PEGASUS-TIMI 54 has low risk of bias.

Patients included in the PEGASUS-TIMI 54 trial might not be reflective of the population in the United Kingdom (UK). According to the UK Clinical Pharmacy Association, the trial "*is not reflective of current UK practice, since we do not actively seek out patients post-event to restart or redefine treatment durations. The other factors specified in the inclusion criteria could be used to define "high risk" patients; ≥ 65 years, diabetes requiring medication, second prior spontaneous MI, multivessel disease and chronic renal dysfunction. However, in view of an increasingly aging population (who are increased risk of bleeding) and with co-morbidities that may warrant treatment with anticoagulation, the results of PEGASUS may not be applicable to the general 'real world' population that present with an ACS* [acute coronary syndrome]*"*.

The primary outcome in PEGASUS-TIMI 54 was time to first occurrence after randomisation of any event from the composite of cardiovascular (CV) death, MI or stroke. However, the CS presented results for the individual components of the composite primary outcome. In principle the individual component end points may lack sufficient power, however given the number of patients enrolled in the study it is likely that any clinically meaningful differences would be detected.

The results of PEGASUS-TIMI 54 showed that ticagrelor 60 mg BID reduced the risk of MI in both the full analysis set (HR: 0.84, 95% CI 0.72 and 0.98) and in the relevant subgroup of patients with MI <2 years ago ([redacted]). It should be noted that in the full analysis set the effect was larger in patients with STEMI (HR: 0.62, 95% CI 0.45 to 0.86) than those with NSTEMI (HR: 0.91, 95% CI 0.76 to 1.09). In patients with MI <2 years ago ticagrelor 60 mg BID reduced the risk of MI more in patients without diabetes (HR: 0.72, 95% CI 0.55 to 0.92) than in patients with diabetes (HR: 0.96, 95% CI 0.70 to 1.32). In patients with MI <2 years ago ticagrelor 60 mg BID reduced the risk of MI to a similar degree in patients with PCI (HR: 0.81, 95% CI 0.65 to 1.00) or without PCI (HR: 0.81, 95% CI 0.51 to 1.31).

Ticagrelor 60 mg BID reduced the risk of stroke to a similar degree in the PEGASUS-TIMI54 full analysis set (HR: 0.75, 95% CI 0.57 to 0.98) and in the subgroup of patients with MI <2 years ago [redacted]. As in the analysis of MI there was a difference in the effect of ticagrelor 60 mg BID on the risk of stroke between patients with or without diabetes however the difference was reversed compared to the analysis of MI. In patients who had MI <2 years ago ticagrelor 60 mg BID reduced the risk of stroke by more in patients with diabetes (HR: 0.59, 95% CI

0.34 to 1.02) than in patients without diabetes (HR: 0.81, 95% CI 0.52 to 1.25). In patients who had MI <2 years ago ticagrelor 60 mg BID reduced the risk of stroke more in patients without a history of PCI (HR: 0.51, 95% CI 0.26 to 1.00) than in those with a history of PCI (HR: 0.81, 95% CI 0.55 to 1.21).

Treatment with ticagrelor 60 mg BID was associated with an increase in the risk of TIMI defined major bleeds compared to placebo. This increase was smaller in patients with MI <2 years ago (HR: 1.50, 95% 1.06 to 2.11) than in the full analysis set (HR: 1.78, 95% CI 0.35 to 2.35). Among patients with MI <2 years ago those with diabetes had a greater increase in the risk of TIMI major bleeds (HR: 3.32, 95% CI 1.51 to 7.31) than those without diabetes (HR: 1.69, 95% CI 1.07 to 2.68). Similarly, patients with a history of PCI had a greater increase in the risk of bleeding (HR: 2.17, 95% CI 1.41 to 3.34) than those without a history of PCI (HR: 1.55, 95% CI 0.59 to 4.06).

There were no statistically significant differences in the risk of intracranial haemorrhage between patients receiving ticagrelor 60 mg BID and those receiving placebo in either the full analysis set or the subgroup of patients with MI < 2 years ago. In both populations the difference between treatment arms amounted to two events. There was an increase in the risk of other major bleeds for patients receiving ticagrelor 60 mg BID in both the full analysis set (HR: 2.53, 95% CI 1.74 to 3.66) and in patients with MI < 2 years ago (HR: 2.19, 95% CI 1.39 to 3.46). The risk of TIMI major or minor bleeds was also increased for patients receiving ticagrelor 60 mg BID in the full analysis set (HR: 1.91, 95% CI 1.51 to 2.42) and in patients with MI < 2 years ago (HR: 1.73 95% CI 1.30 to 2.30).

Ticagrelor 60 mg BID reduced the risk of cardiovascular death to a greater degree in patients with MI <2 years ago [redacted] than in the full analysis set (HR: 0.83, 95% CI 0.68 to 1.01). Within the group of patients with MI <2 years ago the results were similar for patients with or without diabetes and for patients with or without a history of PCI. Ticagrelor 60 mg BID also reduced the risk of all-cause mortality both in patients with MI < 2 years ago [redacted] and in the full analysis set (HR: 0.89, 95% CI 0.76 to 1.04).

Patients receiving ticagrelor 60 mg BID had an increased risk of any serious adverse event compared to placebo both in the full analysis set (HR: 2.08, 95% CI 1.07 to 4.02) and in patients with an MI <2 years ago (HR: 2.71, 95% CI 1.14 to 6.46). The risk of events leading to discontinuation of the study drug was also increased in patients receiving ticagrelor 60 mg BID compared to placebo both in the full analysis set (HR: 5.95, 95% CI 4.42 to 8.01) and in patients with MI <2 years ago (HR: 6.18, 95% CI 4.17 to 9.15).

It should be noted that the results from PEGASUS-TIMI 54 are based on small numbers of events for each outcome compared to the total number of patients in each arm and should therefore be interpreted with a degree of caution.

The annual number of incident continuation therapy ticagrelor 60 mg-eligible patients is likely to be higher than estimated by the company as the underlying figures only included England, i.e. did not include Wales.

1.4 Summary of cost effectiveness submitted evidence by the company

The company conducted systematic reviews to identify relevant cost effectiveness studies, health-related quality of life studies and resource use and costs studies. The company did not identify any

study investigating the cost effectiveness of ticagrelor in the population of interest for the current decision problem, and hence developed a de novo model.

The company developed a state transition model with a cycle duration of three months to capture the long term (40 years) consequences of ticagrelor 60 mg BID + low dose ASA (75 mg) versus low dose ASA (75 mg) monotherapy. Clopidogrel + ASA was not included in the model as a comparator, although it was listed in the scope. In the model all patients start in the 'no event' state. After a non-fatal first event, patients enter either a series of 'post non-fatal MI' or 'post non-fatal stroke' tunnel states, depending on which event they experienced. The first four tunnel states track time since the first event, with a diminishing risk for subsequent fatal and non-fatal MI and stroke. The fifth state applies a constant risk for subsequent fatal and non-fatal MI and stroke from 12 months or more since the first event. Patients who experience a subsequent non-fatal event experience costs and a disutility for the duration of one cycle. Adverse events included in the model are major and minor bleeding and dyspnoea (grade 1-2 or grade 3-4). These events are modelled as events conditional on the patients remaining on treatment, and contribute to costs and quality-adjusted life years (QALYs) for the duration of one cycle. Treatment duration is set to 36 months. After 36 months, the subsequent time periods are modelled without treatment effects, and patients are assumed to continue on low dose ASA monotherapy.

The patient population presented in the economic evaluation includes high risk patients with a history of MI, aged ≥50 years, who tolerate low dose aspirin, and whose most recent MI occurred <2 years ago. This corresponds with the "MI <2 years" subgroup of the PEGASUS TIMI-54 trial (i.e. the 'label' population). The company states that the population in the economic evaluation is a subgroup of the licensed indication, and of the population defined by the scope.

The model used a competing risk framework to model the time to the following events: 'non-fatal MI', 'non-fatal stroke', 'fatal CV event' and 'other fatal event'. The majority of the parametric time-to-event models used in the economic modelling are based on the intention to treat (ITT) population in the PEGASUS-TIMI 54 clinical trial. The company only (partly) adjusted two time-to-event models to reflect the 'label population' in this trial, since the label covariate was not statistically significant for the other time-to-event models. The parametric survival model to estimate other fatal events resulted in a lower mortality probability than would be expected in the general population. In order to avoid underestimation of mortality in the base case, the company has derived this probability from UK life tables (excluding CV-specific mortality).

Utility inputs in the model were based on HRQoL data collected with the EQ-5D-3L at set time intervals in the PEGASUS-TIMI 54 clinical trial. A linear random effects panel data analysis model was used to calculate utility decrements associated with the events and adverse events in the model. The panel data method determines utility decrements as being equal to the difference in utilities before and after the occurrence of an event in a pre-determined time period. Since the use of the linear random effects panel data analysis allowed for values above 1, the company capped the maximal baseline utility value to 1. Baseline utility values calculated by the company, based on scores from patients without events in PEGASUS-TIMI 54, were higher than the general UK population age and gender specific utility values. This seemed improbable according to the company. Therefore, UK general population age and gender specific utility values were used for the 'no event' health state.

The company considered cost data from the ERG assessment of technology appraisal (TA) 317 (inflated to 2015 values) as appropriate for the current decision problem. These costs were supplemented by the ERG assessment report of TA210 and NHS references costs when unit costs were not available from TA317.

The company analysed the model both with an individual patient simulation and a cohort simulation. In the cohort simulation, a cohort of identical patients goes through the model, with risk equations applied to the 'average patient'. In the individual patient simulation, all patients in the 'label population' (n=10,779) go through the model one at a time, hence risk equations are applied to each patient individually.

Ticagrelor 60 mg BID + low dose ASA compared to low dose ASA was associated with a deterministic ICER of £20,098 in the individual patient simulation. The deterministic incremental cost effectiveness ratio (ICER) of the cohort simulation was £24,070. According to the company, the cohort simulation overestimated the results as a result of non-linearity in the model.

Due to time constraints, the probabilistic sensitivity analysis (PSA) was not based on all 10,779 patients of the 'label population'. Instead a single patient was simulated. This patient had a profile that produces an ICER which was the closest to the mean expected ICER of the individual patient simulation. The cost effectiveness acceptability curve (CEAC) shows that ticagrelor 60 mg BID + ASA has a 64.6% and a 100% probability of being cost effective at £20,000 and £30,000 per QALY gained thresholds, respectively.

Deterministic sensitivity analyses showed that the most influential parameters were the choice of the distribution to extrapolate the risk of a first non-fatal MI and non-cardiovascular disease (CVD) death beyond the trial time horizon.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The structure of the de novo model included some simplifications that potentially influence health outcomes and costs: non-explicit modelling of subsequent events and adverse events (and hence only taking into account costs and disutility for the duration of one cycle), not including gout as an adverse event, and not distinguishing between non-fatal disabling and non-disabling stroke. In response to the ERG's request, the company provided a model with gout included as an adverse event. This amendment was used in the ERG's base-case.

In clinical practice, patients who experience a subsequent non-fatal event would probably receive ticagrelor 90 mg BID + low dose ASA for 12 months, followed by ticagrelor 60 mg BID + low dose ASA for 36 months. This was not included in the economic model. Upon request, the company provided a scenario analysis assuming ticagrelor 60 mg BID is given for remaining lifetime from 12 months following a myocardial infarction. This led to an increase of the deterministic ICER of the patient simulation of approximately £100. When assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI, the deterministic ICER of the patient simulation increased with approximately £500.

Clopidogrel + low dose ASA was not included in the model analyses, based on the argument that available evidence did not allow for an indirect comparison. The ERG disagrees with this argument. According to the ERG, the available evidence does allow inclusion of clopidogrel + low dose ASA as a comparator in the model based on an indirect comparison, as long as the assumptions are clearly

reported and the uncertainties are propagated. Other arguments, besides the quality of the available evidence, to not include clopidogrel + low dose ASA as a comparator in the economic model are that this treatment is not licensed for this indication, and that it is not used in the UK in this indication. To underpin this, the company provided the results of a market research among 100 cardiologists, conducted in June 2015, in their response on clarification questions. This research showed that 9/361 (2%) patients were to remain on ASA + clopidogrel more than 12 months after myocardial infarction.

The company only (partly) adjusted two time-to-event models to populate the economic model to reflect the 'label population'. The company preferred to use the ITT population to "maintain the level of precision of the model". The ERG considers this to be a specious argument and strongly disagrees with the line of reasoning: even a perfectly precise model is useless if it is not valid. The ERG would consider it to be more valid to use the 'label population' to estimate the time-to-event models despite the fact that it would potentially result in a decrease in precision. It might be argued that using the ITT population is a conservative approach (based on slides 14 and 15 of the PowerPoint presentation provided with the clarification letter). However, as the company did not explore this scenario and not all label specific estimates are known (e.g. time to treatment discontinuation is unknown), it is unclear to what extent and in which direction the company's approach would bias the estimated ICER for the label population.

The parameterisation for the log-logistic models was unusual, and could not be verified. The company's parameterisation was therefore replaced by the ERG with a standard parameterisation. For adverse events, the company estimated parametric time-to-event models using the exponential distribution only instead of considering different parametric distributions and adopting the distribution with the lowest Akaike information criterion (AIC). This was adjusted in the ERG base-case. Moreover, the linear random effects panel data analysis model used to calculate utility decrements associated with events and adverse events in the model and baseline characteristics allowed utility values to exceed one. According to the ERG this may have introduced a scale effect, and hence utility decrements may be biased. The comparison of the obtained utility decrements with previous literature was not transparent, partly due to reference to secondary sources (reports from previous TAs) instead of the primary sources. In addition, for several utility values from the literature quoted in the CS, the ERG was unable to find the value in the primary source. When compared to literature, the utility decrement for major TIMI bleed seemed relatively small, taking into account that it is only incorporated for one cycle. In its additional analyses the ERG used an alternative utility decrement for major TIMI bleed.

Cost estimates were sourced based on previous TAs and NHS reference costs 2014-15, but, the company did not provide the primary sources of, and the uncertainty around, these estimates. In response to clarification questions, the company provided adjusted cost inputs.

The probabilistic sensitivity analysis for the patient level simulation was not programmed correctly. As a result, the ERG based its base-case and additional analyses on the cohort simulation. The probabilistic ICER from the cohort simulation may be an overestimation of the ICER due to ignoring non linearity in the model.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal. The CS and response to clarification provided sufficient details for the ERG to appraise the searches.

The evidence for clinical effectiveness was based on a large randomised controlled trial. Evidence was presented for the overall ITT population of the PEGASUS-TIMI 54 study and for the subgroup of patients who experienced the qualifying MI <2 years ago. This was consistent with the population set out in the final scope issued by NICE and with the licensed indication for the intervention.

The model approach was generally state of the art. The company developed a patient level state transition model, allowing for non-linearity. In addition a competing risk framework was used to estimate the time to the multiple first events in the model.

1.6.2 Weaknesses and areas of uncertainty

It was unclear how many reviewers were involved in the systematic review to identify clinical effectiveness evidence. The lack of a second reviewer in systematic reviews can increase the risk of bias and error in the review.

The submission from the UK Clinical Pharmacy Association pointed out that the patients included in the PEGASUS-TIMI 54 trial are not representative of the UK patient population as patients are not actively sought out post-event to restart or redefine treatment.

The final scope specified clopidogrel + ASA as a comparator however the CS did not present evidence for the comparison of ticagrelor + ASA versus clopidogrel + ASA. The systematic review included in the CS did not identify any studies that directly compared these two treatments. The company argued that an indirect comparison was not possible due to differences in the design and patient characteristics of the available studies. The ERG agrees that the degree of heterogeneity between studies would make the interpretation of an indirect comparison very difficult.

It is possible that some relevant evidence may not have been identified as a consequence of the study design limits used in the searches.

Subsequent and adverse events were not modelled explicitly and, as a consequence, only had a three month impact. In case of the adverse events, this model simplification is not conservative.

The majority of the time-to-event models used in the economic modelling were based on the ITT population from PEGASUS-TIMI 54, and not adjusted for the 'label population'. Although this may be conservative, the ERG was unable to determine the magnitude and direction of the bias this may have caused. The modelling of time to treatment discontinuation was unclear and may be incorrect. Alternative assumptions increased the ICER.

The company quoted previous TAs as (potential) sources for model input parameters for costs and utilities, but did not reference the primary sources of all identified values. This hampered transparency.

The probabilistic sensitivity analysis for the patient level simulation was not programmed correctly. As a result, the ERG based its base case and additional analyses on the cohort simulation. The

probabilistic ICER from the cohort simulation may be an overestimation of the ICER due to ignoring non-linearity in the model.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG obtained a probabilistic company base-case cohort simulation ICER of £24,072, using the company's updated model as starting point. The ERG was not able to reproduce the company original base-case ICER based on the company's updated model. The ERG base-case and additional analyses are based on the ERG reproduced analysis.

The ERG corrected the parameterisation of the log-logistic models for first and subsequent non-fatal MI or stroke and first fatal event (CVD-related or non-CVD related).

In addition, the ERG fixed the following violations:

- Included the quality of life and economic consequences of gout
- Based the choice of AEs distributions on AIC
- Adjusted health care costs
- Based uncertainty of costs on NHS reference costs in PSA
- The ERG judged it more appropriate to use an alternative (larger) disutility for major bleeds, and alternative (lower) inpatient costs for the 'no event' health state.

The ERG base-case (probabilistic result from the cohort simulation) amounts to £24,711 per QALY. The explorative analyses with alternative assumptions underlying time to treatment discontinuation resulted in an ICER of £33,676.

2 Background

This report provides a review of the evidence submitted by Astra Zeneca in support of ticagrelor (trade name Brilique®) for secondary prevention of atherothrombotic events in patients who have had a myocardial infarction and are at increased risk of atherothrombotic events.

The background section of the report by the Evidence Review Group (ERG) outlines and critiques the company's description of the underlying health problem and the company's overview of current service provision. The information is taken from Chapter 3 of the company submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem

The underlying health problem is cardiovascular disease (CVD) which is described in the CS as comprising *"cardiac disease, vascular diseases of the brain and peripheral arterial disease (PAD)"*. The company submission focuses on patients who have experienced myocardial infarction (MI), a specific component of CVD which is defined in the CS as *"myocardial cell death due to prolonged ischaemia"* which occurs *"when there is sudden impairment or interruption of blood flow to the myocardium, resulting in heart muscle injury. This is usually caused by a blockage due to a rupture of an atherosclerotic plaque and subsequent thrombus formation in the coronary arteries that supply blood to the myocardium"* (Section 3 of the CS).[1]

The company identified the main risk factors for recurrent atherothrombotic events as diabetes mellitus, recurrent MI, multi-vessel coronary artery disease, chronic non-end stage renal disease and age ≥65 years. The company cited real world data from four countries (England, France, Sweden and the United States of America) to show that *"a considerable number of post MI patients have diabetes (23.2% to 48.9%), history of >1 prior MI (9.7% to 14.4%) and history of renal disease (5.4% to 11.2%)"*[2-4] and that *"older age (≥65 years) was also common in these patients (54.5% to 70.3%, excluding the Medicare population)"*.[2] The company highlighted the fact that patients commonly have multiple risk factors. The CS cited a study showing that 76.2% of 7,238 patients who were event free after 12 months had one or more risk factors.[5]

The company reported data on the prevalence of baseline risk factors in patients in England with a history of MI. These data showed that 23.2% of 7,238 patients had diabetes, 12.2% of patients had a history of >1 MI, 7.8% had renal disease and 7.2% had PAD.[2]

According to the CS, *"analysis of data taken from the Swedish Acute Myocardial Infarction Statistics from 1969 to 2001 report that the mean time interval to recurrent MI was 30.3 months for women (median, 13.7; interquartile range [IQR], 3.4 to 41.6) and 39.5 months for men (median, 19.9; IQR, 4.8 to 57.9)"*.[6] The CS cited another study which showed that *"24% of recurrent MIs occurred within the first year after the initial event and approximately 29% of recurrent MIs occurred during years 2 to 4"*.[7]

The company cited results from an analysis of three year risk of atherothrombotic events based on observational data from the APOLLO study programme. *"Patients were included in the study if they had experienced a prior MI, were at high risk of further atherothrombotic events and were alive with no further MI for 12 months following hospitalisation from 2002 to 2011. The total number of patients included in the analysis was 140,880.*[2] *Event rates remained high throughout follow-up with fairly constant risks per year"*.[2] The same study reported *"large differences in the observed 3-year*

cumulative risk for MI, stroke or death across the countries were found (between 17.9% in France and 36.2% in US). After adjustments however, the differences in risk of MI/stroke/death across all four countries was reduced (between 16.7% in France and 21.3% in England)".[2] The observed and adjusted cumulative three year risk of MI, stroke or death reported based on 7,238 patients in England were 24.1% (95% confidence interval (CI) 22.7-25.5) and 21.3% (95% CI 18.2-24.2), respectively.[2]

The company estimated the number of patients who would be eligible for treatment with 60 mg ticagrelor twice daily (BID) as follows: *"The number of hospital admissions for 'actual myocardial infarction' (ICD10 [*10th revision of the International Statistical Classification of Diseases and Related Health Problems] *code; I21) in England in the year 2014/15 was 78,397.*[8] *Each is assumed to represent one patient. Of these patients, 90% are assumed to receive aspirin-based DAPT [*dual antiplatelet therapy] *in the first year following MI.*[9] *Of the resultant cohort, 67% are expected to remain CV [*cardiovascular] *event-free over the next year.*[2] *For the purposes of the budget impact analysis, it is assumed that all of these patients remain on DAPT for the year following MI. Of these patients, 59% are expected to meet the PEGASUS-TIMI 54 inclusion criteria and not meet the exclusion criteria.*[2] *This yields the estimate for the annual number of incident continuation therapy ticagrelor 60 mg-eligible patients to be 27,887".*

ERG comment: The description of acute coronary syndrome was based on the American College of Cardiology/American Heart Association guidelines on the management of patients with unstable angina/ Non-ST segment elevation myocardial infarction (NSTEMI).[2] The definition of MI is based on the universal definition of MI developed by joint task force of the European Society for Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA) and the World Heart Federation (WHF).[10]

The reference on the time to a second MI event from the Swedish Acute Myocardial Infarction statistics was checked and found to be correctly cited and accurately reported.[6] The paper supporting the statement that 24% of recurrent MIs occur within the first year and 29% occurred in years 2-4 was checked and found to report the results of a single study of 307 patients.[7] It was not clear from the publication when or where these patients were recruited and according to what criteria. The authors of the study which was published in 2002 were affiliated to Spanish hospitals. Therefore, one might assume that the study was conducted in Spain 15-20 years ago. As a result it is unclear whether the results of this study are applicable to 2016 and patients in the United Kingdom (UK).

The CS stated that 140,880 patients were included in the analysis however the underlying reference reported results based on 140,887 patients.[2] The reason for this discrepancy was unclear however given the large number of patients involved this is unlikely to substantially alter the estimated risk of MI, stroke or death.

The reference for the number of hospital admissions for acute myocardial infarction was checked and found to be accurate.[8] The reference to support the assumption that 90% of patients will receive aspirin-based DAPT in the first year following MI was not provided despite a request by the ERG to provide all missing references. The data reported by the APOLLO program showed that in England 41% of 7,238 patients were prescribed DAPT at one year post-MI.[2] The reference provided by the company did not report sufficient detail to evaluate the assumption that 67% of patients in England receiving DAPT would remain CV event free for one year or that 59% of those patients would meet the inclusion criteria for PEGASUS-TIMI 54.

2.2 Critique of company's overview of current service provision

The company cited current guidance by the National Institute for Health and Care Excellence (NICE) for secondary prevention of MI which recommends that dual antiplatelet therapy for up to 12 months is offered to all individuals who have experienced an MI followed by acetylsalicylic acid (ASA) monotherapy indefinitely thereafter.[11, 12] The company stated that NICE guidelines recommend aspirin *"should be offered to all patients after an MI, with treatment continuing indefinitely, unless they are intolerant or contraindicated. Aspirin should also be offered to those who had their MI >12 months previously, with therapy continuing indefinitely"* and clopidogrel *"should be offered for up to 12 months to those with NSTEMI (regardless of treatment) and STEMI [*ST segment elevation myocardial infarction] *(if they have received a bare-metal or drug-eluting stent) Should be used instead of aspirin in patients who also have other clinical vascular disease and who have: Had an MI and stopped dual antiplatelet therapy or Had an MI more than 12 months ago"*.[11] The company summarised NICE guidelines regarding the use of ticagrelor stating that *"90 mg BID (following a loading dose of 180 mg) is recommended in combination with low dose aspirin for <12 months in patients with ACS [acute coronary syndrome], but no recommendation exists for MI. Treatment should be continued for ≥1 month to <12 months for patients with STEMI"*.[11]

The company summarised the ESC 2011 guidelines and the later NSTE-ACS (non-ST-elevation acute coronary syndromes) 2015 guidelines[13]:

- *"A loading dose of aspirin (150–300 mg) followed by 75–100 mg once daily (OD) and no higher (class I recommendation, level A evidence) is advised.*

- *In addition, an oral ADP [adenosine diphosphate] receptor inhibitor is recommended for 12 months unless contraindications such as excessive risk of bleeding are present (ticagrelor and prasugrel are preferred over clopidogrel).*

- *Ticagrelor given as a 180 mg loading dose followed by 90 mg two times per day is recommended for those patients at high risk of further ischaemic events, for example, those with elevated cardiac biomarkers, regardless of whether or not a revascularisation strategy is planned (I,B).*

- *Prasugrel (60 mg loading dose followed by 10 mg OD) is recommended as an alternative only in patients in whom PCI [*percutaneous coronary intervention] *is planned, that is, following coronary angiography (I,B).*

- *Clopidogrel (300–600 mg loading dose followed by 75 mg OD) should be reserved for those patients with contraindications to the newer agents (I,B) or who also require oral anticoagulation (I,B).*

- *If CABG [coronary artery bypass graft] is planned, withholding the ADP receptor inhibitor is recommended for 5 days (ticagrelor/clopidogrel) or 7 days (prasugrel), although shorter durations may be guided by platelet function testing in those at lower bleeding risk.*

With regard to patients with ST elevation myocardial infarction (STEMI), the ESC published specific guidelines in 2012.[14] *Once again, clinicians are given the option of using aspirin (I,B) in combination with*

- *ticagrelor (I,B) or*
- *prasugrel (I,B), although only an option in patients with no history of cerebrovascular accident (CVA)/transient ischaemic attack and age <75 years.*
- *Clopidogrel is only advised if the other agents are contraindicated (I,C).*

Aspirin monotherapy is recommended after this 1-year period."

The company reported market research to support their assessment of current clinical practice.

*"The prescribing intention of the cardiologist, as described in the discharge letter, is the most appropriate record of current NHS [*National Health Service] *management of oral antiplatelet (OAP) therapy in the post-MI setting and has been explored in 2 waves of market research conducted on behalf of AstraZeneca in June 2015 (Wave 1, soon after presentation of the PEGASUS-TIMI 54 and DAPT results) and March 2016 (Wave 2, soon after approval of the extension to the licence for ticagrelor for use in the post-MI indication).*[15]

*A total of n=85 cardiologists in Wave 1 and n=115 in Wave 2 were invited to complete 10-15 retrospective patient records regarding adult patients who the cardiologist was treating for MI via a 30-minute online survey. Both clinical cardiologists and interventional cardiologists were recruited (*Table 2.1) *at random and screened upon entering the survey. Qualifying cardiologists had to have specialised in cardiology for 3-30 years, spend ≥60% of their time in direct patient care (vs. teaching, research etc.) and be responsible for writing discharge prescribing instructions to GPs [*general practitioners] *for OAP therapies. The characteristics of the cardiologists surveyed were consistent in the two waves.*

Table 2.1: Characteristics of cardiologists completing the survey in England & Wales

Cardiologist characteristics	**England and Wales (n=85)**	**England, Wales (n=135)**
	June 2015	**March 2016**
Region		
North of England, n (%)	29 (34)	44 (33)
Midlands and East of England, n (%)	23 (27)	34 (25)
London, n (%)	15 (18)	30 (22)
South of England, n (%)	14 (16)	25 (19)
Abertawe Bro Morgannwg University Health Board, n (%)	2 (2)	- (-)
BetsiCadwaladr University Health Board, n (%)	1 (1)	1 (0.5)
Cardiff & Vale University Health Board, n (%)	1 (1)	- (-)
Cwm Taf Health Board, n (%)	- (-)	1 (0.5)
Specialty		
Clinical cardiologist, n (%)	30 (35)	63 (47)
Interventional cardiologist, n (%)	55 (65)	72 (53)
Years specialised as Interventional/ Clinical cardiologist		
Mean, years, n	13.6	13.5

Cardiologist characteristics	England and Wales (n=85)	England, Wales (n=135)
	June 2015	March 2016
Median, years, (range)	12 (5-25)	13 (3-30)
Percentage of professional time spent in direct patient care*		
Mean, %	85.7	85.6
Median, % (range)**	85 (70-100)	90 (60-100)
Number of discharge instructions written for MI patients in a typical month		
Mean, n	35.8	42.4

Source: Based on Table 10 of the CS[1]
Footnotes: * Rather than teaching, research etc. number documented is an approximate figure based on cardiologists' judgement; ** Cardiologists had to spend at least 60% of their time in direct patient care to qualify for the study
CS = company submission; MI = myocardial infarction

Cardiologists were asked to complete anonymised patient record forms for the last 10-15 adult patients that had been treated for MI and had been discharged to primary care with instructions to the patients' GP relating to OAP treatment; this patient selection criteria was included to avoid bias in the data collected. Cardiologists entered information on patient age, type of heart attack, revascularisation, presence of co-morbidities and patient medical history, as well as OAP treatment initiated and the intended duration of treatment as described in the patient's discharge letter.

*Patient records were collected for all patients that had been treated for an MI, at analysis stage the patient population was sub-divided into PEGASUS-like and non-PEGASUS-like patient records according to the selection criteria for the PEGASUS-TIMI 54 trial (*Table 2.2). *It is recognised that there is a difference in time since MI between those patients considered in this study (recent MI) and those in the PEGASUS trial (MI 1-3 years ago), however the term "PEGASUS-like" is used for purposes of simplification. This study elicits cardiologists' OAP prescribing intentions beyond the first year since MI and thus captures the period considered by the PEGASUS-TIMI 54 trial.*

Table 2.2: PEGASUS-like patient criteria

Exclusion criteria (any one of the below)	Inclusion criteria (must be at least one of the below)
• ≤ 50 years old • History of ischaemic stroke • History of intracranial bleed or GI bleed (<6 months) • Treatment with antithrombotics (at time of MI currently described) • Planned coronary, cerebrovascular, or peripheral arterial revascularisation • Aspirin intolerance	• ≥ 65 years old • Diabetes requiring medication • Previous spontaneous MI (prior to the MI currently described) • Multivessel coronary artery disease • Chronic non-end-stage renal disease

Source: Based on Table 11 of the CS[1]
CS = company submission; GI = gastrointestinal; MI = myocardial infarction

A total of 2661 patient records were collected across England and Wales in 2 separate surveys; of these, n=946 (36%) patient records fit the PEGASUS-like criteria and form the basis of the analysis.

*Of the patient records collected, the proportions excluded in line with the PEGASUS exclusion criteria and considered "low risk" i.e. not meeting the PEGASUS inclusion criteria, were consistent across to the 2 surveys (*Table 2.3).

Table 2.3: Patients included in the study and proportion of the sample fitting the PEGASUS-like criteria

Survey date	June 2015	March 2016
Patient records collected	850	1,811
Patients excluded due to not meeting the PEGASUS inclusion criteria	433 (51%)	1,016 (56%)
Patients excluded due to being 'low risk'	102 (12%)	164 (9%)
PEGAUS-like patient records	315 (37%)	631 (35%)

Source: Based on Table 12 of the CS[1]
CS = company submission

*The baseline characteristics of the patients described as PEGASUS-like in this market research were found to be consistent in the 2 waves of research, but differ from the patients recruited for the PEGASUS-TIMI 54 study in terms of age (UK patients are older) and type of qualifying MI (NSTEMI more prevalent than STEMI) and proportion with diabetes (*Table 2.4).

Table 2.4: Characteristics of PEGASUS-like Patients in England and Wales compared with baseline characteristics in the PEGASUS-TIMI 54 study

Patient Characteristics	England and Wales June 2015 (n=315)	England and Wales March 2016 (n=631)	PEGASUS-TIMI 54 study (n=21,162)
Age, y, median (IQR)	71 (65-78)	71.1 (65-77)	65 (59-71)
Qualifying –NSTEMI, n (%)	180 (57)	361 (57)	(41)
Qualifying –STEMI, n (%)	135 (43)	270 (43)	(54)
Qualifying –MI, type unknown (%)	-	-	(5)
Age ≥ 65 years, n (%)	256 (81)	504 (80)	(55)
Diabetes requiring medication, n (%)	139 (44)	273 (43)	(28)
Previous spontaneous MI (prior to current), n (%)	51 (16)	87 (14)	(17)
Multi-vessel CAD, n (%)	104 (33)	230 (36)	(59)
Chronic non-end stage renal disease, n (%)	34 (11)	86 (14)	(6)
Peripheral arterial disease, n (%)	24 (8)	68 (11)	(5)

Source: Based on Table 13 of the CS[1]
CAD = coronary artery disease; CS = company submission; IQR = interquartile range; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction

Of 946 PEGASUS-like patients, 855 (90%) were prescribed DAPT at discharge (Table 2.5). *"Ticagrelor + ASA was the most frequently prescribed regimen at discharge and was prescribed to 421 (45%) patients, followed by clopidogrel + ASA which was prescribed in 366 (39%) cases. Only 88 (9%) patients were prescribed a monotherapy OAP regimen, where in two-thirds of cases the*

agent was ASA. These prescribing behaviours were consistently observed in both waves of the market research.

*For the great majority of patients in both waves of the research, the second OAP or ADP receptor inhibitor was to be stopped at 12 months after discharge, meaning that beyond 12 months, 843 (89%) patients were prescribed ASA monotherapy, 15 (2%) clopidogrel monotherapy and 43 (5%) were prescribed no oral antiplatelet treatment. A small number of patients were recommended to remain on DAPT: 32 (3%) on clopidogrel + ASA, 9 (1%) on ticagrelor + ASA and 4 (>1%) on prasugrel + ASA" (*Table 2.5).

Table 2.5: Cardiologist prescribing intentions for PEGASUS-like Patients in England and Wales

	England & Wales (N=315)	England & Wales (n=631)	Combined (n=946)
	June 2015	**March 2016**	**-**
Therapy at discharge			
ASA monotherapy, n (%)	17 (5)	44 (7)	61 (6)
clopidogrel monotherapy, n (%)	11 (3)	12 (2)	23 (2)
clopidogrel + ASA, n (%)	123 (39)	243 (39)	366 (39)
prasugrel + ASA, n (%)	18 (6)	50 (8)	68 (7)
ticagrelor + ASA, n (%)	145 (46)	276 (44)	421 (45)
clopidogrel + ticagrelor, n (%)	1 (0)	1 (0)	2 (0)
prasugrel monotherapy	- (-)	2 (0)	2 (0)
ticagrelor monotherapy	- (-)	3 (0)	3 (0)
Treatments patients receive post 12 months			
ASA monotherapy, n (%)	281 (89)	562 (89)	843 (89)
clopidogrel monotherapy, n (%)	6 (2)	9 (1)	15 (2)
clopidogrel + ASA, n (%)	8 (3)	24 (4)	32 (3)
prasugrel + ASA, n (%)	2 (1)	2 (0.3)	4 (0)
ticagrelor + ASA, n (%)	3 (1)	6 (1)	9 (1)
No oral antiplatelet prescribed, n (%)	15 (5)	28 (4)	43 (5)

Source: Based on Table 14 of the CS[1]
ASA = acetylsalicylic acid; CS = company submission

"NICE guidelines state that patients should remain on aspirin 'indefinitely'[12] *and SIGN [*Scottish Intercollegiate Guidelines Network] *guidelines state patients should remain on aspirin "long term.*[16] *In concordance with this, 89% of PEGASUS-like patients were set to receive aspirin monotherapy in the post 12 month setting, with 5% of patients receiving no therapy at all post 12 months: only 2% of PEGASUS-like patients were recommended to receive clopidogrel + ASA beyond the initial 12 month acute phase of treatment.*

A key strength of the study design for this research is that the cardiologists taking part were not required to apply any selection criteria to their pool of patients before reporting their prescribing intentions. Rather, they were asked to record the background characteristics for all patients who had

experienced a qualifying MI. This approach is expected to have reduced the potential for selection bias by the cardiologists.

The key limitation of this study is that it is based on the treatment intention of the cardiologist as described in the discharge letter, rather than what the patient actually received in practice. It is unclear how closely those instructions were followed in the primary care setting following discharge and there are many reasons why patients may be switched from one drug to another, treatment prolonged or stopped sooner than recommended by the cardiologist.

Conclusion
The prescribing intention data collected in this survey confirms that prescribing to PEGASUS-like patients is 12 months DAPT followed by (lifelong/indefinite) use of aspirin; this is in accordance with both marketing authorisations for the antiplatelet treatment options considered, as well as recommendations from both NICE guidance and international professional guidelines. 90% of PEGASUS-like patients in England and Wales received ASA monotherapy in the 12 months post-MI setting and it can therefore be concluded that ASA monotherapy represents established clinical practice in the NHS for these patients".

ERG comment: The company's description of the treatment options is based on existing NICE guidance which is appropriate and relevant to the decision problem.[11] This guidance was updated in 2013. Although there were some changes to the wording of the guidance the statements made in the CS remain correct.[12] The existing NICE guidance was supported by guidelines from the ESC.[13] The reference to support the market research conducted by the company was not provided and therefore could not be checked.

3 Critique of company's definition of decision problem

The company presents its response to the decision problem in Section 1.1 of the CS. This is reproduced below.

Table 3.1: Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults who have had a myocardial infarction and are at increased risk of atherothrombotic events.	Adults who have had a myocardial infarction between 1 and 2 years ago and are at increased risk of atherothrombotic events.	This is a pre-specified subgroup within the limits of the marketing authorisation in this indication.
Intervention	Ticagrelor co-administered with aspirin	Ticagrelor 60 mg BID co-administered with aspirin for up to 3 years.	This is the dose specified in the marketing authorisation and there is limited data beyond 3 years.
Comparator(s)	• Aspirin • Clopidogrel in combination with aspirin	• Aspirin	Comparison with clopidogrel + aspirin is not presented. There is [sic] no head-to-head trial data and robust indirect comparison of pivotal trial outcomes is not feasible owing to important differences between studies Clopidogrel + aspirin is not established NHS clinical practice in the population of interest Clopidogrel + aspirin does not have a licence in this indication
Outcomes	The outcome measures to be considered include: • non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary revascularisation	The outcome measures considered include: • non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary revascularisation	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• bleeding events • mortality • adverse effects of treatment • health-related quality of life	• bleeding events • mortality • adverse effects of treatment • health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year. The time horizon in the model is 40 years. At this point 98.8% of patients have died and all important differences in costs and CV outcomes are captured. Costs are considered from an NHS and Personal Social Services perspective	NA
Subgroups to be considered	If the evidence allows following subgroups will be considered separately: • People with or without diabetes • People who have or have not had prior revascularisation	Consideration has been given to the following subgroups: • People with or without diabetes • People with or without a history of PCI	"History of PCI" was a pre-specified subgroup in the pivotal trial and is used as a proxy. Results for the primary efficacy and safety endpoints are presented for both subgroups requested in the ITT analysis and in a subset of patients who had an MI <2 years ago. Data for other key endpoints are presented for the subset who had an MI <2 years ago only.

Source: Based on Table 1 of the CS[1]

BID = twice daily; CS = company submission; ITT = intention to treat; mg = milligram; MI = myocardial infarction; NA = Not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction

3.1 Population

The patient population described in the final scope is *"Adults who have had a myocardial infarction and are at increased risk of atherothrombotic events"*.[17]

The definition of the patient population addressed in the CS is *"Adults who have had a myocardial infarction between 1 and 2 years ago and are at increased risk of atherothrombotic events"*.[1]

ERG comment: The patient population addressed in the CS is based on the PEGASUS-TIMI 54 trial. The overall population in this study was patients who had experienced a prior MI between one and three years ago who also had ≥1 additional atherothrombosis risk factor.[18] The patient population addressed in the CS is a subpopulation of the overall study population who had experienced a prior MI between one and two years ago who also had ≥1 additional atherothrombotic risk factor.

This subpopulation excludes patients who had an MI <1 year ago which is in line with the licensed indication which states that patients must have a history of MI of at least one year to be eligible for treatment with ticagrelor 60 mg BID.[19]

The patient population addressed in the CS also excludes those patients who had an MI between two and three years ago. The licensed indication for ticagrelor 60 mg BID states that treatment may be initiated up to two years following an MI or within one year after stopping treatment with a previous ADP receptor inhibitor.[19] In principle patients who had been treated with an ADP receptor inhibitor for the first two years following their MI would be eligible for treatment, i.e. up to three years from the initial MI. The company acknowledged this in the CS but argued that there were relatively few patients that meet these criteria in practice. Given that there are few ADP inhibitors licensed for use beyond 12 months following an MI and that most patients receive ASA monotherapy after the first 12 months the ERG agrees with the company that the subgroup specified is the CS represents the most relevant available evidence for the population requested in the final scope.

3.2 Intervention

The intervention in the CS is "*ticagrelor 60 mg BID co-administered with aspirin for up to 3 years*".[1] This is in line with the scope which specified "*ticagrelor co-administered with aspirin*".[17]

ERG comment: According to the CS, the recommended dose of ticagrelor specified in the license is 60 mg twice daily co-administered with aspirin.[1] The stipulation that treatment is for up to three years reflects the fact that the PEGASUS-TIMI 54 study, the only study of ticagrelor in the population of interest, treated patients for up to three years.[20]

3.3 Comparators

The comparators in the scope issued by NICE were aspirin monotherapy or clopidogrel in combination with aspirin.[17]

The CS only included aspirin monotherapy as a comparator.[1] The company argued that clopidogrel in combination with aspirin does not have a licensed indication in the population of interest as it is not established as clinical practice in the NHS. The company further argued that there is no evidence to support the comparison of ticagrelor plus aspirin versus clopidogrel plus aspirin as there is no head to head trial comparing these treatments and an indirect comparison was not possible.

ERG comment: The clinical indications for clopidogrel are described in the summary of product characteristics (SmPC)[21] as:

- *"Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.*

- *Patients suffering from acute coronary syndrome:*
    - *Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).*
    - *ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy."*

The population of patients with ACS includes those who have experienced an MI. The trials which supported the licensed indication of clopidogrel continued treatment for up to 12 months in these patients.[21] NICE recommends clopidogrel as a treatment option for up to 12 months in patients who have had NSTEMI or in patients who have had STEMI and received a bare metal or drug eluting stent. Clopidogrel is also recommended by NICE as a treatment option instead of aspirin in patients who have other cardiovascular disease and have either: had an MI and stopped dual antiplatelet therapy, or had an MI more than 12 months ago.[12] The latter recommendation indicates that clopidogrel may be used beyond 12 months post-MI in some circumstances. This is supported by the submission from the UK Clinical Pharmacy association (UKCPA) which indicates that the duration of treatment may be extended on a case-by-case basis.[22]

The ERG agrees with the company that the differences between trials of ticagrelor plus aspirin versus placebo plus aspirin and trials of clopidogrel plus aspirin versus placebo plus aspirin were such that an indirect comparison was not feasible.

These differences are discussed in more detail in Section 4.4.

3.4 Outcomes

The outcomes reported in the CS[1] are in line with the outcomes listed in the scope specified by NICE.[17]

3.5 Other relevant factors

No other relevant factors were identified.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company stated in Section 4.1 of the CS that "*a systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy, tolerability and safety of prolonged DAPT (ticagrelor, clopidogrel, prasugrel, vorapaxar in combination with aspirin) including rivaroxaban in adult patients with a history of MI in September 2014. This review was updated in January 2015 and again in December 2015*".[1]

ERG comment: The systematic review will be critiqued in this section of the report.

4.1.1 Searches

Description and critique of the company's search strategies

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[23] The submission was checked against the STA specification for company/sponsor submission of evidence.[24] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1.

Clinical effectiveness

The CS states that a systematic review was conducted to retrieve relevant efficacy, tolerability and safety data from the published literature about DAPT in adults with a history of myocardial infarction.

Searches were initially conducted on 8 September 2014, then updated on 6 January 2015, and updated once more on 1 December 2015. The databases searched were MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase and the Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment Database (HTA)). The host provider for each database was listed; the date span of the databases searched and the specific date the searches were conducted were provided. The manufacturer additionally searched the following clinical trials registers: European Union (EU) Clinical Trials Register, ClinicalTrials.gov, the Australian New Zealand Trials Registry (ANZCTR), and the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP). Conference proceedings were also searched: ESC, AHA, and American College of Cardiology (ACC). Detailed search strategies for the latest update searches were reported in Appendix 2 of the CS. The CS did not provide full details of the clinical trials register searches or conference proceedings searches. Details of the clinical trials register searches, apart from the WHO ICTRP search, and of the conference proceedings searches were provided in response[25] to the ERG request for clarification letter.[26]

The company translated the research question into appropriate search strategies and the ERG considered the searches to be satisfactory. Searches were clearly structured and divided into population and intervention/comparator facets, using an appropriate combination of index terms, free text and synonyms for the population, interventions and comparators. The search strategies included Boolean, truncation and proximity operators. No date or language limits were used. Study design limits to identify RCTs and systematic reviews were applied. The study design filters were not referenced, so it was unclear whether the filters used were published objectively derived filters.

However, the filters do appear to be those designed by and available from the website of the Scottish Intercollegiate Guidelines Network (SIGN).[27]

The search strategies included all currently available comparators alongside the intervention, though only aspirin alone, and aspirin combined with clopidogrel were considered in the NICE scope. Including the comparators in the search strategy ensured greater sensitivity.

Searches of clinical trials registers were conducted. The CS reported the trials registers searched in the main report (Section 4.1), but not in Appendix 2. The search strategies, dates of searches, and results were not reported. Such details would have been helpful to the ERG, followed current practice in literature search reporting, and ensured transparency. The ERG requested full details of the search methods used to search the clinical trials registers in the ERG request for clarification letter,[26] and they were provided in response.[25]

Searches of conference proceedings were conducted. In the main report (Section 4.1), the CS reported the names of the conferences searched and that the last three years were searched. The list of conference proceedings searched was then repeated in the Appendix (A2.4 Additional searches), but with an additional conference included, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and that only 2015 proceedings were searched. There were no specific details about the search methods used, the exact dates searched, or the results of the searches. It was not clear which particular ISPOR conference/s were searched, i.e. International meeting, European, Asia-Pacific, and/or Latin America. Full details of the methods used to search conference proceedings were requested in the ERG request for clarification letter,[26] and were provided in response.[25]

Indirect and mixed treatment comparisons
The CS reported that the clinical effectiveness searches reported above were used to identify studies that could potentially be used in an indirect comparison.

Non-randomised and non-controlled evidence
No searches for non-randomised studies were reported.

Adverse events
The PEGASUS-TIMI 54 trial[28] was used to assess safety and tolerability. The searches used for the clinical effectiveness section were described as being used to identify the efficacy, tolerability and safety of DAPT. Appendix 9*:* Search strategy for adverse reactions (Section 4.12.3) refers to Appendix 2. Guidance by the Centre for Reviews and Dissemination[29] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used.

4.1.2 Inclusion criteria

The eligibility criteria used to identify studies for inclusion in the review are presented in Table 4.1. The CS states that *"non-relevant studies were excluded on 1st pass, and studies for potential inclusion were retrieved for full review on 2nd pass"* and that *"identified studies on 2nd pass were independently assessed by a reviewer in order to ascertain whether they met the pre-specified inclusion and exclusion criteria. Any uncertainties around inclusion were resolved by discussion with a second reviewer"*.[1]

Table 4.1: Eligibility criteria used in search strategy

	Inclusion criteria	Exclusion criteria
Population	Adult patients with previous MI (STEMI or NSTEMI) occurring prior to study randomisation with ≥18 months of DAPT received between randomisation and study completion/results reporting	Patients without a previous MI or receiving DAPT for <18 months
Interventions	DAPT (comprising ticagrelor, clopidogrel, prasugrel, vorapaxar, or rivaroxaban in combination with aspirin)	-
Comparators	Placebo Monotherapy Triple therapy	-
Outcomes	Efficacy: Composite of CV death, MI or stroke (total, fatal, non-fatal) CV death MI (total, fatal, non-fatal) Stroke (total, fatal, non-fatal) All-cause mortality Composite of CV death or coronary or cerebrovascular arterial thrombosis hospitalisation Composite of coronary heart disease death, MI or stroke Coronary stent thrombosis QoL Safety, including but not limited to: Dyspnoea TIMI-defined major/minor bleeding PLATO-defined major bleeding GUSTO-defined major/minor bleeding	-
Study design	RCTs: blinded, open-label, open-label extensions of parallel group trials, phase 2 and above	-
Language restrictions	No restriction	-

Source: Based on Table 15 of the CS[1]

CS = company submission; CV = cardiovascular; DAPT = dual anti-platelet therapy; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; MI = myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction; PLATO = Platelet Inhibition and Patient Outcomes; QoL = quality of life; RCT = randomised controlled trial; STEMI = ST segment elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction

ERG comment: The methods used to select studies for the review appear to be appropriate in terms the outcomes and study design.

The inclusion criteria for the interventions in the CS[1] are broader than those given in the NICE scope.[17] The final scope states that the intervention is ticagrelor in combination with aspirin and the comparators are aspirin monotherapy or clopidogrel in combination with aspirin.[17] The interventions included in the review were any DAPT including ticagrelor, clopidogrel, prasugrel, vorapaxar or

rivaroxaban each given in combination with aspirin. The included comparators were placebo, monotherapy or triple therapy. The CS did not specify which treatments were eligible as monotherapy or triple therapy.

The criteria relating to study population specifically excluded patients who had received <18 months dual antiplatelet therapy. The choice of 18 months treatment as a cut off appears arbitrary and no justification for this decision was provided by the company.

The number of reviewers who assessed studies for inclusion in the review was unclear. The text of the CS implies that one reviewer assessed titles an abstracts in the first pass and that studies identified for inclusion at the second pass were checked by a second reviewer. Only using one reviewer for screening of titles and abstracts would not be considered best practice[30] and increases the risk of relevant studies being missed.

4.1.3 Critique of data extraction

The company states that "*data extraction Table (DET) in Microsoft Excel file was developed and pilot tested for possible data extraction of eligible RCTs on prolonged (at least 18 months) dual anti-platelet therapy involving aspirin, ticagrelor, clopidogrel, vorapaxar, prasugrel or rivaroxaban*".[1]

ERG comment: The company did not specify which data were extracted or how many reviewers were involved in the data extraction process. The CS did not report sufficient information to determine whether the extracted data were assessed for accuracy.[1]

4.1.4 Quality assessment

The CS reported the assessment of methodological quality using the Cochrane risk of bias tool in the studies identified in the systematic review.[1]

ERG comment: The company did not report the number of reviewers involved in the assessment of risk of bias. The use of only one reviewer to conduct the quality assessment would not be considered best practice[30] and increases the risk of inappropriate assessment.

4.1.5 Evidence synthesis

The company did not report details of the methods of evidence synthesis for either direct or indirect comparisons.

ERG comment: The systematic review reported in the CS identified only one study directly comparing ticagrelor plus aspirin to any of the included comparators therefore no formal meta-analysis was possible.[1] The details of this study are discussed in Section 4.2

The company assessed the similarity of the three studies identified by the systematic review for potential inclusion in a network meta-analysis but concluded that the studies were not comparable therefore no methods for network meta-analysis were reported.[1] The study design and patient characteristics in these trials are discussed in Section 4.3.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company states in Section 4.1 that "*the original systematic review and subsequent updates of the available clinical evidence identified nine records covering three unique RCTs examining prolonged DAPT in the population of interest*".[1]

A comparison of the population, intervention, comparator, outcomes and study designs for the three trials is given in Table 4.2. There was only one study which included the intervention of interest for this appraisal, PEGASUS-TIMI 54. The details of this study are discussed here. The details of the CHARISMA and DAPT studies will be discussed in Sections 4.3 and 4.4 in the context of indirect comparisons.

The PEGASUS-TIMI 54 trial randomised patients to ticagrelor 90 mg BID + ASA versus ticagrelor 60 mg BID + ASA versus placebo + ASA. The company noted in Section 1.3 of the CS that the intervention of interest for this appraisal is ticagrelor 60 mg BID + ASA.[1] The details of the ticagrelor 90 mg BID arm will not be considered here.

Table 4.2: Comparison of population, intervention, comparator, outcomes and study design

Trial	PEGASUS-TIMI 54 (NCT0122556)	CHARISMA (NCT00050817)	DAPT (NCT00977938)
Population	Patients with a spontaneous MI 1-3 years prior to study enrolment, aged ≥50 years, and with at least one of additional high-risk factors: (i) age ≥65 years; (ii) DM requiring medication; (iii) a second prior spontaneous MI; (iv) multi-vessel coronary artery disease; or (v) chronic renal dysfunction defined as an estimated creatinine clearance of <60 ml/minute.	Full study cohort: patients with documented CAD, cerebrovascular disease, or PAD, or with multiple risk factors for atherothrombosis Post hoc analysis: patients with a documented prior MI, documented prior IS, or symptomatic PAD from full study cohort	Patients with CAD, candidates for DAPT and who received treatment with FDA-approved DES and BMS devices Post-hoc analysis: patients with MI compared with those without
Intervention	Ticagrelor 60 mg BID + ASA 75-150 mg/day	Clopidogrel + ASA	Thienopyridine (clopidogrel or prasugrel) + ASA
Comparators	Placebo + ASA 75-150 mg/day	Placebo + ASA	Placebo + ASA
Outcomes	Composite of CV death, MI or stroke TIMI-defined major bleeding CV death All-cause mortality ICH Fatal bleeding	Composite of CV death, MI or stroke GUSTO-defined severe bleeding CV death, MI, stroke or rehospitalisation for UA, TIA, or a revascularisation procedure GUSTO-defined moderate bleeding	Incidence of definite or probable stent thrombosis and incidence of MACCE GUSTO-defined moderate or severe bleeding MI
Study Design	Double blind, placebo-controlled RCT	Double-blind, placebo-controlled RCT	Double blind, placebo-controlled RCT

Source: Based on Table 16 of the CS[1]
ASA = acetyl salicylic acid; BMS = bare metal stent; CAD = coronary artery disease; CS = company submission; CV = cardiovascular; DAPT = dual anti-platelet therapy; DES = drug-eluting stent; DM = diabetes

Trial	PEGASUS-TIMI 54 (NCT0122556)	CHARISMA (NCT00050817)	DAPT (NCT00977938)
mellitus; FDA = US Food and Drug Administration; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; ICH = intracranial haemorrhage; IS = ischaemic stroke; MACCE = major adverse cardiac and cerebrovascular event; mg = milligram; MI = myocardial infarction; PAD = peripheral artery disease; RCT = randomised controlled trial; TIA = transient ischaemic attack; TIMI = Thrombolysis in Myocardial Infarction; UA = unstable angina			

Table 4.3 summarises the eligibility of the PEGASUS-TIMI 54 study and the efficacy and safety outcomes are summarised in Table 4.4.

Table 4.3: Eligibility criteria of the PEGASUS-TIMI 54 study

Inclusion Criteria	Exclusion Criteria

• Aged ≥50 years
• Spontaneous MI 12–36 months prior
• At least one of the following risk factors:
  • Aged ≥65 years
  • Diabetes mellitus on medication
  • A second prior MI
  • Multi-vessel CAD (≥50% in more than two coronary territories)
  • Chronic renal dysfunction (non-end stage, creatinine clearance <60 ml/min)
• Taking aspirin 75–150 mg daily
• Contraception in women of child-bearing potential
• Provided written informed consent
	• Planned use of ADP receptor blockers, dipyridamole or cilostazol
	• Planned revascularisation (coronary, peripheral, cerebrovascular)
	• Potent inducer/inhibitor/substrate of CYP3A use
	• Chronic anticoagulation
	• Known bleeding diathesis or coagulation disorder
	• Increased risk of bleeding defined as:
	  • A history of intracranial bleed at any time
	  • A central nervous system tumour or intracranial vascular abnormality (e.g. aneurysm, arteriovenous malformation) at any time
	  • Intracranial or spinal cord surgery within 5 years
	  • A GI bleed within the past 6 months
	  • Major surgery within 30 days
	  • History of ischaemic stroke
	  • Patients considered to be at risk of bradycardic events (e.g. known sick sinus syndrome or second or third degree atrioventricular block) unless already treated with a permanent pacemaker
	  • CABG in the last 5 years
	• Known severe liver disease
	• Renal failure requiring dialysis
	• Pregnancy or lactation
	• Life expectancy <1 year
	• Any condition judged by the investigator to make participation unsafe for the patient
	• Concern for inability to comply with the protocol
	• Prior participation in a trial with Ticagrelor (if treated with active Ticagrelor)
	• Involvement in planning or conduct of the study
	• Participation in another clinical study with an investigational product during the prior 30 days

Source: Based on Table 17 of the CS[1] ADP =: adenosine diphosphate; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CS =	

Inclusion Criteria	Exclusion Criteria
company submission; CYP3A = cytochrome P450; GI = gastrointestinal; mg = milligram; MI = myocardial infarction; ml = millilitre	

Table 4.4: Efficacy and safety outcomes of PEGASUS-TIMI 54

Outcome	Definition	Inclusion in final scope
Primary		
Composite endpoint of CV death, MI or stroke	Time to first occurrence of any event after randomisation from the composite of CV death, MI or stroke	No – final scope does not include composite outcomes. Non-fatal MI and non-fatal stroke are each included separately
Secondary		
CV death	Time to occurrence of CV death after randomisation	No
All-Cause mortality	Time to occurrence of all-cause mortality after randomisation	Yes – final scope specifies "mortality" as an outcome
Composite of CV death, non-fatal MI, non-fatal stroke or urgent coronary revascularisation	Time to first occurrence of any event after randomisation from the composite of CV death, non-fatal MI, non-fatal stroke, or urgent coronary revascularisation	No – final scope does not include composite outcomes. Non-fatal MI, non-fatal stroke and urgent coronary revascularisation are each included separately
Composite of CV death or coronary or cerebrovascular arterial thrombosis hospitalisation (including non-fatal MI, non-fatal stroke, urgent coronary revascularisation, unstable angina, or transient ischaemia attack).	Time to first occurrence of any event after randomisation from the composite of CV death or coronary or cerebrovascular arterial thrombosis hospitalisation. The individual components were also to be examined in an analogous manner	No – final scope does not include composite outcomes. Non-fatal MI, non-fatal stroke and urgent coronary revascularisation are each included separately
Composite of CHD death, non-fatal MI, or non-fatal stroke	Time to first occurrence of any event after randomisation from the composite of CHD death, non-fatal MI, or non-fatal stroke. The individual component of CHD death was also to be examined in an analogous manner	No – final scope does not include composite outcomes. Non-fatal MI and non-fatal stroke are each included separately
Composite of CV death, non-fatal MI, non-fatal stroke, or TIMI Major bleeding	Time to first occurrence of any event after randomisation from the composite of CV death, non-fatal MI, non-fatal stroke, or TIMI Major bleeding	No – final scope does not include composite outcomes. Non-fatal MI, non-fatal stroke and "bleeding events" are each included separately
Incidence of coronary stent thrombosis	Time to first occurrence of coronary stent thrombosis after randomisation	No
Safety		
Thrombolysis in	Time to first thrombolysis in	Yes - final scope specifies

Outcome	Definition	Inclusion in final scope
myocardial infarction (TIMI) Major bleeding event	myocardial infarction (TIMI) Major bleeding event following the first dose of study drug	"bleeding events" as an outcome
TIMI Major or Minor bleeding	Time to first TIMI Major or Minor bleeding	Yes - final scope specifies "bleeding events" as an outcome
Discontinuation of study drug due to any bleeding event	Time to discontinuation of study drug due to any bleeding event	No – Treatment discontinuation was not explicitly listed in the final scope however the number of patients who discontinued due to bleeding could be considered relevant information.
Evaluation of AEs	NR	Yes – final scope specifies "adverse effects of treatment" as an outcome
Quality of Life		
Health care utilisation associated with hospitalisations and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D)	NR	Yes – final scope specifies "quality of life" as an outcome

Source: Based on Section 4.3 of the CS[1] and final scope[17]
AEs = Adverse events, CHD = coronary heart disease; CS = company submission; CV = Cardiovascular, MI = myocardial infarction, TIMI = Thrombolysis in myocardial infarction

The baseline characteristics and geographic regions of patients in the overall study population in the PEGASUS-TIMI 54 trial are summarised in Tables 4.5 and 4.6. The baseline characteristics of the subgroup with MI <2 years ago which represents the base case population for the CS are summarised in Table 4.7.

Table 4.5: Baseline characteristics of the overall study population in PEGASUS-TIMI 54

Baseline characteristic	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)
Age – years (±SD)	65.2 ± 6.4	65.4 ± 8.3
Female sex – n (%)	1,661 (23.6%)	1,717 (24.3%)
White race – n (%)[†]	6,077 (86.3%)	6,124 (86.7%)
Weight – kg (±SD)	82.0 ± 17.0	81.8 ± 16.6
Hypertension – n (%)	5,461 (77.5%)	5,484 (77.6%)
Hypercholesterolemia – n (%)	5,380 (76.4%)	5,451 (77.1%)
Current smoker – n (%)	1,206 (17.1%)	1,143 (16.2%)
DM – n (%)	2,308 (32.8%)	2,257 (31.9%)
Multi-vessel CAD – n/total n (%)	4,190/7,042 (59.5%)	4,213/7,067 (59.6%)
History of PCI – n/total n (%)[‡]	5,879/7,044 (83.5%)	5,837/7,066 (82.6%)
>1 prior MI – n (%)	1,168 (16.6%)	1,188 (16.8%)
eGFR <60 ml/min/1.73m^2 – n/total	1,547/6,955 (22.2%)	1,649/6,985 (23.6%)

Baseline characteristic	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)
n (%)[§]		
Qualifying event[¥]		
Median years since MI	1.7	1.7
Interquartile range	1.2–2.3	1.2–2.3
Type of MI – n/total n (%)		
STEMI	3,757/7,035 (53.4%)	3,809/7,057 (54.0%)
NSTEMI	2,842/7,035 (40.4%)	2,843/7,057 (40.3%)
Unknown type	436/7,035 (6.2%)	405/7,057 (5.7%)
Medication at enrolment – n (%)		
Aspirin at any dose	7,036 (99.9%)	7,057 (99.9%)
Statin	6,495 (92.2%)	6,583 (93.2%)
Beta-blocker	5,796 (82.3%)	5,878 (83.2%)
ACE inhibitor or ARB	5,631 (79.9%)	5,697 (80.6%)
Previous treatment with an ADP receptor inhibitor – n (%)		
Any	6289 (89.3%)	6285 (88.9%)
Clopidogrel	5915 (84.0%)	5878 (83.7%)
Prasugrel	317 (4.5%)	325 (4.6%)
Ticlopidine	35 (0.5%)	38 (0.5%)
Ticagrelor	26 (0.4%)	38 (0.5%)
Missing	1 (0.0%)	5 (0.1%)

Source: Based on Table 19 of the CS[1]

Footnotes: [†] Race was self-reported; [‡] A total of 96.5% of PCIs involved stenting; [§] The eGFR was calculated with the use of the Modification of Diet in Renal Disease equation; [¥] Patients for whom it could not be verified that they had had an MI were excluded from the denominator (10 patients in the 60 mg group and 10 in the placebo group) as well as from the calculation for the median years since the MI.

ACE = angiotensin-converting enzyme; ADP = Adenosine diphosphate; ARB = angiotensin II receptor blocker; BID = twice daily; CAD = coronary artery disease; CS = company submission; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; kg = kilogram; mg = milligram; MI = myocardial infarction; min = Minute; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST segment elevation myocardial infarction

Table 4.6 Geographic region of the overall study population in PEGASUS-TIMI 54

Geographic region	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)
Asia and Australia	788 (11.2%)	788 (11.2%)
Europe and South Africa	4,146 (58.9%)	4,154 (58.8%)
North America	1,297 (18.4%)	1,303 (18.4%)
South America	814 (11.6%)	822 (11.6%)

Source: Based on Table 10 of the CSR[31]

BID = twice daily; CSR = clinical study report; mg = milligram

Table 4.7 Baseline characteristics of the MI <2 years ago subgroup in PEGASUS-TIMI 54

Baseline characteristic	Ticagrelor 60 mg BID (n=4,331)	Placebo (n=4,333)
Age – years (±SD)	65.2 ± 8.5	65.4 ± 8.3
Female sex – n (%)	1,021 (23.6%)	1,070 (24.7%)
White race – n (%)[†]	3,734 (86.2%)	3,740 (86.3%)
Weight – kg (±SD)	82 ± 16.9	81.4 ± 16.5
Hypertension – n (%)	3,354 (77.4%)	3,346 (77.2%)
Hypercholesterolemia – n (%)	3,265 (75.4%)	3,332 (76.9%)
DM – n (%)	1,419 (32.8%)	1,322 (30.5%)
Multi-vessel CAD – n/total n (%)	2,601 (60.1%)	2,586 (59.7%)
History of PCI – n/total n (%)[‡]	3,638 (84.0%)	3,623 (83.6%)
>1 prior MI – n (%)	709 (16.4%)	699 (16.1%)
eGFR <60 ml/min/1.73m^2 – n/total n (%)[§]	806 (18.9%)	853 (20.0%)
Qualifying event[¥]		
Median months since MI	16	16
Range	3 - 24	2 - 24
Type of MI – n/total n (%)		
STEMI	2,309 (53.3%)	2,370 (54.7%)
NSTEMI	1,770 (40.9%)	1,759 (40.6%)
Unknown type	252 (5.8%)	204 (4.7%)
Medication at enrolment – n (%)		
Aspirin at any dose	4,324 (99.8%)	4,322 (99.7%)
Statin	3,958 (91.4%)	4,021 (92.8%)
Beta-blocker	3,616 (83.5%)	3,661 (84.5%)
ACE inhibitor or ARB	3,500 (80.8%)	3,513 (81.1%)

Source: Based on Table 20 of the CS[1]

Footnotes: [†] Race was self-reported; [§] The eGFR was calculated with the use of the Modification of Diet in Renal Disease equation; [¥] Patients for whom it could not be verified that they had had an MI were excluded from the denominator as well as from the calculation for the median years since the MI

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BID = twice daily; CAD = coronary artery disease; CS = company submission; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; kg = kilogram; mg = milligram; MI = myocardial infarction; min = Minute; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST segment elevation myocardial infarction

The final scope issued by NICE also requested evidence in specific patient subgroups: people with or without diabetes and people who have or have not had prior revascularisation. The baseline characteristics for people with or without diabetes are summarised in Table 4.8 and for people with or without history of PCI in Table 4.9.

Table 4.8: Baseline characteristics of patients who had an MI <2 years ago with or without diabetes

Baseline characteristic	Diabetes		No Diabetes	
	Ticagrelor 60 mg BID (n=1,419)	Placebo (n=1,322)	Ticagrelor 60 mg BID (n=2,912)	Placebo (n=3,011)
Age – years (±SD)	63.9 ± 8.3	64.1 ± 8.3	65.7 ± 8.6	66 ± 8.2
Female sex – n (%)	379 (26.7%)	380 (28.7%)	642 (22.0%)	690 (22.9%)
White race – n (%)[†]	1,153 (81.3%)	1,096 (82.9%)	2,581 (88.6%)	2,644 (87.8%)
Weight – kg (±SD)	85.5 ± 18.1	85.4 ± 18.6	80.3 ± 16.1	79.7 ± 15.2
Hypertension – n (%)	1,225 (86.3%)	1,128 (85.3%)	2,129 (73.1%)	2,218 (73.7%)
Hypercholesterolemia – n (%)	1,120 (78.9%)	1,053 (79.7%)	2,145 (73.7%)	2,279 (75.7%)
Multi-vessel CAD – n/total n (%)	705 (49.7%)	690 (52.2%)	1,896 (65.1%)	1,896 (63.0%)
History of PCI – n/total n (%)[‡]	1,152 (81.2%)	1,065 (80.6%)	2,486 (85.4%)	2,558 (85.0%)
>1 prior MI – n (%)	228 (16.1%)	222 (16.8%)	481 (16.5%)	477 (15.8%)
eGFR <60 ml/min/1.73m^2 – n/total n (%)[§]	237 (17.0%)	245 (18.8%)	569 (19.8%)	608 (20.5%)
Qualifying event[¥]				
Median months since MI	16.1	16	16	15.9
Range	3 - 24	4.7 - 24	3 - 24	2 - 24
Type of MI – n/total n (%)				
STEMI	738 (52.0%)	695 (52.6%)	1,571 (53.9%)	1,675 (55.6%)
NSTEMI	604 (42.6%)	564 (42.7%)	1,166 (40.0%)	1,195 (39.7%)
Unknown type	77 (5.4%)	63 (4.8%)	175 (6.0%)	141 (4.7%)
Medication at enrolment – n (%)				
Aspirin at any dose	1,417 (99.9%)	1,320 (99.8%)	2,907 (99.8%)	3,002 (99.7%)
Statin	1,292 (91.1%)	1,212 (91.7%)	2,666 (91.6%)	2,809 (93.3%)
Beta-blocker	1,196 (84.3%)	1,131 (85.6%)	2,420 (83.1%)	2,530 (84.0%)
ACE inhibitor or ARB	1,186 (83.6%)	1,102 (83.4%)	2,314 (79.5%)	2,411 (80.1%)

Source: Based on Table 21 of the CS[1]

Footnotes: [†] Race was self-reported; [§] The eGFR was calculated with the use of the Modification of Diet in Renal Disease equation; [¥] Patients for whom it could not be verified that they had had an MI were excluded from the denominator as well as from the calculation for the median years since the MI

ACE = angiotensin-converting enzyme; ARB = Angiotensin II receptor blockers; BID = twice daily; CAD = coronary artery disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; kg = kilogram; mg = milligram; MI = myocardial infarction; ml = millilitre; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST segment elevation myocardial infarction

Table 4.9: Baseline characteristics of patients who had an MI <2 years ago with or without history of PCI

Baseline characteristic	History of PCI		No history of PCI	
	Ticagrelor 60 mg BID (n=3,638)	Placebo (n=3,623)	Ticagrelor 60 mg BID (n=692)	Placebo (n=709)
Age – years (±SD)	64.8 ± 8.4	65.1 ± 8.1	67 ± 8.9	67.1 ± 8.8
Female sex – n (%)	776 (21.3%)	821 (22.7%)	245 (35.4%)	249 (35.1%)
White race – n (%)[†]	3,148 (86.5%)	3,142 (86.7%)	585 (84.5%)	598 (84.3%)
Weight – kg (±SD)	82.5 ± 16.9	81.8 ± 16.7	78.9 ± 16.7	79.3 ± 15.5
Hypertension – n (%)	2,751 (75.6%)	2,761 (76.2%)	603 (87.1%)	585 (82.5%)
Hypercholesterolemia – n (%)	2,801 (77.0%)	2,833 (78.2%)	464 (67.1%)	498 (70.2%)
DM – n (%)	1,152 (31.7%)	1,065 (29.4%)	267 (38.6%)	256 (36.1%)
Multi-vessel CAD – n/total n (%)	2,434 (66.9%)	2,398 (66.2%)	166 (24.0%)	187 (26.4%)
>1 prior MI – n (%)	576 (15.8%)	553 (15.3%)	133 (19.2%)	145 (20.5%)
eGFR <60 ml/min/1.73m^2 – n/total n (%)§	616 (17.2%)	670 (18.8%)	190 (27.8%)	183 (26.2%)
Qualifying event[¥]				
Median months since MI	15.9	15.9	16.5	16.2
Range	3 - 24	2 - 24	3 - 24	5.7 - 24
Type of MI – n/total n (%)				
STEMI	2,042 (56.1%)	2,077 (57.3%)	267 (38.6%)	293 (41.3%)
NSTEMI	1,449 (39.8%)	1,407 (38.8%)	320 (46.2%)	352 (49.6%)
Unknown type	147 (4.0%)	139 (3.8%)	105 (15.2%)	64 (9.0%)
Medication at enrolment – n (%)				
Aspirin at any dose	3,631 (99.8)	3614 (99.8)	692 (100.0)	707 (99.7)
Statin	3,373 (92.7%)	3390 (93.6%)	585 (84.5%)	630 (88.9%)
Beta-blocker	3,064 (84.2%)	3077 (84.9%)	551 (79.6%)	583 (82.2%)
ACE inhibitor or ARB	2,931 (80.6%)	2949 (81.4%)	568 (82.1%)	563 (79.4%)

Source: Based on Table 22 of the CS[1]

Footnotes: [†] Race was self-reported; [§] The eGFR was calculated with the use of the Modification of Diet in Renal Disease equation; [¥] Patients for whom it could not be verified that they had had an MI were excluded from the denominator as well as from the calculation for the median years since the MI

ACE = angiotensin-converting enzyme; ARB: Angiotensin II receptor blockers; BID: twice daily; CAD: coronary artery disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; kg = kilogram; mg = milligram; MI: myocardial infarction; ml = millilitre; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SD = standard deviation; STEMI: ST segment elevation myocardial infarction

ERG comment:

Eligibility criteria

The patients recruited in the PEGASUS-TIMI 54 were those with a history of MI at least 12-36 months prior and at least one additional risk factor for subsequent atherothrombotic events. This reflects the population defined in the final scope which specified "*adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events*" but did not specify a minimum or maximum time since the qualifying MI.[17] The submission by the United Kingdom Clinical Pharmacy Association (UKCPA) – Cardiac Group stated that "*PEGASUS is not reflective of current UK practice, since we do not actively seek out patients post-event to restart or redefine treatment durations. The other factors specified in the inclusion criteria could be used to define "high risk" patients; ≥ 6 years, diabetes requiring medication, second prior spontaneous MI, multivessel disease and chronic renal dysfunction. However, in view of an increasingly aging population (who are increased risk of bleeding) and with co-morbidities that may warrant treatment with anticoagulation, the results of PEGASUS may not be applicable to the general 'real world' population that present with an ACS* [acute coronary syndrome]*".*[22]

It should be noted that, according to Figure 18 of the CS, the treatment effect on the primary endpoint (composite of CV death, MI or stroke) is greater for Caucasians (HR 0.81, 95% CI 0.71 to 0.92) than for non-Caucasians (HR 1.07, 95% CI 0.77 to 1.48).[1]

Outcomes

The final scope specified seven outcome measures relevant for this appraisal: non-fatal myocardial infarction (STEMI and NSTEMI), non-fatal stroke, urgent coronary revascularisation, bleeding events, mortality, adverse effects of treatment and health related quality of life.[17] The main primary and secondary outcomes of the PEGASUS-TIMI 54 study were composite outcomes which included the individual outcomes specified in the scope.

The primary outcome in PEGASUS-TIMI 54 was time to first occurrence after randomisation of any event from the composite of CV death, non-fatal MI or non-fatal stroke.[31]

The CS presented results for the individual components of the composite primary outcome in Sections 4.7 and 4.8 (summarised below).[1] The PEGASUS-TIMI 54 study was powered to detect differences in the composite primary outcome and therefore may not have had sufficient power to detect differences in the individual components of the primary and secondary outcomes. In principle the individual component end points may lack sufficient power, however given the number of patients enrolled in the study it is likely that any clinically meaningful differences would be detected.

Patient characteristics

The population which formed the base case for the CS was a subgroup of the overall study population in PEGASUS-TIMI 54 who had experienced their qualifying MI <2 years ago. The company argued that "*the focus of this submission is on patients who had an MI <2 years ago. The licence (as described in Section 1.2) focusses eligibility on those patients for whom the benefit:harm profile was most favourable in the PEGASUS-TIMI 54 study and allows it to be used in MI ≤2 years or ≤12 months since last ADP inhibitor treatment. As such, the licence allows ticagrelor 60 mg BID to be initiated in patients who were beyond 2 years from MI but within 1 year of treatment with a previous ADP receptor inhibitor. Based on clinical practice in England, we believe there to be very few such patients, so it is most relevant to focus solely on patients who experienced an MI <2 years*

ago. Feedback from UK cardiologists indicates that when considering a strategy of prolonged DAPT in high-risk patients, ticagrelor 60 mg BID will be used as "continuation therapy" following an initial one-year treatment with an ADP receptor inhibitor as described in the licence".[1]

In the overall study population of the PEGASUS-TIMI 54 trial, there were 7,045 patients in the ticagrelor 60 mg + ASA arm and 7,067 patients in the placebo + ASA arm. In the subgroup of patients who had their MI <2 years ago there were 4,331 patients in the ticagrelor 60 mg BID + ASA arm and 4,333 patients in the placebo + ASA arm. This implies that there were 2,714 patients in the ticagrelor 60 mg BID arm and 2,734 patients in the placebo + ASA arm who had their MI >2 years ago that were excluded from the base case population.

The baseline characteristics for the subgroup of patients with MI <2 years ago were similar to those of the overall study population although the percentage of patients who had received previous treatment with an ADP inhibitor prior to enrolment was not reported for the subgroup.

The CS also provided evidence for the patient subgroups with or without diabetes and with or without a history of PCI as requested in the final scope.[1, 17] These subgroups were reported as a subset within the group of patients who experienced a qualifying MI < 2 years ago.

Quality assessment

The methodological quality of the PEGASUS-TIMI 54 study was assessed using the Cochrane risk of bias tool. The results of the quality assessment are summarised in Table 4.10. In the original CS the study was rated as unclear for selective outcome reporting. In response to a request for clarification from the ERG the company stated "*this was a mistake in the report and this should be recorded as 'Low risk' since the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way*".[25]

Table 4.10: Quality assessment of PEGASUS-TIMI 54

Domain	PEGASUS-TIMI 54	
Selection bias		
Random sequence generation.	Randomisation was performed using a central computerised telephone or web-based system	Low risk
Allocation concealment.	Randomisation was performed using a central computerised telephone or web-based system	Low risk
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes).	Assignment was double-blinded; a modified study drug option (blinded, double-dummy ticagrelor or clopidogrel) was provided to investigators for patients with an indication for ADP receptor blockade	Low risk
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of	A central clinical-events committee, whose members were unaware of treatment assignments, adjudicated all efficacy end points and bleeding	Low risk

Domain	PEGASUS-TIMI 54	
outcomes).	episodes	
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes).	Missing outcome data balanced across groups and similar reasons for missing data across groups (trial CONSORT diagram provided in Supplementary appendix)	Low risk
Reporting bias		
Selective reporting.	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest have been reported in the pre-specified way.	Low risk
Other bias		
Other sources of bias.	The study appears to be free of other sources of bias	Low risk

Source: Based on Table 24 of the CS[1] and response to request for clarification[25]
ADP = adenosine diphosphate; CONSORT = Consolidated Standards Of Reporting Trials; CS = company submission

ERG comments: Randomisation and allocation concealment were carried out appropriately. Procedures for blinding of patients, care providers and outcome assessors appear to be appropriate. ITT analysis was reported for the main efficacy outcomes. The ERG could find no evidence that outcomes had been collected but not reported.

Results of the study

The results of the PEGASUS-TIMI 54 trial are summarised in Table 4.11 for the full study population and for the subgroup of patients who experienced an MI <2 years ago which forms the base case in the CS. The subgroup of patients who experienced an MI >2-3 years ago is also shown for comparison.

Table 4.11: Overview of clinical effectiveness results from PEGASUS-TIMI 54

Outcome	Full Analysis Set			Patients with MI <2 years ago			Patients with MI >2-3 years ago		
	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID vs. placebo	Ticagrelor 60 mg BID (n=4,331)	Placebo (n=4,333)	Ticagrelor 60 mg BID vs. placebo	Ticagrelor 60 mg BID (n=NR)	Placebo (n=NR)	Ticagrelor 60 mg BID vs. placebo (n=5,428)
	Patients with events n (%)		HR (95% CI)	Patients with events n (%)		HR (95% CI)	Patients with events n (%)		HR (95% CI)
Composite of CV death, MI or stroke	487 (6.9)	578 (8.2)	0.84 (0.74, 0.95)	NR	NR	0.77 (0.66, 0.90)	NR	NR	0.96 (0.79, 1.17)
CV death	174 (2.5)	210 (3.0)	0.83 (0.68, 1.01)	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]
MI	285 (4.0)	338 (4.8)	0.84 (0.72, 0.98)	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]
STEMI	NR	NR	0.62 (0.45, 0.86)	NR	NR	NR	NR	NR	NR
NSTEMI	224 (3.1)	246 (3.5)	0.91 (0.76, 1.09)	NR	NR	NR	NR	NR	NR
Stroke	91 (1.3)	122 (1.7)	0.75 (0.57, 0.98)	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]
Urgent coronary revascularisation	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
All-cause mortality	289 (4.1%)	326 (4.6%)	0.89 (0.76, 1.04)	NR	NR	[redacted]	NR	NR	[redacted]

Source: Based on Tables 25, 26, and 35 as well as Figure 15 of the CS[1] and Table 33 as well as Figure 1 of the response to request for clarification[25]
Footnotes: * Calculated by the ERG based on the sum of patients with/without diabetes
BID = twice daily; CI = confidence interval; CS = company submission; CV = cardiovascular; HR = Hazard ratio; mg = milligram; MI = myocardial infarction; NR = not reported; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction

ERG comment: The final scope issued by NICE set out non-fatal MI and non-fatal stroke as outcomes. The PEGASUS-TIMI 54 study reported these outcomes as part of the primary outcome which was a composite outcome including CV death, non-fatal MI and non-fatal stroke.

Myocardial infarction

The result reported for the overall study population in PEGASUS-TIMI 54 showed that there was a statistically significant reduction in the risk of MI for patients treated with ticagrelor 60 mg BID + ASA compared to placebo + ASA (HR 0.84, 95% CI 0.72 to 0.98). [redacted] was observed in the base case population, those patients who experienced MI <2 years ago [redacted]. In the subgroup of patients who were excluded from the base case, those patients who experienced an MI >2-3 years ago, treatment with ticagrelor 60 mg BID + ASA [redacted]

The effect of ticagrelor 60 mg BID + ASA on STEMI and NSTEMI respectively was only reported for the overall study population in PEGASUS-TIMI 54. Treatment with ticagrelor 60 mg BID + ASA significantly reduced the risk of STEMI compared to placebo + ASA (HR 0.62, 95% CI 0.45 to 0.86). There was [redacted] in the risk of NSTEMI [redacted]

Stroke

In the overall study population from PEGASUS-TIMI 54 treatment with ticagrelor 60 mg BID + ASA reduced the risk of stroke compared to placebo + ASA (HR 0.75, 95% CI 0.57 to 0.98). In the base-case population, patients who experienced MI <2 years ago, the result was similar [redacted]. In the subgroup who had an MI >2-3 years ago the risk of stroke was reduced in patients treated with ticagrelor 60 mg BID + ASA compared to placebo [redacted]

Urgent coronary revascularisation

The effect of ticagrelor 60 mg BID + ASA on urgent coronary revascularisation for unstable angina was only reported for the overall study population in PEGASUS-TIMI 54. The hazard ratio showed that treatment with ticagrelor 60 mg BID + ASA reduced the number of patients who required revascularisation [redacted]

All-cause mortality

In the PEGASUS-TIMI 54 study treatment with ticagrelor 60 mg BID + ASA reduced the risk of all-cause mortality compared to placebo + ASA in the overall study population however the difference was not statistically significant (HR 0.89, 95% CI 0.76 to 1.04). In the base case population of patients who experienced MI <2 years ago there was a [redacted] in all-cause mortality in response to treatment with ticagrelor 60 mg BID + ASA compared to placebo + ASA [redacted]. In the group of patients who were excluded from the base case, those who had an MI >2-3 years ago, there was [redacted] in all-cause mortality in response to treatment with ticagrelor 60 mg BID + ASA [redacted].

Safety

Bleeding events in the PEGASUS-TIMI 54 study were analysed according to the thrombolysis in myocardial infarction (TIMI), Platelet Inhibition and Patient Outcomes (PLATO), Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial (GUSTO), and International Society on Thrombosis and Haemostasis (ISTH) definitions. The results in the CS were reported according to the TIMI definition which is reported in Table 4.12.

In the original company submission, the company presented the results of safety outcomes in the on-treatment (OT) population, i.e. patients were censored seven days after their last dose of study drug and grouped according to the actual treatment received (CS Section 4.3[1]). In response to a clarification request by the ERG the company provided data for safety outcomes in the ITT population.[25] An overview of results related to bleeding events is reported in Table 4.13. The results for adverse events with a frequency >1% are summarised in Table 4.14. The company reported Kaplan-Meier estimates for a subset of the safety endpoints. These results are summarised in Table 4.15.

Table 4.12: TIMI bleeding classification system

Category	Definition
Major	Any intracranial bleeding, or Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dl (or when haemoglobin is not available, a fall in haematocrit of ≥15%), or Fatal bleeding (a bleeding event that directly led to death within 7 days).
Minor	Any clinically overt sign of haemorrhage (including imaging) that is associated with a fall in haemoglobin of 3 to <5 g/dl (or, when haemoglobin is not available, a fall in haematocrit of 9 to <15%).
Medical attention	Any overt sign of haemorrhage that meets one of the following criteria and that does not meet criteria for a major or minor bleeding event, as defined above: Requiring intervention: defined as medical practitioner-guided medical or surgical treatment to stop or treat bleeding including temporarily or permanently discontinuing or changing the dose of a medication or study drug. Leading to hospitalisation: defined as leading to or prolonging hospitalisation. Prompting evaluation: defined as leading to unscheduled contact with a healthcare professional and diagnostic testing (laboratory or imaging).
Minimal	Any overt bleeding event that does not meet the criteria above.

Source: Based on Table 18 of the CS[1]
CS = company submission; dl = decilitre; TIMI = Thrombolysis in Myocardial Infarction

Table 4.13: Overview of bleeding events from PEGASUS-TIMI 54 - ITT analysis

Outcome	Full Analysis Set			Patients with MI <2 years ago		
	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID vs. placebo	Ticagrelor 60 mg BID (n=4,331)	Placebo (n=4,333)	Ticagrelor 60 mg BID vs. placebo
	Patients with events n (%)		HR (95% CI)	Patients with events n (%)		HR (95% CI)
TIMI Major bleeding	138 (2.0%)	78 (1.1%)	1.78 (1.35, 2.35)	82 (1.9%)	55 (1.3%)	1.50 (1.06, 2.11)
Fatal	13 (0.2%)	15 (0.2%)	0.87 (0.41, 1.82)	10 (0.2%)	10 (0.2%)	1.00 (0.42, 2.40)
Intracranial Haemorrhage	35 (0.5%)	33 (0.5%)	1.06 (0.66, 1.71)	20 (0.5%)	22 (0.5%)	0.91 (0.50, 1.67)
Other Major	98 (1.4%)	39 (0.6%)	2.53 (1.74, 3.66)	59 (1.4%)	27 (0.6%)	2.19 (1.39, 3.46)
TIMI Major or Minor bleeding	201 (2.9%)	106 (1.5%)	1.91 (1.51, 2.42)	129 (3.0%)	75 (1.7%)	1.73 (1.30, 2.30)

Source: Based on Table 41 of the CS[1] and Table 41b of the response to request for clarification[25]
BID = twice daily; CI = confidence interval; CS = company submission; HR = Hazard ratio; ITT = intention to treat; mg = milligram; TIMI = Thrombolysis in Myocardial Infarction

Table 4.14: Most common AEs (including bleeding) by preferred term (with frequency >1%) – ITT analysis

Outcome	Full Analysis Set		Patients with MI <2 years ago	
	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID (n=4,331)	Placebo (n=4,333)
	Patients with events n (%)		Patients with events n (%)	
Patients with any AE	5,342 (75.8%)	4,941 (69.9%)	3,261 (75.3%)	3,022 (69.7%)
Dyspnoea	895 (12.7%)	335 (4.7%)	524 (12.1%)	213 (4.9%)
Dyspnoea SAE	24 (0.3%)	11 (0.2%)	17 (0.4%)	7 (0.2%)
Dyspnoea non-SAE	877 (12.4%)	327 (4.6%)	512 (11.8%)	208 (4.8%)

Outcome	Full Analysis Set		Patients with MI <2 years ago	
	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID (n=4,331)	Placebo (n=4,333)
	Patients with events n (%)		Patients with events n (%)	
Epistaxis	432 (6.1%)	164 (2.3%)	264 (6.1%)	*93 (2.1%)*
Increased tendency to bruise	418 (5.9%)	63 (0.9%)	252 (5.8%)	45 (1.0%)
Contusion	356 (5.1%)	107 (1.5%)	209 (4.8%)	53 (1.2%)
Nasopharyngitis	347 (4.9%)	363 (5.1%)	199 (4.6%)	211 (4.9%)
Non-cardiac chest pain	393 (5.6%)	414 (5.9%)	248 (5.7%)	262 (6.0%)
Dizziness	311 (4.4%)	270 (3.8%)	202 (4.7%)	149 (3.4%)
Spontaneous haematoma	221 (3.1%)	46 (0.7%)	136 (3.1%)	24 (0.6%)
Hypertension	300 (4.3%)	305 (4.3%)	176 (4.1%)	194 (4.5%)
Bronchitis	201 (2.9%)	186 (2.6%)	118 (2.7%)	115 (2.7%)
Diarrhoea	239 (3.4%)	186 (2.6%)	146 (3.4%)	102 (2.4%)
Back pain	243 (3.4%)	235 (3.3%)	150 (3.5%)	148 (3.4%)
Traumatic haematoma	160 (2.3%)	51 (0.7%)	101 (2.3%)	27 (0.6%)
Headache	185 (2.6%)	186 (2.6%)	112 (2.6%)	104 (2.4%)

Source: Based on Table 43 of the CS[1] and Table 43b of the response to request for clarification[25]
AE = adverse event; BID: twice daily; CI: confidence interval; ITT = intention to treat; mg = milligram; MI: myocardial infarction; SAE: serious adverse event

Table 4.15: Safety endpoints as three year Kaplan-Meier estimates – ITT analysis

Outcome	Full Analysis Set			Patients with MI <2 years ago		
	Ticagrelor 60 mg BID (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg BID vs placebo	Ticagrelor 60 mg BID (n=4,331)	Placebo (n=4,333)	Ticagrelor 60 mg BID vs placebo
	Patients with events n (%)		HR (95% CI)	Patients with events n (%)		HR (95% CI)
Dyspnoea	1,019 (14.5)	418 (5.9)	2.60 (2.32, 2.91)	593 (13.7)	259 (6.0)	2.41 (2.09, 2.79)
Event leading to study drug discontinuation	297 (4.2)	51 (0.7)	5.95 (4.42, 8.01)	176 (4.1)	29 (0.7)	6.18 (4.17, 9.15)
Serious AE	27 (0.4)	13 (0.2)	2.08 (1.07, 4.02)	19 (0.4)	7 (0.2)	2.71 (1.14, 6.46)
Bradyarrhythmia	147 (2.1)	124 (1.8)	1.19 (0.94, 1.51)	107 (2.5)	75 (1.7)	1.43 (1.07, 1.92)
Gout	114 (1.6)	86 (1.2)	1.33 (1.01, 1.76)	67 (1.5)	54 (1.2)	1.24 (0.87, 1.78)

Source: Based on Table 44 of the CS[1] and Table 44b of the response to request for clarification[25]
AE = Adverse Event; BID = twice daily; CI: confidence interval; CS = company submission; HR = Hazard ratio; ITT = intention to treat; mg = milligram; MI = myocardial infarction

ERG comment: All results are summarised for the ITT analysis of the PEGASUS-TIMI 54 study in the overall study population and in the base case population, patients who had an MI <2 years ago. The results for the on-treatment analysis are available in the CS.[1] It should be noted that although a number of adverse events showed statistically significant differences between treatment groups the absolute number of patients who experienced events represent a small proportion of the total number of patients treated.

Bleeding events

In the overall study population from PEGASUS-TIMI 54 there was a statistically significant increase in TIMI major bleeding events in patients treated with ticagrelor 60 mg BID + ASA compared to treatment with placebo + ASA (HR: 1.78, 95% CI 1.35 to 2.35). In the base case population who had an MI <2 years ago the increase in TIMI major bleeding events was smaller but the difference was still statistically significant.

In the overall study population, treatment with ticagrelor 60 mg BID + ASA reduced the risk of fatal bleeding events compared to placebo + ASA although the difference was not statistically significant (HR: 0.87, 95% CI 0.41 to 1.82). In the base case population there was no difference in fatal bleeding events between ticagrelor 60 mg BID + ASA and placebo + ASA (HR: 1.00, 95% CI 0.42 to 2.40).

Ticagrelor 60 mg BID + ASA had small effects on the risk of intracranial haemorrhage (ICH). In the PEGASUS-TIMI 54 overall study population ticagrelor 60 mg + ASA increased the risk of ICH compared to placebo + ASA (HR: 1.06, 95% CI 0.66 to 1.71) whereas in the base case population there was a decrease in the risk of ICH (HR: 0.91, 95% CI 0.50 to 1.67).

The risk of other major bleeding events was significantly increased in response to treatment with ticagrelor 60 mg BID + ASA both in the overall study population (HR: 2.53, 95% CI 1.74 to 3.66) and in the base case population (HR: 2.19, 95% 1.39 to 3.46).

The risk of TIMI major or minor bleeding events was significantly increased in response to treatment with ticagrelor 60 mg BID + ASA both in the overall study population (HR: 1.91, 95% CI 1.51 to 2.42) and in the base case population (HR: 1.73, 95% 1.39 to 2.30).

Common adverse events

The frequency of any AE was higher in the ticagrelor 60 mg BID + ASA arm compared to the placebo arm in both the overall study population (75.8% vs 69.9%) and the base case population (75.3% vs 69.7%).

In both, the overall study population and the base case population, there were a number of adverse events that were more than twice as frequent in patients treated with ticagrelor 60 mg BID + ASA compared to patients treated with placebo + ASA: dyspnoea, epistaxis, tendency to bruise, contusion, spontaneous haematoma and traumatic haematoma.

Serious adverse events

There was a statistically significant increase in the number of patients in the overall study population treated with ticagrelor 60 mg BID + ASA who experienced dyspnoea compared to patients treated

with placebo + ASA (HR: 2.60, 95% CI 2.32 to 2.91). A similar statistically significant increase in dyspnoea was reported in the base case population (HR: 2.41, 95% CI 2.09 to 2.79).

There were significantly more patients treated with ticagrelor 60 mg BID + ASA who experienced events leading to study drug discontinuation compared to patients treated with placebo + ASA both in the overall study population (HR: 5.95, 95% CI 4.42 to 8.01) and in the base case population (HR: 6.18, 95% CI 4.17 to 9.15).

There were significantly more patients treated with ticagrelor 60 mg BID + ASA who experienced serious AE compared to patients treated with placebo + ASA both in the overall study population (HR: 2.08, 95% CI 1.07 to 4.02) and in the base case population (HR: 2.71, 95% CI 1.14 to 6.46). It should be noted that the absolute number of patients who experienced serious AEs was <0.5% of the number of patients treated.

There was an increase in the risk of bradyarrhythmia in patients treated with ticagrelor 60 mg BID + ASA compared to patients treated with placebo + ASA. The difference was not statistically significant in the overall study population (HR: 1.19, 95% CI 0.94 to 1.51) however the difference was statistically significant in the base case population (HR: 1.43, 95% CI 1.07 to 1.92).

There was an increase in the risk of gout in patients treated with ticagrelor 60 mg BID + ASA compared to patients treated with placebo + ASA. The difference was statistically significant in the overall study population (HR: 1.33, 95% CI 1.01 to 1.76) however the difference was not statistically significant in the base case population (HR: 1.24, 95% CI 0.87 to 1.78).

Subgroup analysis – clinical effectiveness

The final scope issued by NICE requested evidence in subgroups of patients with or without diabetes and in patients with or without prior revascularisation if data were available. In the CS the company noted "*that the PEGASUS-TIMI 54 trial did not record or stratify patients according to revascularization specifically. However, primary analysis was stratified according to a history of percutaneous coronary intervention (PCI) and the results of the primary efficacy endpoint for these, as well as those according to diabetes status in the full PEGASUS-TIMI 54 population are presented in Figure 17 and Figure 18.*

The licensed population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically sound as the trial was not powered to draw conclusions about (non-pre-specified) subgroups of subgroups. However, in order to provide evidence for these specific subgroups of patients aligned with the base case for this submission and within the limits of the marketing authorisation, we present subgroup analyses of composite and components of the primary efficacy endpoint for patients who experienced an MI <2 years ago, with or without diabetes, and with or without a history of PCI. Caution is advised when interpreting these results for the reasons set out above."[1]

The relevant results from Figure 17 of the CS are reproduced in Table 4.16. The subgroups in this table are subsets of the overall study population in PEGASUS-TIMI 54. The results in the corresponding subgroups of the base case population who had an MI <2 years ago are summarised in Table 4.17 and Table 4.18.

Table 4.16: Primary efficacy endpoint from PEGASUS-TIMI 54 across patient subgroups

Population	No of patients	Composite of CV death, MI or stroke HR (95% CI)
Diabetes		
Patients with diabetes	6,806	0.83 (0.69 to 1.00)
Patients without diabetes	14,355	0.84 (0.72 to 0.98)
PCI		
Patients with a history of PCI	17,568	0.83 (0.72 to 0.96)
Patients without a history of PCI	3,591	0.87 (0.69 to 1.11)

Source: Based on Figure 17 of the CS[1]
CI = confidence interval; CS = company submission; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention

Table 4.17: Key efficacy endpoints for patient subgroup: (full analysis set; patients with MI <2 years ago, with and without diabetes)

Outcome	Patients with diabetes			Patients without diabetes		
	Ticagrelor 60 mg BID (n=1,419)	Placebo (n=1,322)	Ticagrelor 60 mg BID vs. placebo	Ticagrelor 60 mg BID (n=2,912)	Placebo (n=3,011)	Ticagrelor 60 mg BID vs. placebo
	Patients with events n (%)		HR (95% CI)	Patients with events n (%)		HR (95% CI)
Composite of CV death, MI or stroke	128 (9.0)	144 (10.9)	0.82 (0.64, 1.04)	165 (5.7)	231 (7.7)	0.73 (0.60,0.89)
CV death	47 (3.3)	64 (4.8)	0.68 (0.47, 0.99)	47 (1.6)	73 (2.4)	0.66 (0.46, 0.96)
MI	79 (5.6)	76 (5.7)	0.96 (0.70, 1.32)	101 (3.5)	145 (4.8)	0.72 (0.55, 0.92)
STEMI	NR	NR	NR	NR	NR	NR
NSTEMI	NR	NR	NR	NR	NR	NR
Stroke	21 (1.5)	33 (2.5)	0.59 (0.34, 1.02)	36 (1.2)	46 (1.5)	0.81 (0.52, 1.25)
Urgent coronary revascularisation	NR	NR	NR	NR	NR	NR
All-cause mortality	NR	NR	NR	NR	NR	NR

Source: Based on Table 35 of the CS[1]

BID = twice daily; CI = confidence interval; CS = company submission; CV = cardiovascular; HR = Hazard Ratio; MI = myocardial infarction; NR = not reported; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction

Table 4.18: Key efficacy endpoints for patient subgroup: (full analysis set; patients with MI <2 years ago, with and without a history of PCI)

Outcome	Patients with a history of PCI			Patients without a history of PCI		
	Ticagrelor 60 mg BID (n=3,638)	Placebo (n=3,623)	Ticagrelor 60 mg BID vs. placebo	Ticagrelor 60 mg BID (n=692)	Placebo (n=709)	Ticagrelor 60 mg BID vs. placebo
	Patients with events n (%)		HR (95% CI)	Patients with events n (%)		HR (95% CI)
Composite of CV death, MI or stroke	218 (6.0)	277 (7.6)	0.78 (0.65, 0.93)	75 (10.8)	98 (13.8)	0.76 (0.56, 1.02)
CV death	51 (1.4)	81 (2.2)	0.63 (0.44, 0.89)	43 (6.2)	56 (7.9)	0.77 (0.52, 1.14)
MI	148 (4.1)	182 (5.0)	0.81 (0.65, 1.00)	32 (4.6)	39 (5.5)	0.82 (0.51, 1.31)
STEMI	NR	NR	NR	NR	NR	NR
NSTEMI	NR	NR	NR	NR	NR	NR
Stroke	44 (1.2)	54 (1.5)	0.81 (0.55, 1.21)	13 (1.9)	25 (3.5)	0.51 (0.26, 1.00)
Urgent coronary revascularisation	NR	NR	NR	NR	NR	NR
All-cause mortality	NR	NR	NR	NR	NR	NR

Source: Based on Table 36 of the CS[1]

BID = twice daily; CI = confidence interval; CS = company submission; CV = cardiovascular; HR = Hazard ratio; MI = myocardial infarction; NR = not reported; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST segment elevation myocardial infarction

ERG comment: The individual components of the composite primary endpoint were not reported in the CS for subgroups of the overall study population from PEGASUS-TIMI 54. The results for the composite endpoint were similar in patients with diabetes from the overall study population (HR: 0.83, 95% CI 0.69 to 1.00) and in patients with diabetes from the base case population (HR: 0.82, 95% CI 0.64 to 1.04). In both cases treatment with ticagrelor 60 mg BID + ASA reduced the risk of an event compared to treatment with placebo + ASA however the differences were not statistically significant.

In patients without diabetes in the base case population treatment with ticagrelor 60 mg BID + ASA was reported to be more effective compared to placebo + ASA (HR: 0.73, 95% CI 0.60 to 0.89) than in patients without diabetes in the overall study population from PEGASUS-TIMI 54 (HR: 0.84, 95% CI 0.72 to 0.98).

Treatment with ticagrelor 60 mg BID was reported in the CS to be more effective in patients with a history of PCI in the base case population (HR: 0.78, 95% CI 0.65 to 0.93) than in patients with a history of PCI in the overall study population (HR: 0.83, 95% CI 0.72 to 0.96). In patients without a history of PCI treatment with ticagrelor 60 mg BID + ASA was also reported to be more effective in the base case population (HR: 0.76, 95% CI 0.56 to 1.02) than in the overall study population (HR: 0.87, 95% CI 0.69 to 1.11).

The individual components of the composite primary endpoint were reported for subgroups of the base case population. There were no results reported for urgent coronary revascularisation or all-cause mortality in patient subgroups.

Myocardial infarction
In patients with diabetes there was no significant difference in the risk of MI in response to treatment with ticagrelor 60 mg BID + ASA compared to placebo + ASA (HR: 0.96, 95% CI 0.70 to 1.32). In patients without diabetes there was a statistically significant decrease in the risk of MI in patients treated with ticagrelor 60 mg BID + ASA compared to treatment with placebo + ASA (HR: 0.72, 95% CI 0.55 to 0.92).

The effect of treatment with ticagrelor 60 mg BID + ASA on the risk of MI was similar in patients with or without a history of PCI. In patients with a history of PCI ticagrelor 60 mg BID + ASA reduced the risk of MI compared to placebo + ASA (HR: 0.81, 95% CI 0.65 to 1.00). The result was similar in patients without a history of PCI (HR: 0.82, 95% CI 0.51 to 1.31).

There were no results reported for the effect of ticagrelor 60 mg BID + ASA on the risk of STEMI or NSTEMI separately in patient subgroups.

Stroke
Treatment with ticagrelor 60 mg BID + ASA reduced the risk of stroke more in patients with diabetes (HR: 0.59, 95% CI 0.34 to 1.02) than in patients without diabetes (HR: 0.81, 95% CI 0.52 to 1.25) compared to treatment with placebo + ASA.

There was also a difference in the effect of treatment in patients with or without a history of PCI. Treatment with ticagrelor 60 mg BID + ASA reduced the risk of stroke compared to placebo + ASA in both populations however the effect was larger in patients without a history of PCI (HR: 0.51, 95% CI 0.26 to 1.00) than in patients with a history of PCI (HR: 0.81, 95% CI 0.55 to 1.21).

Subgroup analysis – safety

Safety results for patient subgroups were only reported for TIMI major bleeding events which was the primary safety endpoint in the PEGASUS-TIMI 54 study. In the CS the company noted "*that the PEGASUS-TIMI 54 trial did not record or stratify patients according to revascularization specifically. However, patients were stratified according to a history of percutaneous coronary intervention (PCI) and the results of the primary safety endpoint for these, as well as those according to diabetes status in the ITT analysis population are presented*

The licensed population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically sound as the trial was not powered to draw conclusions about (non-pre-specified) subgroups of subgroups. However, in order to provide evidence for these specific subgroups of patients within the limits of the marketing authorization, we present subgroup analyses of composite and individual primary endpoints for patients who experienced an MI <2 years ago, with or without diabetes and with or without a history of PCI. Caution is advised when interpreting these data for the reasons set out above."

The results in subgroups from the overall study population are reported in Table 4.19. The corresponding results in subgroups of the base case population are reported in Table 4.20 based on an on-treatment analysis. The results for the ITT population were not reported.

Table 4.19: Primary safety endpoint from PEGASUS-TIMI 54 across patient subgroups

Population	No of patients	TIMI major bleeding HR (95% CI)
Diabetes		
Patients with diabetes	6,735	2.47 (1.40, 4.35)
Patients without diabetes	14,207	2.25 (1.52, 3.33)
PCI		
Patients with a history of PCI	17,379	2.42 (1.70, 3.44)
Patients without a history of PCI	3,562	1.85 (0.81, 4.22)

Source: Based on Figure 29 of the CS[1]
CS = company submission; HR = Hazard ratio, PCI = Percutaneous Coronary Intervention; TIMI = Thrombolysis in Myocardial Infarction

Table 4.20: Primary safety endpoint for patient subgroups: (on treatment analysis; patients with MI <2 years ago)

Population	TIMI major bleeding		
	Ticagrelor 60 mg BID	Placebo	Ticagrelor 60 mg BID vs. placebo
	Patients with events n (%)		HR (95% CI)
Diabetes			
Patients with diabetes	27/1402 (1.9)	8/1310 (0.6)	3.32 (1.51, 7.31)
Patients without diabetes	45/2877 (1.6)	30/2977 (1.0)	1.69 (1.07, 2.68)
PCI			
Patients with a history of PCI	62/3595 (1.7)	31/2585 (0.9)	2.17 (1.41, 3.34)

Population	TIMI major bleeding		
	Ticagrelor 60 mg BID	Placebo	Ticagrelor 60 mg BID vs. placebo
	Patients with events n (%)		HR (95% CI)
Patients without a history of PCI	10/684 (1.5)	7/701 (1.0)	1.55 (0.59, 4.06)

Source: Based on Tables 48 and 49 of the CS[1]
BID = twice daily, CS = company submission; HR = Hazard ratio, PCI = Percutaneous Coronary Intervention

ERG comment: The results from the subgroups of the overall study population were described as based on the ITT analysis in the CS however the number of patients in each subgroup for the safety outcomes did not match the number reported in each subgroup for the primary efficacy outcome (see Table 4.16).

In all four subgroups treatment with ticagrelor 60 mg BID + ASA increased the risk of TIMI major bleeds compared to treatment with placebo + ASA. In patients with diabetes treatment with ticagrelor 60 mg BID increased the risk of TIMI major bleeds more in patients with diabetes in the base case population (HR: 3.32, 95% CI 1.51 to 7.31) than in patients with diabetes in the overall study population (HR: 2.47, 95% CI 1.40 to 4.35).

In patients without diabetes the effect of treatment with ticagrelor 60 mg BID + ASA was greater in patients without diabetes in the overall study population (HR: 2.25, 95% CI 1.52 to 3.33) than in patients without diabetes in the base case population (HR: 1.69, 95% CI 1.07 to 2.68).

The effect of treatment with ticagrelor 60 mg BID + ASA on TIMI major bleeds was greater in patients with a history of PCI in the overall study population (HR: 2.42, 95% CI 1.70 to 3.44) than in patients with a history of PCI in the base case population (HR: 2.17, 95% CI 1.41 to 3.34).

Similarly, the effect of treatment with ticagrelor 60 mg BID + ASA on TIMI major bleeds was greater in patients without a history of PCI in the overall study population (HR: 1.85, 95% CI 0.81 to 4.22) than in patients without a history of PCI in the base case population (HR: 1.55, 95% CI 0.59 to 4.06).

It should be noted that although there were differences between treatment groups and between populations the absolute number of patients who experienced major bleeds was small. There was a high degree of uncertainty surrounding the treatment effects due to the small number of events observed.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company did not report any indirect comparison or multiple treatment comparison. The systematic review identified two studies in addition to the PEGASUS-TIMI 54 study that were potentially eligible for inclusion in an indirect comparison. The CHARISMA study compared clopidogrel + ASA versus placebo + ASA. The DAPT study included two arms comparing thienopyridine (clopidogrel or prasugrel) + ASA versus placebo + ASA. The design details of these two studies are summarised in Table 4.2 (Section 4.2).

The full study cohort in the CHARISMA study was patients with documented CAD, cerebrovascular disease, or PAD, or with multiple risk factors for atherothrombosis which is broader than the population specified in the scope. Data were also available from a post-hoc analysis in patients with a documented prior MI, documented prior IS, or symptomatic PAD.[32]

The full study cohort in the DAPT study was patients with CAD who were candidates for DAPT and who received treatment with FDA-approved drug eluting stents (DES) or bare metal stents (BMS), i.e. all patients in this study had received stent treatment. In a post-hoc analysis results were reported for patients who presented with MI.[33]

The patient baseline characteristics in the subpopulations presenting with prior MI from DAPT and CHARISMA respectively are shown in Table 4.21. The baseline characteristics of the overall study population in PEGASUS-TIMI 54 are also reproduced here for comparison.

The quality assessment based on the Cochrane risk of bias tool for the two studies eligible for inclusion in an indirect comparison are summarised in Table 4.22.

Table 4.21: Patient characteristics in studies eligible for indirect comparison

Patient Characteristics	PEGASUS-TIMI 54		DAPT MI patients only		CHARISMA MI patients only	
	Ticagrelor 60 mg BID + ASA (n=7,045)	Placebo + ASA (n=7,067)	Thienopyridine + ASA (n=1,805)	Placebo + ASA (n=1,771)	Clopidogrel + ASA (n=1,903)	Placebo + ASA (n=1,943)
Follow up in months – Median (IQR)	33 (28-37)		18		NR	
Age in years Mean (SD)	65.2 (8.4)	65.4 (8.3)	57.9 (10.5)	57.7 (10.5)	NR	NR
Sex (female), n (%)	1,661 (23.6)	1,717 (24.3)	NR (22.4)	NR (21.2)	NR	NR
STEMI, n (%)	3,757 (53.4)	3,809 (54.0)	NR (46.8)	NR (47.2)	NR	NR
NSTEMI, n (%)	2,842 (40.4)	2,843 (40.3)	NR (53.2)	NR (52.9)	NR	NR
Other/unknown, n (%)	436 (6.2)	405 (5.7)	NR (0)	NR (0)	NR	NR
Time since MI (yrs), Median (IQR)	1.7 (1.2-2.3)	1.7 (1.2-2.3)	NR	NR	NR	NR
Diabetes, n (%)	2,308 (32.8)	2,257 (31.9)	NR (20.8)	NR (21.0)	NR	NR
Hypertension, n (%)	5,461 (77.5)	5,484 (77.6)	NR (59.8)	NR (56.4)	NR	NR
Current smoker, n (%)	1,206 (17.1)	1,143 (16.2)	NR (41.8)	NR (41.8)	NR	NR
Weight (kg)	82.0 (17.0)	81.8 (16.6)	89.7 (19.7)	90.8 (19.0)	NR	NR

Source: Based on Table 38 of the CS[1]

ASA = acetylsalicylic acid; BID: twice daily, IQR = interquartile range; kg = kilogram; mg = milligram; MI: myocardial infarction, NR = not reported; NSTEMI: non-ST segment elevation myocardial infarction; SD = standard deviation; STEMI: ST segment elevation myocardial infarction

Table 4.22: Quality assessment of studies eligible for indirect comparison

Domain	DAPT trial		CHARISMA trial	
	Support for judgement	**Review authors' judgement**	**Support for judgement**	**Review authors' judgement**
Selection bias				
Random sequence generation.	A computer-generated randomisation schedule was used to assign subjects to treatment, stratified by DES/BMS use	Low risk	Patients were randomised but details of the sequence generation were not reported; insufficient information	Unclear risk
Allocation concealment.	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk
Performance bias				
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes).	Treating physicians, subjects, personnel at investigative sites, Clinical Events Committee, and all study staff and investigators, other than data safety monitoring board and one statistician and programmer, were blinded to treatment assignment	Low risk	Randomisation was double-blinded; no further details provided	Low risk
Detection bias				
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes).	Clinical Events Committee were blinded to treatment assignments	Low risk	Clinical events were validated by the Cleveland Clinic Clinical Events Adjudication Committee	Unclear risk
Attrition bias				
Incomplete outcome data Assessments should be made	CONSORT diagram provided; missing outcome data appears balanced across	Low risk	Insufficient information to permit judgement of 'Low risk' or 'High	Unclear risk

Domain	DAPT trial		CHARISMA trial	
	Support for judgement	**Review authors' judgement**	**Support for judgement**	**Review authors' judgement**
for each main outcome (or class of outcomes).	groups and similar reasons for missing data across groups		risk'	
Reporting bias				
Selective reporting.	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear risk
Other bias				
Other sources of bias.	The study appears to be free of other sources of bias	Low risk	The study appears to be free of other sources of bias	Low risk

Source: Based on Table 37 of the CS[1]

BMS = bare metal stent; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CONSORT = Consolidated Standards Of Reporting Trials; CS = company submission, DAPT = dual antiplatelet therapy; DES = drug-eluting stent

ERG comment: The overall study populations in each of the CHARISMA and DAPT studies were not consistent with the population specified in the final scope for this appraisal. The population specified in the scope was "*Adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events*".[17] The full study cohort in the CHARISMA study included patients with CAD, cerebrovascular disease, PAD or with multiple risk factors for atherothrombosis.[34] This was a wider population than that specified in the final scope. A subsequent post-hoc analysis reported results for a limited set of outcomes in a subgroup of patients with either prior MI, prior IS or symptomatic PAD within which some outcomes were reported specifically for patients with MI.[32]

In CHARISMA patients were randomised to placebo + ASA or clopidogrel + ASA. The duration of the CHARISMA study was event driven. Patients were followed until 1,040 primary end point events were observed.[34] In practice, this resulted in a median follow-up of 28 months in the overall study population. The mean or median follow-up in the subgroup of patients with either prior MI, prior IS or symptomatic PAD was not reported.[32]

The full study cohort in the DAPT study was patients with CAD who were candidates for DAPT and who received treatment with FDA-approved drug eluting stents or bare metal stents, i.e. all patients in this study had received stent treatment. In contrast, in the PEGASUS-TIMI 54 study 83% of patients had a history of PCI at baseline of which 96.5% of PCIs involved stenting.[20] In addition, the study population in the PEGASUS-TIMI 54 was defined as patients who had at least one additional risk factor for subsequent CV events from the set of age >65 years, diabetes requiring medication, second MI, multivessel coronary artery disease or chronic renal dysfunction.[20] There was no indication that the study population in the DAPT trial had similar risk factors.

In the DAPT study all enrolled patients received 12 months of open label treatment with a thienopyridine (either clopidogrel or prasugrel) in combination with ASA following the initial stent placement. After 12 months of treatment those patients who were event free from death, MI, stroke, repeat coronary revascularisation, stent thrombosis and GUSTO defined moderate or severe bleeding and who also demonstrated compliance with thienopyridine treatment were eligible for randomisation. These patients were randomised to either 18 months further thienopyridine treatment (30 months DAPT) or placebo (12 months DAPT). Both arms continued to receive ASA for the duration of the study. The choice of clopidogrel or prasugrel was made according to local standard practice at the individual study sites, i.e. this component of treatment allocation was not randomised.[35]

The baseline characteristics of the subgroup of patients in CHARISMA with prior MI were not reported therefore the similarity of these patients to those in PEGASUS-TIMI 54 cannot be assessed. The subgroup of patients in the DAPT study with prior MI differed in several baseline characteristics compared to the patients in PEGASUS-TIMI 54. The DAPT subgroup included fewer patients with diabetes (~21%) compared to PEGASUS-TIMI 54 (~32%). There were also fewer patients with hypertension in the DAPT subgroup (56.4-59.8%) compared to PEGASUS-TIMI 54 (77.5-77.6%). PEGASUS-TIMI 54 included less than half as many current smokers (16.2-17.1%) compared to the DAPT subgroup (41.8% in both arms).

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company did not report any indirect comparison or multiple treatment comparison and cited a number of differences in the design and patient characteristics of the available studies as justification that these studies are not comparable.

In the CS the company stated "*whilst all patients in the included trials were randomised to either DAPT or placebo plus aspirin, patients in the DAPT trial had also received treatment with a ADP receptor inhibitor for 12 months prior to randomisation. Patients who tolerated this treatment and did not experience an event, were then randomised to thienopyridine plus aspirin or placebo plus aspirin.*[36] *This could introduce selection bias to the patient population and impact on the time to event, as patients who tolerate treatment could be considered a less 'at risk' population than those who experienced an event within the initial 12 months.*

The detailed inclusion criteria of the PEGASUS-TIMI 54 trial state that patients may or may not have previously been on an ADP receptor inhibitor and could be randomised on cessation of ADP receptor therapy. It is reported that all patients included in the sub-analysis of the PEGASUS-TIMI 54 trial (89% of patients from the primary analysis) had received prior therapy with an ADP blocker at some point leading up to randomisation; however the precise duration of the prior treatment was not reported.[37] *There are no details reported regarding the prior treatment of patients enrolled in the CHARISMA trial*[32] *".*[1]

The company also highlighted differences in the PCI history of patients in each of the three available studies, i.e. "*all patients enrolled in the DAPT trial also received either a drug eluting stent* (*DES) or a bare metal stent (BMS) as a form of PCI prior to receiving DAPT*".[1] In comparison "*Eighty percent of patients enrolled on the PEGASUS-TIMI 54 trial had a history of PCI. Of these, 51% (n=8597) received a BMS and 49% (n=8294) a DES.*[38] *The eligibility criteria detailed in the CHARISMA trial included patients who had documented coronary artery disease, cerebrovascular disease, or PAD, or with multiple risk factors for atherothrombosis and therefore not all patients had received a PCI.*[34] *The sub-analysis of the CHARISMA trial focused on patients with history of MI and only 26% of patients in both the clopidogrel + ASA and placebo + ASA treatment arms had received a PCI*[32] *".*

The company also identified differences in the patient baseline characteristics between studies. These differences are discussed in Section 4.3 above.

According to the CS, "t*he different types of initial MIs experienced (STEMI or NSTEMI) are broadly comparable across the PEGASUS-TIMI 54 and DAPT trials however it is important to note that patients in the CHARISMA trial were excluded from enrolment if the patient required prolonged clopidogrel therapy, such as patients who have had a recent non–ST-segment elevation ACS*[34]*".*

The company identified a set of assumptions that would be required in order to consider the three available studies sufficiently comparable to justify an indirect comparison.[1]

- *"Baseline characteristic data are not reported for the subgroup of interest (history of MI) in the CHARISMA trial and therefore it is assumed there were no important differences between the baseline characteristics across all included trials.*
- *Patients who experienced multiple different prior atherothrombotic events (MI, stroke or PAD) have the same response to treatment regardless of the prior event.*
- *There is a class effect of thienopyridines (clopidogrel and prasugrel) in the DAPT study.*
- *The relative treatment effects of prolonged treatment with dual antiplatelets (i.e. clopidogrel, prasugrel or ticagrelor with low-dose ASA) are NOT impacted by the following:*
    - *The selection bias in patients who had tolerated treatment in the first 12 months of the DAPT trial*

- *Prior duration of antiplatelet therapy*
- *Time since cessation of prior antiplatelet therapy*
- *Time since prior MI*
- *The type of MI experienced (STEMI or NSTEMI)*
- *Known risk factors for cardiovascular events including age, smoking, diabetes status, incidence of hypertension*
- *Previous PCI (and the type of stent)*
- *Treatment duration of 18 months (DAPT), and assumed follow-up of 28 months (CHARISMA) and 33 months (PEGASUS-TIMI 54) can be considered comparable (assuming that relative treatment effects remain constant over time).''*

In response to a clarification request by the ERG the company provided an additional table to show which outcome measures were available in the three relevant studies for patients with prior MI. This information is reproduced as Table 4.23 below.

Table 4.23 Outcome measures available for prior MI patients in three potentially relevant studies

Study	DAPT trial MI subgroup			CHARISMA trial MI subgroup	PEGASUS-TIMI 54
Treatment	**Thienopyridine (n=3,576)**	**Clopidogrel[*] (n=2,361)**	**Prasugrel[*] (n=1,251)**	**Clopidogrel (n=3,846)**	**Ticagrelor[**] (n=14,112)**
Outcome measures specified in Decision Problem					
Non-fatal MI	(AVAILABLE)[#]	(AVAILABLE)[#]	(AVAILABLE)[#]	-	AVAILABLE
Non-fatal stroke	-	-	-	-	AVAILABLE
Urgent coronary revascularisation	-	-	-	-	AVAILABLE
Bleeding events	GUSTO	GUSTO	GUSTO	-	TIMI, PLATO, GUSTO
Death	AVAILABLE	-	-	-	AVAILABLE
Adverse effects of treatment	-	-	-	-	AVAILABLE
HRQoL	-	-	-	-	AVAILABLE
Other Outcome measures of interest					
Baseline characteristics	AVAILABLE	-	-	-	AVAILABLE
Composite of CV death, MI or stroke	-	-	-	AVAILABLE	AVAILABLE
Composite of (All-cause) death, MI or stroke	AVAILABLE	-	-	-	AVAILABLE

Source: Based on Table 1 of the response to clarification request[25]

Footnotes: [*] Available in Table 3 of the Supplementary Materials to Yeh 2015[33]; - Data not available; [**] Based on full analysis population from PEGASUS-TIMI 54 study for patients in the ticagrelor 60 mg and placebo arms; [#] Reported as MI

CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CV = cardiovascular; DAPT = dual antiplatelet therapy; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, HRQoL = Health-related Quality of Life; mg = milligram; MI = Myocardial infarction; PLATO = Platelet Inhibition and Patient Outcomes; TIMI = Thrombolysis in Myocardial Infarction

ERG comment: Overall the ERG agrees that the three studies include sufficient differences in terms of design and patient characteristics that the studies cannot be considered comparable without making implausible assumptions.

In principle indirect comparisons of DAPT and PEGASUS-TIMI 54 could have been constructed for the incidence of non-fatal MI or for bleeding events according to the GUSTO definition. The results of such comparisons would be difficult to interpret. Any differences observed between treatments in such an analysis could represent true differences between treatments however the effect may also be attributable to the differences in design and patient population between these studies.

Similarly, an indirect comparison of PEGASUS-TIMI 54 and CHARISMA could have been constructed for the composite of CV death, MI or stroke however this outcome was not included in the final scope.[17] In addition, the CHARISMA study excluded patients with NSTEMI (see Section 4.3) who were included in PEGASUS-TIMI 54. Furthermore the baseline characteristics for the subgroup of patients in CHARISMA with prior MI were unavailable therefore the assumption that there are no differences compared to the patient population in PEGASUS-TIMI 54 cannot be verified.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The CS reported only one study that compared ticagrelor to any of the comparators listed in the final scope. PEGASUS-TIMI 54 was a large randomised controlled trial comparing ticagrelor 60 mg BID + ASA versus placebo + ASA in patients who experienced an MI 1-3 years ago. The CS also reported results from subgroup of patients who had an MI <2 years ago which was consistent with the final scope of the appraisal and the licensed indication for ticagrelor. Subgroup data were also reported for patients who had an MI <2 years ago with/without diabetes and patients with an MI <2 years ago with/without a prior history of PCI.

The results of PEGASUS-TIMI 54 showed that ticagrelor 60 mg BID reduced the risk of a subsequent MI compared to placebo both in the full analysis set and in the subgroup of patients who had an MI <2 years ago. It should be noted that the treatment effect was larger in patients with STEMI than those with NSTEMI. In the subgroups of patients with an MI <2 years ago the treatment effect was greater in patients without diabetes than in those without diabetes. Ticagrelor had similar effects on the risk of MI in patients with or without PCI.

Ticagrelor 60 mg BID was also shown to reduce the risk of stroke to a similar degree in the full analysis set and in the subgroup of patients with an MI <2 years ago. Patients with or without diabetes showed differential effects of ticagrelor 60 mg BID on the risk of stroke within the group of patients with an MI < 2 years ago. Patients with diabetes experienced a larger reduction in the risk of stroke than patients without diabetes which is the opposite of the effect on the risk of MI.

Ticagrelor 60 mg BID was associated with an increased risk of TIMI major bleeds and the increase was greater in those with diabetes than those without diabetes. Patients with a history of PCI also had a greater increase in the risk of major bleeding events than those without a history of PCI.

Ticagrelor 60 mg BID reduced the risk of cardiovascular death to a greater degree in patients with MI <2 years ago than in the full analysis set. Within the group of patients with MI <2 years ago the

results were similar for patients with or without diabetes and for patients with or without a history of PCI.

It should be noted that the results from PEGASUS-TIMI 54 are based on small numbers of events for each outcome compared to the total number of patients in each arm, therefore, although there are differences in the relative risk of events the absolute risk remains quite low.

The final scope specified clopidogrel + ASA as a comparator however the CS did not present evidence for the comparison of ticagrelor + ASA versus clopidogrel + ASA. There were no studies that directly compared these two treatments and the company argued that an indirect comparison was not possible due to differences in the design and patient characteristics of the available studies. As a result there is a lack of evidence regarding the relative effectiveness of ticagrelor compared to clopidogrel.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

The CS states that a systematic review of the published literature was conducted to identify cost effectiveness studies assessing DAPT in adults with history of myocardial infarction.

The literature searches were conducted on 1 December 2015 in the following databases: MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase and the Cochrane Library (NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment Database (HTA)). The host provider for each database was listed and specific dates the searches were conducted were provided. The company additionally searched conference proceedings for the last three available years. The conference proceedings searched were not reported in the main CS (Section 5.1), but were provided in Appendix 11: European Society of Cardiology (ESC), American Heart Association (AHA), American College of Cardiology (ACC), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Full details of the methods used to search conference proceedings were not reported, so were requested in the ERG request for clarification.[26] Full details were provided in response to the ERG request for clarification.[25] Detailed search strategies for the database searches were reported in full in Appendix 11.

ERG comment: The company translated the research question into appropriate search strategies and the ERG considered the searches to be satisfactory. Searches were clearly structured and divided into population, intervention/comparator and cost effectiveness facets. The search strategies included Boolean, truncation and proximity operators. No date or language limits were included. It is not clear whether a validated study design filter was used for the cost effectiveness facet of search terms.

The searches for cost effectiveness were quite precise, and may have retrieved additional studies with a more sensitive search strategy, i.e. searching for 'economic evaluation OR models', rather than 'economic evaluation AND models'.

Although not reported in the main CS as a database searched, EconLit was reported in the list of databases searched in Appendix 11. However, no search strategy for EconLit was reported, so full details were requested in the ERG request for clarification.[26] Details of the EconLit search strategy, host provider, date range searched, date of search, and results were provided in response to the ERG request for clarification.[25]

A search of other economic resources, such as the CEA Registry and ScHARRHUD, for cost-utility analyses might have been a useful addition to the literature searches.

In the MEDLINE search strategy it appears that search line #35 was inadvertently combined with search line #34. Search line #34 comprises search terms for economic evaluation, whilst the facet which includes line #35 is comprised of search terms for 'models': these facets were then combined using Boolean AND. Search line #35 consists of a set of acronyms for economic analyses (CEA, CBA, CUA etc.) and should have been included in that facet of search terms (search line #34). In the Embase search strategy the corresponding search lines were line #42 (economic evaluation) and #41 (economic analyses acronyms).

There are redundant search terms where hyphenated phrases have been replicated: the databases searched do not recognise hyphens, and so the same results are achieved with or without hyphens. e.g., 'cost benefit analysis' retrieves the same as 'cost-benefit analysis'.

The results from the Cochrane Library search would have been better reported per database rather than as a total.

5.1.2 Inclusion/exclusion criteria used in the study selection

Screening of publications by title and abstract was performed; followed by full publication review. Eligibility criteria for the review are presented in Table 5.1.

Table 5.1: Eligibility criteria used for the economic review (CS, Appendix 11, Table 14)

	Inclusion criteria	Exclusion criteria
Population	Adult patients with previous MI (STEMI or NSTEMI) occurring prior to study randomization with at least 18 months of DAPT received between randomisation and study completion/results reporting)	Patients without prior MI or patients receiving <18 months DAPT
Interventions	DAPT, comprising ticagrelor, clopidogrel, vorapaxar, prasugrel, or rivaroxaban in combination with aspirin	-
Comparators	Placebo Monotherapy Triple therapy	-
Outcomes	Range of ICERs as per sensitivity analyses Assumptions underpinning model structures Key costs drivers Sources of clinical, cost and quality of life inputs Discounting of costs and health outcomes Model summary and structure	-
Study design	Cost-utility analyses Cost effectiveness analyses Cost-minimisation analyses Cost-benefit analyses	-
Language restrictions	No restriction	-

Source: Based on Table 14 of CS appendices[39]

CS = company submission; DAPT = dual anti-platelet therapy; MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction

ERG comment: The in- and exclusion criteria seem appropriate for the objective of this review.

5.1.3 Included/excluded studies in the cost effectiveness review

After the removal of duplicates (n=53), title and abstract screening (n=640), full paper review (n=132) and the identification of one eligible publication via hand searching, five relevant papers were identified (Table 5.2). Six publications were tagged. Details of the included studies are provided in Tables 51 to 53 of the CS. A quality assessment of the five included studies is provided in Table 18 of Appendix 12 of the CS.[39]

Table 5.2: Summary of study details of included economic evaluations

Study, Country	Population	Interventions and comparators	Treatment duration	Outcomes reported	Study perspective	Model summary
Banerjee, 2015[40] Canada	Adult patients with a diagnosis of ACS or PVD; the reference group had an average age of 60 years	Clopidogrel + aspirin Aspirin monotherapy Clopidogrel monotherapy	Base case: ACS: treatment duration was assumed to be one year for interventions, followed by lifetime of aspirin treatment PVD: treatment duration was assumed to be 2 years for interventions, followed by lifetime of aspirin treatment	Costs and QALYs	Payer – Canadian provincial ministry of health	Separate Markov models for ACS (6 health states) and PVD (7 health states), considers MI within and beyond 12 months, one year cycle length, only relevant direct medical costs were included, 40 year time horizon (lifetime), 5% discount rate for costs and outcomes[†]
Begum, 2015[41] Sweden	Adult post-ACS patients with elevated cardiac biomarkers and without a prior history of stroke or TIA; the reference cohort had an average age of 62 years	Rivaroxaban + ST-APT[§] ST-APT alone[§]	Base case: Rivaroxaban was assumed to be prescribed for a maximum of two years Clopidogrel and ticlopidine were assumed to be discontinued after one year	Costs and QALYs	Societal	Markov model, 16 health states representing the occurrence of single and multiple CV events over time (MI, IS, HS/ICH, and death), 12 weekly cycles from 0-2 years and 6 month cycles from 2-40 years, 40 year (lifetime) horizon, 3.0% discount rate for all costs and health outcomes[‡]
Chen, 2009[42] USA	Patients with either established coronary, cerebrovascular or PAD, or with multiple risk factors for CV events, as outlined in the CHARISMA trial (number of patients with prior MI: clopidogrel + aspirin, 40.7%; aspirin, 41.9%)	Clopidogrel + aspirin Aspirin monotherapy	Duration of treatment was assumed to be a median of 28 months, as in the CHARISMA trial	Costs and LYG	Payer – US healthcare system	Trial-based analysis (based on CHARISMA trial), lifetime horizon, discounting not stated

Study, Country	Population	Interventions and comparators	Treatment duration	Outcomes reported	Study perspective	Model summary
Chen, 2011[43] Canada	Patients with established CV disease or patients with multiple CV risk factors (number of patients with prior MI: clopidogrel + aspirin, 40.7%; aspirin, 41.9%)	Clopidogrel + aspirin Aspirin monotherapy (+ placebo)	Mean duration of treatment was assumed to be 28 months, as in the CHARISMA trial	Costs and LYG	Payer – Canadian healthcare system	Trial-based analysis, time horizon not stated, 5.0% discount rate for costs and life expectancy
Gaspoz, 2002[44] USA	US patients aged 35-84 years in whom coronary disease developed during or before 2003 to 2027 and who survived their first month after diagnosis	Six secondary prevention strategies (A-F): A - Zero utilisation B - Current use of aspirin (85%) C - Aspirin for all eligible patients D - Aspirin for all eligible patients and clopidogrel for remaining 5.7% E - Clopidogrel for all patients F - Combination of clopidogrel for all patient plus aspirin for eligible patients	Unclear (interventions with benefits were modelled for up to three years)	Costs and QALYs	NR	Computer simulation model, 25 year time horizon, 3% discount rate of costs and health outcomes

Source: Based on Table 51 of CS[1]

Footnotes: † For ACS patients, one year of treatment with clopidogrel or clopidogrel + aspirin, followed by remaining lifetime of aspirin treatment, was assumed for the base case; for PVD patients, two years of treatment with clopidogrel or clopidogrel + aspirin, followed by remaining lifetime on aspirin treatment, was assumed in the base case; ‡ A maximum treatment duration of 2 years was assumed for rivaroxaban, and to comply with current clinical guidelines for ACS, the maximum treatment duration of clopidogrel or ticlopidine in both arms of the analysis was 1 year; § Standard anti-platelet therapy was defined as aspirin monotherapy or aspirin in combination with clopidogrel or ticlopidine

ACS = acute coronary syndrome; CAD = Canadian dollar; CEA = cost effectiveness analysis; CUA = cost utility analysis; CV = cardiovascular; DAPT = dual antiplatelet therapy;

Study, Country	Population	Interventions and comparators	Treatment duration	Outcomes reported	Study perspective	Model summary
HS = haemorrhagic stroke; ICER = incremental cost effectiveness ratio; ICH = intracranial haemorrhage; IS = ischaemic stroke; LYG = life years gained; MI = myocardial infarction; NR = not reported; PAD = peripheral artery disease; PVD = peripheral vascular disease; QALY = quality adjusted life year; QoL = quality of life; SEK = Swedish Krona; ST-APT = standard anti-platelet therapy; TIA = transient ischaemic attack; UK = United Kingdom; USA = United States; USD = United States dollar						

ERG comment: The rationales for excluding studies after full paper reviewing seem appropriate given the defined in- and exclusion criteria. The company did not identify any study investigating the cost effectiveness of ticagrelor 60 mg BID + ASA in the population of interest for the current decision problem.

5.1.4 Conclusions of the cost effectiveness review

No relevant evidence was retrieved from the cost effectiveness review.

ERG comment: The company provided a broad overview of the included studies but did not relate these to the current decision problem. The ERG agrees with the company and does not consider the included studies as relevant for the current decision problem.

5.1.5 Objective and searches of health-related quality of life review

The CS states that a systematic literature review was conducted to identify HRQoL and utility studies relevant to the decision problem using the search strategy reported in Appendix 13.3.

The databases searched were not reported in this section of the report (Section 5.4), but were provided in the PRISMA flow diagram: MEDLINE, Embase and Cochrane. Hand searching yielded two relevant studies according to the PRISMA flow diagram, but there was no description of what hand searching entailed.

Full details of the searches used to identify HRQoL and utility data are provided in Appendix 13. The CS stated that *"in order to be consistent with the previously conducted SR as part of TA236, the following databases were searched"*: MEDLINE, MEDLINE In-Process, Embase and the Cochrane Library, specifically NHS EED. The host platform and date of searches (15 February 2016) were provided. The date range was reported as being from inception 'to present' for MEDLINE, but a specific date range was given for Embase. A date limit was used in each of the database searches, although there was no explanation why. The MEDLINE and Embase search strategies included a facet of search terms for HRQoL and utilities, but it was not clear if this was a published, objectively derived search filter. This facet did not include any subject heading indexing (Medical Subject Headings (MeSH) or EMTREE).

ERG comment: The lack of subject heading index terms probably had little or no impact on the search results because of the use of the 'mp' field tag, which enables searching in the subject heading index field. Subject heading index terms were included in the population facet of the search strategies, though incorrectly in the Embase strategy, where MEDLINE MeSH index terms were used instead. It appears that the MEDLINE search strategy was used to search Embase without being translated to the specific Embase syntax.

A search of other economic resources, such as the CEA Registry and ScHARRHUD, for cost-utility analyses might have provided additional useful HRQoL data.

Conference proceedings searches were not reported in the main CS (Section 5.4), but were provided in the Appendix (A13.4 Additional searches): European Society of Cardiology (ESC), American Heart Association (AHA), American College of Cardiology (ACC), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Full details of the methods used to search conference proceedings were not reported, so were requested in the ERG request for clarification.[26]

The company provided full details of the methods used to search conference proceedings in response to the ERG request for clarification.[25]

There were no MeSH or EMTREE subject heading terms in the HRQoL facet of search terms. The date limits used were different in MEDLINE to those used in Embase: 'dd' (date delivered) was used in Embase, whilst 'ed' (entry date) was used in MEDLINE. There was a misspelling in search line #8 in both MEDLINE and Embase, 'short form thiry' instead of 'short form thirty'. There were no proximity operators in the HRQoL facet of search terms. This would have increased sensitivity, and improved the search strategy. There was a mistake in search line #37, 'ora nonSTEMI' instead of 'or nonSTEMI'. Incorrect EMTREE index terms were used in the Embase search strategy, e.g., the MeSH term 'myocardial infarction/' was used instead of 'heart infarction/'. Similarly, the MeSH term 'unstable, angina/' was used instead of 'unstable angina pectoris/', and the MeSH term 'Coronary Thrombosis/' was used instead of the EMTREE term 'coronary artery thrombosis/'.

5.1.6 Inclusion/exclusion criteria used in the health-related quality of life study selection

Screening of publications by title and abstract was performed; followed by full publication review. Eligibility criteria for the health-related quality of life review are presented in Table 5.3.

Table 5.3: Eligibility criteria used for the utility review

	Inclusion criteria	Exclusion criteria
Population	Adult patients with previous MI (STEMI or NSTEMI) occurring prior to study randomization	Patients without prior MI
Interventions	No restriction	-
Comparators	No restriction	-
Outcomes	• EQ-5D (3L/5L) utilities • Mapping studies (disease-specific or other preference-based measure to EQ-5D)	• Utilities from non-NICE reference case preference-based measures of HRQoL (e.g. HUI2, HUI3, AQoL, AQoL 2, SF-6D, 15D, QWB) • Directly elicited (TTO, SG) utilities
Study design	No restriction	-
Language restrictions	No restriction	-
Publication date	2010 to present (inclusive)	Pre-2010

Source: Source: Based on Table 22 of CS appendices[39]
15D = 15 dimensions; AQoL = Assessment of Quality of Life; DAPT = dual anti-platelet therapy; EQ-5D = European Quality of Life-5 Dimensions; HUI2/3 = Health Utilities Index 2/3; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; NSTEMI = non-ST segment elevation myocardial infarction; QWB = Quality of Well Being; SF-6D = Short Form-6 Dimensions; SG = standard gamble; STEMI = ST segment elevation myocardial infarction; TTO = time trade off.

ERG comment: The in- and exclusion criteria seem appropriate for the objective of this review.

5.1.7 Included/excluded studies in the health-related quality of life review

In total, 4,092 papers were identified through the electronic database searches; 698 were duplicates and 3,175 were excluded based on title and abstract screening. From the remaining 219 studies, 203 were excluded after full text review. Two relevant studies were identified via hand searching. This resulted in 18 relevant studies for final inclusion. Details of the included studies are provided in Tables 92 and 93 of the CS. The relevance of each study to the NICE reference case is provided in Table 94 of the CS.[1]

The following potentially relevant submissions were identified on the NICE website:

- NICE (2009). TA182: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention.[45]
- NICE (2010). TA210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events.[46]
- NICE (2011). TA236:Ticagrelor for the treatment of acute coronary syndromes.[47]
- NICE (2014). TA317: Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes.[48]
- NICE (2015). TA335: Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome.[49]

ERG comment: The rationales for excluding studies after full paper reviewing seem appropriate given the defined in- and exclusion criteria.

5.1.8 Conclusions of the health-related quality of life review

The company concluded that six of the 18 included studies met the NICE reference case criteria (Table 5.4). Utility values from Sullivan et al.[50] and TA335[49] were seen as the most appropriate for the current decision problem and were used in sensitivity analysis because *"*[TA335] *providing disutility values for the broadest number of endpoints and Sullivan providing differentiated disabilities for the acute and longer term time periods following MI"*[1] (Section 5.2.11).

Table 5.4: Summary of HSUVs associated with adult patients with prior MI identified by the utility review update, listed according to study year and meeting the NICE reference case (n=6)

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation
De Smedt, 2014[51] Multi-national (Europe) (Full publication)	Patients aged 18-80 years, hospitalised for CABG, PCI, acute MI, or myocardial ischaemia N=7,472 Mean age, 63.1 years (SD 9.2) Male, 75%	NA	Between 6 months and 3 years (median, 1.24 years)	Utilities were derived directly from patients using the EQ-5D [SF-6D utilities were also reported but have not been extracted]	Health states were valued using the UK TTO tariff
Lewis, 2014[52] Multi-national (Argentina, Australia, Canada, Denmark, France, Germany, Italy, Sweden, UK, USA) (Full publication)	Patients aged ≥18 years with an acute MI occurring 12 hours to 10 days prior to randomisation in the VALIANT trial; 1,785 patients did not experience a subsequent CV event (18.7% had prior MI) and 597 patients experienced a subsequent event and had available EQ-5D data (33.5% had prior MI)[†] Mean age: patients with CV event + EQ-5D data, 68.6 years (SD 11) Female: patients with CV event + EQ-5D data, 31.5%	Captopril Valsartan Combination of both	Baseline, 6, 12, 20 and 24 months (annually there-after)	Utilities were derived directly from patients using the EQ-5D	Health states were valued using UK and US TTO tariffs
Nam, 2015[53] UK (Full publication)	Patients with recent NSTEMI N=NR Mean age, 62 years Gender distribution, NR	FFR Standard coronary angiography (without FFR)	Baseline, 6 and 12 months	Utilities were derived directly from patients using the EQ-5D-3L	Health states were valued using the UK TTO tariff

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation
Stafford, 2012[54] UK (Full publication)	Adult participants in the HSE 2003 and 2006; patients with MI, 2.3% N=26,104 Mean age, NR Male, 50.2%	NA	NR	Utilities were derived directly from patients using the EQ-5D	Health states were valued using the UK TTO tariff
Sullivan, 2011[50] UK (Full publication)	Adult individuals aged ≥18 years from the MEPS 2000-2003 sample (N=79,522); sub-set of patients had acute MI according to the CCC classification (N=496) Mean age: MEPS entire sample, 42.8 years; patients with acute MI, 63.1 years Gender distribution for patients with acute MI, NR	NA	NR	Utilities were derived directly from participants using the EQ-5D	Health states were valued using the UK TTO tariff
Van Stel, 2012[55] Netherlands (Full publication)	Patients enrolled in five clinical trials: three trial recruited patients with CHD (Benestent II, ARTS, and Octopus) and two trials recruited patients with PAD (BOA and DIST)[‡] N=3,972 (PAD, 1,379; CHD, 2,593); 126 MIs occurred post-intervention in the trials Mean age, NR Gender distribution, NR	Various vascular interventions as detailed by the five clinical trials	Baseline and post-intervention (12-36 months)	Utilities were derived directly from patients using the EQ-5D	Health states were valued using the UK TTO tariff

Source: Based on Table 92 of the CS[1]

Footnotes: [†] The distribution of subsequent CV events was as follows (overall, N=597): (i) heart failure hospitalisation, N=309; (ii) recurrent MI, N=214; (iii) stroke, N=57; (iv) resuscitated sudden death, N=17; [‡] Cardiovascular events (including death, MI, cerebrovascular accident, amputation, infrainguinal-vein-graft occlusion, extracranial bleeding, and re-interventions) occurring after the vascular intervention under study in the five clinical trials were considered to be secondary events.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAP = Care Assessment Platform; CCC = Clinical Classification Categories; CHD = coronary heart disease; CI = confidence interval; EQ-5D = European Quality of Life-5 Dimensions; FFR = fractional flow reserve; HRQoL = health-related quality of life; HSE = Health Survey for England; HSUV = health state utility value; ICD = International Classification of Disease; IHD = ischaemic heart disease; IQR = interquartile range;

Study, Country	Population	Treatment	Follow up	Method used to derive utilities	Method of health state valuation
KHNANES = Korean National Health and Nutrition Examination Survey; MEPS = Medical Expenditure Panel Survey; MI = myocardial infarction; NA = not applicable; NICE = National Institute for Health and Care Excellence; NR = not reported; NSTEMI = non-ST segment elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; RIKS-HIA = The Register of Information and Knowledge about Swedish Heart Intensive Care Administrations; SD = standard deviation; SE = standard error; SEPHIA = Secondary Prevention after Heart Intensive Care Admission; STEMI = ST segment elevation myocardial infarction; TTO = time trade off; UA = unstable angina; UK = United Kingdom; US = United States					

ERG comment: The ERG agrees with the conclusion of the company.

5.1.9 Objective and searches of the resource use and costs review

The CS states that *"alongside the economic literature search, two separate literature reviews were facilitated in Pubmed aiming to obtain articles reporting cost data for pre-specified health states incorporated in the economic analysis of this decision problem"*. One search was designed to identify studies with cost data relating to myocardial infarction/acute coronary syndrome, specifically the cost of MI event health state, cardiovascular related death health state, non-cardiovascular related death health state, TIMI major and minor bleeding event, and dyspnoea. A second search was undertaken to inform the model with data relating to the health state of stroke. Both searches were designed to identify specific data and were not intended to be comprehensive systematic literature searches. To focus the searches further, a date limit for studies published in the last five years was included, as well as a geographical limit designed to identify UK related studies. Full details of the PubMed searches were reported in Appendix 14, including the URL, the date searched, and search strategy.

The CS reported that the NICE website was searched for completed HTA submissions of other oral antiplatelets, and that five HTA submissions were identified from which they extracted data for the model.

ERG comment: Although not cited, the 'resource use' search terms were based on the SIGN search filter designed to identify economic studies[27] (which itself was adapted from the search strategy designed by the NHS Centre for Reviews and Dissemination at the University of York[56]). The SIGN search filter terms were copied almost verbatim directly into PubMed, and so retained Ovid search syntax not intended for use in PubMed. For example the MeSH term *Economics/* was used with Ovid syntax, when it should have been using the PubMed syntax *"Economics"[Mesh]*. This error was repeated in the population facet, e.g. **myocardial infarction/* instead of *"Myocardial Infarction"[Mesh]*. There were numerous redundant search lines used throughout the strategy.

5.1.10 Inclusion/exclusion criteria used in the resource use and costs study selection

Identified studies were first screened according to pre-specified eligibility criteria (Table 5.5 and Table 5.6), full text review was performed. After this included articles from both searches were grouped.

Table 5.5: Eligibility criteria used for the ACS and MI resource use review

	Inclusion criteria	Exclusion criteria
Population	UK, adult patients studied as total study population or as a study subgroup that have experienced a stroke	Non-UK children and Adolescents(< 18 years) that have never experienced a stroke
Interventions/Comparators	Any	-
Outcomes	Health state costs or event costs of the following: • MI • Stroke • TIMI major bleeding • TIMI minor bleeding • CV related death • Non-CV related death • Dyspnoea (ideally divided by Grade1-2; Grade3-4; Overall) • Long term cost of not having	Efficacy, Safety, QoL, unit costs

	Inclusion criteria	Exclusion criteria
	an event (only valid for ACS studies)	
Study design	Economic Evaluations, cost studies, observational, survey, RCTs, burden of illness, large cohort studies	Review studies, non-systematic reviews, pooled analyses, animal studies, editorials, letters, genetic studies, case reports, commentaries, interview-based research, legal cases, newspaper articles, debates, general or independent central reviews, opinions, protocols, workshops, assay studies, cytogenetic studies. surgical studies, or educational material for patients
	Meta-analyses Systematic reviews	
	Articles published within the last 5 years	Articles published prior to the last 5 years
Language restrictions	English studies	Non-English studies
Source: Source: Based on Table 26 of CS appendices[39] ACS = acute coronary syndrome; CS = company submission; CV = cardiovascular; MI = myocardial infarction; QoL = quality of life; RCT = randomised controlled trial; TIMI = Thrombolysis in Myocardial Infarction; UK = United Kingdom		

Table 5.6: Eligibility criteria used for the stroke resource use review

	Inclusion criteria	Exclusion criteria
Population	UK, adult patients studied as total study population or as a study subgroup that have experienced an ACS or MI	Non-UK children and Adolescents(< 18 years) that have never experienced an ACS or MI
Interventions/Comparators	Any	-
Outcomes	Health state costs or event costs of the following: • MI • Stroke • TIMI major bleeding • TIMI minor bleeding • CV related death • Non-CV related death • Dyspnoea (ideally divided by Grade1-2; Grade3-4; Overall) • Long term cost of not having an event (only valid for ACS studies)	Efficacy, Safety, QoL, unit costs
Study design	Economic Evaluations, cost studies, observational, survey, RCTs, burden of illness, large cohort studies	Review studies, non-systematic reviews, pooled analyses, animal studies, editorials, letters, genetic studies, case reports,

	Inclusion criteria	Exclusion criteria
	Meta-analyses Systematic reviews	commentaries, interview-based research, legal cases, newspaper articles, debates, general or independent central reviews, opinions, protocols, workshops, assay studies, cytogenetic studies. surgical studies, or educational material for patients
	Articles published within the last 5 years	Articles published prior to the last 5 years
Language restrictions	English studies	Non-English studies

Source: Source: Based on Table 27 of CS appendices[39]
ACS = acute coronary syndrome; CS = company submission; CV = cardiovascular; MI = myocardial infarction; QoL = quality of life; RCT = randomised controlled trial; TIMI = Thrombolysis in Myocardial Infarction; UK = United Kingdom

ERG comment: The in- and exclusion criteria seem appropriate for the objective of this review.

5.1.11 Included/excluded studies in the resource use and costs review

After screening, full text review and grouping studies from both searches, 45 articles were included (MI review: n=16; stroke review: n=29). Seven studies were common between the searches, which leaves 38 appropriate studies for resource use and costs data (CS, Appendix 14, Table 28).

The following potentially relevant submissions were identified on the NICE website:

- NICE (2009). TA182: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention.[45]
- NICE (2010). TA210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events.[46]
- NICE (2011). TA236:Ticagrelor for the treatment of acute coronary syndromes.[47]
- NICE (2014). TA317: Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes.[48]
- NICE (2015). TA335: Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome.[49]

ERG comment: The rationale for excluding studies after full paper reviewing seems appropriate given the defined in- and exclusion criteria.

5.1.12 Conclusions of the resource use and costs review

The company considered cost data from the ERG assessment report of TA317[57] (inflated to 2015 values[58]) as appropriate for the current decision problem. These costs were supplemented by the ERG assessment report TA210[59] and NHS references costs[60] when unit costs were not available from TA 317.

ERG comment: Whilst the ERG agrees that these identified TAs are appropriate to inform the current decision problem, it requested that more contemporary sources be used rather than simply inflation-adjusting values used in earlier studies. The ERG is grateful to the company for providing some alternatives – see Table 5.25.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.7: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A state transition model was developed with a cycle duration of three months to capture the long-term (40 years) consequences of ticagrelor 60 mg BID + low-dose ASA (75 mg) versus low-dose ASA (75 mg) monotherapy.		Section 5.2 (pg. 169)
States and events	The following health states are explicitly incorporated in the model: 'No event' (starting state); 0-3 months post non-fatal MI (tunnel state); 3-6 months post non-fatal MI (tunnel state); 6-9 months post non-fatal MI (tunnel state); 9-12 months post non-fatal MI (tunnel state); 12+ months post non-fatal MI; 0-3 months post non-fatal stroke (tunnel state); 3-6 months post non-fatal stroke (tunnel state); 6-9 months post non-fatal stroke (tunnel state); 9-12 months post non-fatal stroke (tunnel state); 12+ months post non-fatal stroke; death due to fatal CV event; death due to fatal other event Subsequent non-fatal events (after the first non-fatal MI or stroke) and adverse events are not explicitly incorporated in the model structure. Instead, patients experience costs and a disutility for the duration of one cycle.	*"Explicitly modelling repeat events over the relatively short time frame of the trial would add substantially to the complexity of the model (i.e. modelling multiple sets of tunnel states for acute phases), which would not be expected to alter estimates of life years or QALYs. While this is a simplification of reality, it is a structural assumption that will not significantly change overall health outcomes and associated costs."* TIMI bleeding and dyspnoea are not modelled using health states, as they do not have a long-term impact on prognosis in terms of long-term mortality or permanent utility decrements.	Section 5.2 (p. 169-172)

	Approach	Source / Justification	Signpost (location in CS)
Comparators	Ticagrelor 60 mg BID + low dose (75mg) ASA daily; Low dose (75mg) ASA daily. The scope requested clopidogrel + ASA to be considered a comparator for this appraisal, which was not included.	Comparison with clopidogrel + aspirin is not presented as "there is no head-to-head trial data and robust indirect comparison of pivotal trial outcomes is not feasible owing to important differences between studies", "clopidogrel + aspirin is not established NHS clinical practice in the population of interest", and "clopidogrel + aspirin does not have a licence in this indication".	Section 1.1 (p.15) 5.2 (p.174)
Population	The population in the base case economic evaluation is a subgroup of the licensed indication (and population defined by the scope), corresponding to those patients with a history of MI and a high risk of developing an atherothrombotic event, who tolerate low dose aspirin, whose most recent MI occurred <2 years ago.	This is a pre-specified subgroup within the limits of the marketing authorisation in this indication.	Section 1.1 (p.15) 5.2 (p.168)
Treatment effectiveness	Ticagrelor 60 mg BID co-administered with aspirin for up to 3 years.	This is the dose specified in the marketing authorisation and there is limited data beyond 3 years.	Section 1.1 (p.15)
Adverse events	TIMI bleeding events, major and minor, and dyspnoea events, major (grade 3–4) and minor (grade 1–2) were considered. These events are modelled as events that are conditional upon the patient remaining on treatment and contribute to the costs and QALYs (via disutility) in the model.	A small excess of gout was observed in PEGASUS-TIMI 54 for ticagrelor 60 mg BID vs. placebo (0.46% ARI; HR 1.48; 95% CI 1.10 to 2.00; p=0.01). Gout is not modelled as an adverse event within the economic model.	Section 5.2 (p.171) 5.4 (p.258 & p.264)
Health related QoL	Health-related QOL EQ-5D data was collected in the PEGASUS TIMI-54 trial. Panel data methods have been used to estimate utility decrements for the events non-fatal MI; post non-fatal MI; non-fatal stroke; post non-fatal stroke; TIMI major bleeds; TIMI minor bleeds; dyspnoea (grade 3–4); dyspnoea (grade 1–2).		Section 5.4 (p.259)

	Approach	Source / Justification	Signpost (location in CS)
Resource utilisation and costs	The model includes costs for four broad categories: acute inpatient costs; acute outpatient and maintenance costs (within 12 months from event); long-term outpatient and maintenance costs (over 12 months from event) and; adverse events. Resource and cost data were obtained from literature reviews.		Section 5.5 (p. 266-282)
Discount rates	Discount of 3.5% for utilities and costs	As per NICE scope	Section 5.2 (p.173)
Sub groups	Subgroup analyses were performed for patients continuing therapy (ADP < 30 days), patients with and without diabetes and patients with and without a history of PCI.	As per NICE scope	Section 5.9 (p.212,213)
Sensitivity analysis	Both the DSA and PSA are performed for a single individual patient profile chosen by selecting the patient with the ICER that most closely represents that of the deterministic 'complete' analysis.	Due to the computational requirements in undertaking an individual patient level sensitivity analysis a traditional DSA and PSA were deemed infeasible.	Section 5.8 (p.295-303)

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; BID = twice daily; CS = company submission; CV = cardiovascular; DSA = deterministic sensitivity analysis; EQ-5D = European Quality of Life-5 Dimensions; ICER = incremental cost effectiveness ratio; mg = milligram; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted Life Year; TIMI = Thrombolysis in Myocardial Infarction

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.8: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	N	The population was a pre-specified subgroup within the limits of the marketing authorisation in this indication.
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	The scope additionally requested clopidogrel + ASA to be considered a comparator for this appraisal, which was not included.
Type of economic evaluation	Cost effectiveness analysis	Y	
Perspective on costs	NHS and Personal Social Services (PSS)	Y	
Perspective on outcomes	All health effects on individuals	Y	
Time horizon	Sufficient to capture differences in costs and outcomes	Y	After 40 years 98.8% of patients have died in the model.
Synthesis of evidence in outcomes	Systematic review	Y	
Measure of health effects	Quality adjusted life years (QALYs)	Y	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Y	The EQ-5D-3L health status questionnaire was used to collect HRQoL data for patients in the PEGASUS-TIMI 54 study.
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Y	The UK TTO valuations have been used as a default for the EQ-5D-3L questionnaire, converting questionnaire responses to utilities which are applied in the economic model.
Discount rate	An annual rate of 3.5% on both costs and health effects	Y	

Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	
Sensitivity analysis	Probabilistic modelling	N	In the individual patient simulation, the PSA evaluates the uncertainty around the incremental costs and incremental effects for one patient selected profile instead of the entire population. For the cohort simulation no PSA results were presented.
EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Clinical Excellence; PSA = probablistic sensitivity analysis; quality-adjusted life years; PSS = Personal Social Services; TTO = Time trade off; UK = United Kingdom			

5.2.2 Model structure

The company developed a state transition model with a cycle duration of three months to capture the long term (40 years) consequences of ticagrelor 60 mg BID + low dose ASA (75 mg) versus low dose ASA (75 mg) monotherapy. All patients start in the 'no event' state. The model uses a competing risk framework to model the risks for: 'non-fatal MI', 'non-fatal stroke', 'fatal CV event', and 'other fatal event'. Patients having a fatal event enter the absorbing 'death' state. After a non-fatal first event, patients enter either a series of five 'post non-fatal MI' or 'post non-fatal stroke' tunnel states, depending on which event they experienced. The first four tunnel states (0-3 months, 3-6 months, 6-9 months, 9-12 months) track time since the first event, with a diminishing risk for subsequent events ('non-fatal MI', 'non-fatal stroke', 'fatal CV event', and 'other fatal event'). The fifth state applies a constant risk for subsequent events from 12 months or more since the first event. Patients who experience a subsequent non-fatal event do not enter a separate series of tunnel states. Instead, they remain in their health state and experience costs and a disutility for the duration of one cycle (i.e. subsequent non-fatal events are not explicitly modelled). The company states that it is assumed that this simplification of reality will not significantly change the overall health outcomes and associated costs.

Adverse events included in the model are TIMI (major and minor) bleeding and dyspnoea (grade 1-2 or grade 3-4). These events are not explicitly modelled using health states, but as transient events conditional on the patients remaining on treatment. The adverse events contribute to costs and QALYs (via disutility) for a duration of one cycle.

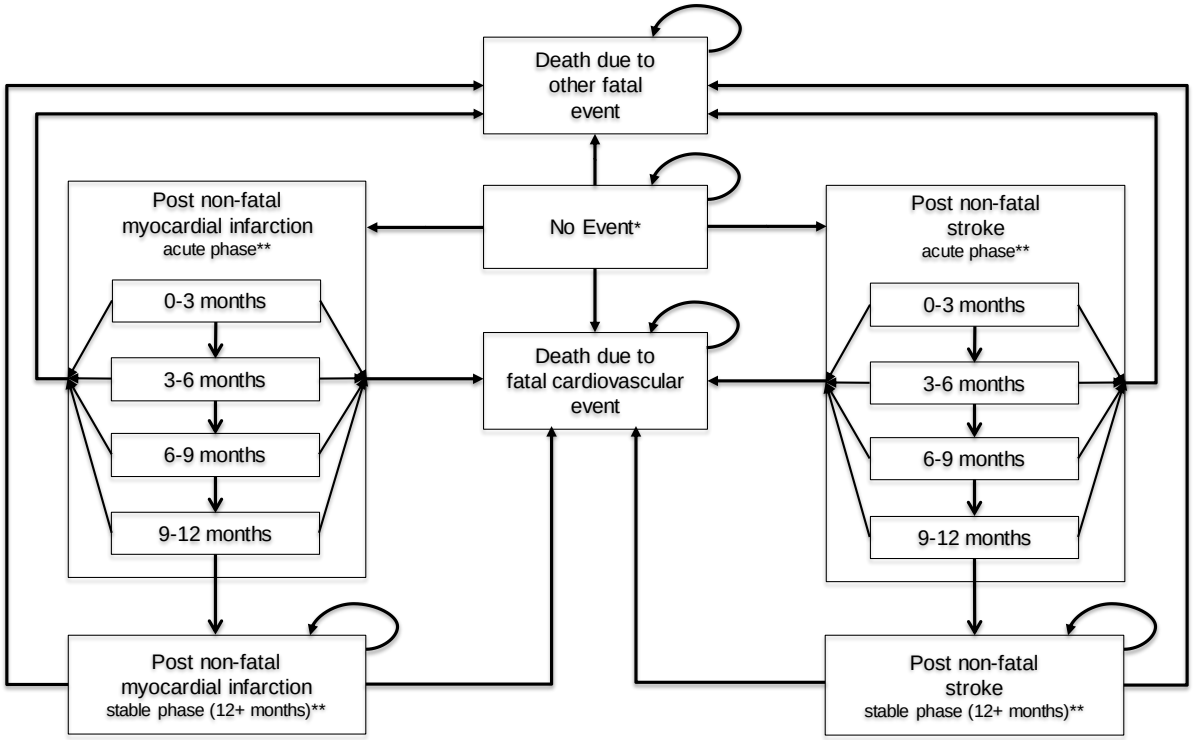
Treatment duration is set to 36 months. After 36 months, the subsequent time periods are modelled without treatment effects, and patients are assumed to continue on low dose ASA monotherapy.

All patients in the model accrue outpatient and maintenance costs. A proportion of the patients in health states and experiencing fatal events accrue inpatient costs. It was assumed that all patients experiencing a non-fatal MI, a non-fatal stroke or a major adverse event will be hospitalised.

ERG comment: The model structure includes some simplifications that potentially influence health outcomes and costs: non-explicit modelling of subsequent events and adverse events, not including gout as an adverse event, not distinguishing between non-fatal disabling and non-disabling stroke, and incorporating a difference in the occurrence of adverse events between treatments until ticagrelor 60 mg BID + ASA treatment discontinuation only.

As a result of not explicitly modelling non-fatal subsequent events and adverse events the occurrence of these events does not impact survival and only has a temporary (three months) impact on costs and quality of life. The ERG developed a graphical representation of the model structure to present the model structure more clearly (Figure 5.1).

Figure 5.1: Graphical representation of the model structure



* Patients in the no event health state can experience adverse events (major and minor bleeding and major and minor dyspnoea). The risk is dependent on treatment and disutility and costs are incurred for the duration of one cycle (3 months).

** Patients in the post non-fatal myocardial infarction and the post non-fatal stroke states can experience adverse events (major and minor bleeding and major and minor dyspnoea) and subsequent non-fatal myocardial infarction and stroke. These risks are dependent on treatment and disutility and costs are incurred for the duration of one cycle (3 months).

The ERG asked the company to adjust the model to incorporate the impact of non-fatal subsequent events and AE on survival and costs and quality of life beyond three months. In addition, it was asked to perform a scenario analysis explicitly incorporating subsequent events and the potential impact on survival to show that the model simplification did not impact health outcomes and costs. The company did not provide the model adaptation and scenario analysis. The following justification was provided for not explicitly modelling subsequent events:

"A pragmatic decision was made to simplify the health states needed to model transition probabilities through the acute and sTable phase subsequent events, without losing important information. Therefore the risk equations were designed to capture the likelihood of multiple subsequent events (during the acute and sTable phase) in addition to the greater risk of a subsequent given the occurrence of a first event.

Should the model slightly underpredict the occurrence of 3rd events (and beyond), this would represent a conservative modelling approach from the perspective of ticagrelor 60 mg BID + ASA, owing to the treatment effect observed for first events in PEGASUS-TIMI 54 and the influence of first events on subsequent events".[25]

The ERG agrees that the non-explicit modelling of subsequent events is likely to result in an underestimation of the impact of these events on costs and health outcomes, which is likely to be conservative.

The justification provided by the company for not explicitly modelling adverse events is as follows: *"it should be noted that within PEGASUS-TIMI 54, ticagrelor 60 mg BID + ASA was not associated with an increase in fatal bleeding or intracranial haemorrhage (ICH) meaning the observed excess related to TIMI major non-fatal and non-ICH bleeds. Therefore we feel it appropriate to model AEs including TIMI major bleeding as a temporal event".*[25]

According to the ERG the modelling of adverse events by the company may result in an underestimation of the impact of major bleeding in particular, as the consequences of this adverse event are likely to exceed three months. Therefore, in the ERG base-case a more conservative disutility for major bleeding is used.

The model did not consider gout, although according to the company submission (page 264) *"a small excess of gout was observed in PEGASUS-TIMI 54 for ticagrelor 60 mg BID vs. placebo (0.46% ARI; HR 1.48; 95% CI 1.10 to 2.00; p=0.01)".*[1] The ERG requested the company to incorporate the impact of gout on costs and quality of life in the economic analyses. In response, the company provided an updated model that included gout. The results of this analysis are presented in Section 5.2.11, and used in the ERG's base-case and additional analyses.

The model structure does not distinguish between non-fatal disabling and non-disabling strokes, while these have different clinical and economic impacts. The ERG asked the company to implement treatment-specific utility values and costs for stroke in the model based on the breakdown of disabling and non-disabling strokes as observed in the trial. The company's response included data on the occurrence on non-fatal disabling and non-disabling strokes 30 days after the event as observed in the PEGASUS-TIMI 54 trial. Patients treated with ticagrelor 60 mg BID + ASA are associated with a numerically lower percentage of non-fatal disabling strokes [redacted] than patients treated with placebo + ASA [redacted]. Based on this, the company argued that the application of disutility and costs for the post-stroke states in the model in the current manner is conservative for ticagrelor 60 mg BID + ASA.[25]

The ERG agrees that not distinguishing between non-fatal disabling and non-disabling stroke based on data from PEGASUS-TIMI 54 trials is conservative.

5.2.3 Population

The patient population presented in the economic evaluation includes patients with a history of myocardial infarction (MI), aged ≥50 years, whose most recent MI occurred <2 years ago, who tolerate low dose aspirin, and:

exhibit at least one of:

- age ≥65 years, diabetes requiring medication, >1 prior MI, multivessel Coronary Artery Disease, chronic renal dysfunction,

but do not exhibit:

- planned use of PY12 antagonist, dipyridamole, cilostazol or anticoagulant, bleeding disorder, history of ischaemic stroke, intracerebral hemorrhage, CNS tumour or vascular abnormality, recent gastro-intestinal bleed or major surgery, risk of bradycardia, dialysis or severe liver disease.

This corresponds with the "MI <2 years" subgroup of the PEGASUS TIMI-54 trial (the 'label' population). The company states that the population in the economic evaluation is a subgroup of the licensed indication, and of the population defined by the scope.

ERG comment: The company states that the modelled population is a subpopulation of the licensed population and the population in the scope. However, in the European Public Assessment Report (EPAR)[19], it is stated that ticagrelor 60 mg BID (Brilique®) may be initiated "*up to 2 years from the MI,* or *within one year after stopping previous ADP receptor inhibitor treatment*." This implies that the modelled population is very close to the licensed population. The only differences is that patients *"within one year after stopping previous ADP receptor inhibitor treatment"* are included in the licensed indication but not specifically mentioned in the description of the modelled population. In practice, these populations may be similar. See Table 5.9 for a comparison of the population in the scope, the recommended population in EPAR, and the 'label' population.

It should be noted that not all analysis of the PEGASUS-TIMI 54 trial to inform the parameters in the model reflect the 'label' population; most analyses are based on the ITT population instead without adjustment to reflect the 'label' population. See Section 5.2.6 for more details.

Table 5.9: Population defined in the scope, in the European Public Assessment Report and the "MI <2 years" subgroup of PEGASUS-TIMI 54 trial

	Scope	**EPAR**	**PEGASUS TIMI-54 trial MI <2 yrs subgroup 'label' population**
Population	Adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events.	When an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event (see section 5.1). Treatment may be started without interruption as continuation therapy after the initial one-year treatment with Brilique 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment.	Patients with a history of myocardial infarction, aged ≥50 years, whose most recent MI occurred <2 years ago, who tolerate low dose aspirin. And exhibit at least one of: Age ≥65 years; Diabetes requiring medication; >1 prior MI; Multivessel Coronary Artery Disease; Chronic renal dysfunction. But do not exhibit: Planned use of PY12 antagonist, dipyridamole, cilostazol or anticoagulant; Bleeding disorder; History of ischaemic stroke, intracerebral hemorrhage, CNS tumour or vascular abnormality; Recent GI bleed or major surgery; Risk of bradycardia; Dialysis or severe liver disease.

Source: Bonaca et al. 2015[20], EPAR[19], Final scope[17]

ACS = acute coronary syndrome; ADP = adenosine diphosphate; CNS = central nervous system; EPAR = European Public Assessment Report; GI = gastrointestinal; MI = Myocardial infarction

5.2.4 Interventions and comparators

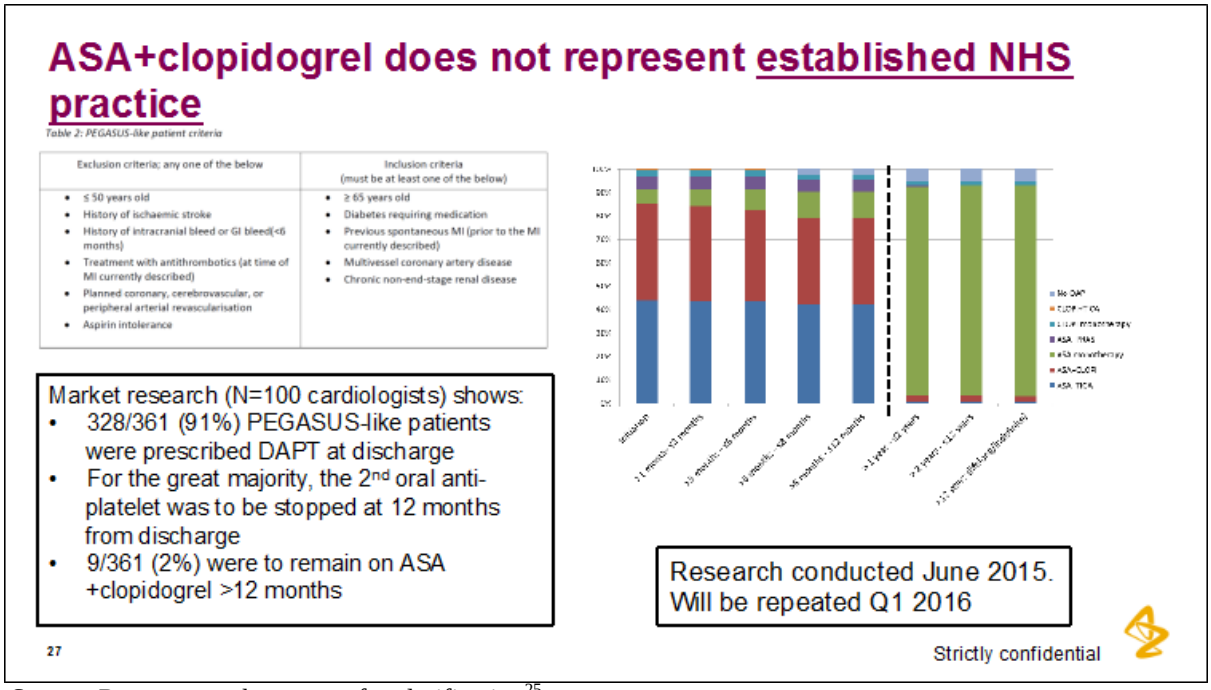
The company included 'ticagrelor 60 mg BID + low dose (75 mg) ASA daily for the duration of 36 months' and 'low dose (75mg) ASA daily' as comparators in the economic evaluation.

Additionally, the scope requests clopidogrel + ASA to be considered as a comparator for this appraisal. This comparator is not included in the economic evaluation, "*owing to the absence of a head-to-head trial in the population of interest and a lack of available trial evidence for clopidogrel + ASA that would facilitate a robust indirect comparison to the ticagrelor 60 mg BID + low dose ASA arm of the PEGASUS TIMI-54 trial (or MI<2 years subgroup thereof).*"[1]

ERG comment: The treatment pathway was unclear to the ERG. Specifically, it was unclear how patients who experience a subsequent non-fatal event are treated in the model. The ERG asked the company to clarify whether these patients would receive ticagrelor 90 mg for 12 months, followed by ticagrelor 60 mg for 36 months. The company responded that the use of dual antiplatelet therapy after a subsequent event in the model could take place in clinical practice as patients are 'reset' as new ACS patients. In addition, the company clarified that this was not incorporated in the model, due to complexity and time constraints. The company did provide a scenario analysis whereby the cost associated to the post non-fatal myocardial infarction (12+ months) health state is increased by £178.06 per cycle (the cost of ticagrelor 60 mg BID per three months). This is similar to assuming ticagrelor 60 mg BID is given for remaining lifetime from 12 months following a myocardial infarction. As such, this scenario analysis overstates the impact on the ICER, but is illustrative of directional impact on the ICER.[25] Moreover, the company provided a scenario analysis assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI. The results of this analyses are provided in Section 5.2.10.

Clopidogrel +ASA was not included as a comparator in the model. It should be noted that the electronic Medicines Compendium (eMC) states "clinical trial data support use of clopidogrel + ASA up to 12 months following the [index] event".[21] Nevertheless, clopidogrel + ASA was listed in the scope. Therefore, the ERG asked the company to perform an indirect comparison of ticagrelor 60 mg twice daily + low dose (75mg) ASA daily for the duration of 36 months versus clopidogrel + low dose ASA and use the results to include clopidogrel + low dose ASA in the model. The company did not provide this analysis, and justified this by repeating the arguments from the company submission. According to the ERG, the available evidence does allow inclusion of clopidogrel + low dose ASA as a comparator in the model based on an indirect comparison, as long as the assumptions are clearly reported and the uncertainties are propagated. Other arguments, besides the quality of the available evidence, to *not* include clopidogrel + low dose ASA as a comparator in the model are that this treatment is not licensed for this indication, and that it is not used in the UK in this indication.[25] To underpin this, the company provided the results of a market research among 100 cardiologists, conducted in June 2015, in their response on clarification questions. This research showed that 9/361 (2%) patients were to remain on ASA + clopidogrel more than 12 months after myocardial infarction (see Figure 5.2).[25]

Figure 5.2: Results of market research



Source: Response to the request for clarification[25]

5.2.5 Perspective, time horizon and discounting

The perspective adopted by the company is NHS and PSS. The time horizon is 40 years. Costs and health outcomes were discounted by 3.5%.

ERG comment: The ERG agrees with the perspective, time horizon and discount rates used by the company.

5.2.6 Treatment effectiveness and extrapolation

Multiple parametric time-to-event models were used (based on the PEGASUS-TIMI 54 trial) to estimate:

- time to the first event (i.e. non-fatal MI, non-fatal stroke, fatal CV event or other fatal event);
- time to subsequent event (i.e. non-fatal MI, non-fatal stroke, fatal CV event or other fatal event after a first non-fatal MI or non-fatal stroke);
- time to treatment discontinuation;
- time to adverse events (i.e. TIMI major bleeds and dyspnoea grade 3-4; see Section 5.2.7)

Of these parametric time-to-event models, only the time to the first event and mortality after the first event were explicitly incorporated in the model structure. The other time-to-event models were only used to incorporate costs and disutilities for the duration of one cycle (three months).

The company stated that the parametric survival model to estimate other fatal events resulted in a lower mortality probability than would be expected in the general population. In order to avoid underestimation of mortality in the base-case, the company has derived this probability from UK life tables. As life tables reflect all-cause mortality, including deaths from CV-related causes, CV-specific mortality was excluded from the standard life tables used in the model.

Hospitalisation was incorporated into the model using a Poisson regression model. Duration of hospitalisation was not explicitly modelled (this was assumed to be reflected in the costs per hospitalisation).

All models are estimated based on the intention-to-treat population and possibly adjusted (in part) to reflect the label population. In the 'complete' (i.e. individual patient) analysis the characteristics of individual patients were used in the economic model whereas for the 'simple' (i.e. cohort) analysis the average characteristics of the label population in the PEGASUS-TIMI 54 trial were used (see Table 5.33).

Time to first event

A competing risk approach was used by the company to estimate the time to the first event, either a non-fatal MI, non-fatal stroke, fatal CV event or other fatal event. This approach entails censoring patients from the 'at-risk' population when a competing event occurs. Moreover, the company introduced a 30-day rule, defining that any MI or stroke which occurred within 30 days before a CV death was handled as a fatal CV event only.

To estimate the time-to-event models, the following steps were followed:

1) Selection of baseline covariates for inclusion in the model using Cox regression analysis. This approach was used by the company as the Cox proportional hazards model does not impose a restriction or assumption with regard to the form of the underlying hazard.
   a) Individually regress all candidate baseline covariates against the outcome of interest and selecting covariates using an alpha (significance level) of 0.05.
   b) Incorporating all selected covariates in a stepwise regression using an alpha of 0.10.
   c) Incorporating all covariates excluded in previous steps one by one, retaining the variables at an alpha of 0.10.
   d) Covariates were tested for the proportional hazards assumption (based on Schoenfeld residuals test using an alpha of 0.05 and log cumulative hazard plots) and interaction terms were examined if this assumption did not hold.
2) Account for the interaction effect for patients in the label population using Cox regression analysis.
   a) Incorporating the following covariates in the model (developed in step 1):
      i) 'Offlabel' - identifies patients included or excluded from the label population.
      ii) 'Tic60 * offlabel' - interaction term. Patients receiving ticagrelor 60 mg who are not included in the label population.
      iii) 'Tic90 * offlabel' - interaction term. Patients receiving ticagrelor 90 mg who are not included in the label population.
   b) Similar variables (as those included in step 2a) were dropped to isolate the effect of being in the label population (no objective decision rule/statistical test is specified).
   c) The interaction terms included in step 2a were evaluated using an alpha of 0.05. In case the p-value was between 0.05 and 0.10, a collapsed interaction term was evaluated using an alpha of 0.05.
   d) In case no interaction term was considered significant in step 2c, then the covariate 'offlabel' was evaluated using an alpha of 0.05.
   e) If neither of the variables evaluated in steps 2c and 2d are statistically significant, then the original risk equation developed in step 1 is used.
   f) The final model was examined for multicollinearity between the 'offlabel' variable and the following variables:

i) 'qev2rnd' - indicating time since previous MI.
ii) 'tADP_12mplus' - indicating patients receiving an ADP blocker more than 12 months ago.

If multicollinearity is suspected (no objective decision rule/statistical test is specified), the collinear variables were dropped keeping the 'offlabel' variable.

3) Selecting the parametric survival model.
   a) The parametric survival model with the lowest Akaike information criterion (AIC) was selected using the following distributions:
      i) Exponential.
      ii) Weibull.
      iii) Gompertz.
      iv) Log-normal.
      v) Log-logistic.

Based on the AIC, the log-logistic distribution was preferred for all time-to-event models. An overview of the final selected models is provided in Table 5.10. The estimated time to first event of these models and the accompanying Kaplan-Meier estimates are presented in Table 5.11. In the economic model it is assumed that the time to the first event is different between the two treatments for the first three years, afterwards the transition probabilities for ticagrelor 60 mg are assumed to be equal as those for ASA.

Table 5.10: Overview of parametric time-to-event models for time to first event

First event	**Non-fatal MI**	**Non-fatal stroke**	**Fatal CV**	**Fatal other**
Distribution	Log-logistic	Log-logistic	Log-logistic	Log-logistic
Variable[a]	**Coefficient**	**Coefficient**	**Coefficient**	**Coefficient**
Offlabel	0.2771		0.3194	
Tic60	0.2057	0.2674	0.2032	
Tic90	0.1860	0.1647	0.2092	-0.2276
Tic60 * offlabel			-0.0255	
Tic90 * offlabel			-0.4135	
Age	-0.0130	-0.0355	-0.2248	-0.0468
Angina pectoris	-0.3164			0.1800
ASA dose			-0.4924	
Asia/ Australia	0.3051			
BMI			-0.6528	0.0462
CABG history	-0.8230			
Congestive heart failure		-0.5899	0.0115	-0.1838
Creatinine clearance rate ≥60 ml/min	0.2789	0.5293	-0.0044	0.3555
Diabetes	-0.4085	-0.3982	0.4503	-0.3006
Hypercholesterolaemia		-0.4511		
Hypertension			-0.3977	
MI history	-0.7613		-0.3830	
Multivessel coronary artery disease	-0.3111		-0.3269	
North America	-0.4164			0.2294
Peripheral arterial disease history	-0.2420	-0.6216	0.8067	-0.3635
Qualifying event was STEMI	-0.1945			
Sex		-0.3845	-0.4003	

First event	Non-fatal MI	Non-fatal stroke	Fatal CV	Fatal other
Distribution	Log-logistic	Log-logistic	Log-logistic	Log-logistic
Variable[a]	**Coefficient**	**Coefficient**	**Coefficient**	**Coefficient**
Smoker current	-0.5086	-0.3579	-0.6490	-0.6724
Smoker former	-0.2321			-0.2456
South America		-0.3865	-0.0447	
Stent (ever received)			-0.4157	
Stroke history		-1.0763		
Supine SBP (mm Hg)	-0.0102	-0.0114		
Time since last ADP blocker > 12 months		0.3879		
Transient ischaemic attack history		-1.0498		
Weight			-0.2262	-0.0136
_cons	13.1700	16.2000	12.6182	12.9254
Shape[b]	0.0728	0.1054	-0.2010	-0.3480

Source: Based on Tables 58, 60, 62, 65 and 67 of the CS[1]

Footnotes: [a] Baseline characteristics unless stated otherwise see Table 58 of the CS for more detailed variable descriptions; [b] Shape variables take the following form: Log Logistic – ln(gamma)

ADP = Adenosine diphosphate; ASA = acetylsalicylic acid; BMI = body mass index; CABG = coronary artery bypass graft; CV = cardiovascular; Hg = mercury; MI = myocardial infarction; mm = millimetre; SBP = systolic blood pressure; STEMI = ST segment elevation myocardial infarction

Table 5.11: Estimated time to first event; parametric survival models and the accompanying Kaplan-Meier estimates[a]

Time to event	Ticagrelor 60 mg		ASA	
Non-fatal MI	**KM**	**Log-logistic**	**KM**	**Log-logistic**
1 year	98.3%	97.5%	97.8%	97.0%
2 year	96.9%	95.4%	96.0%	94.5%
3 year	95.4%	93.5%	94.8%	92.3%
4 year		91.7%		90.3%
5 year		90.1%		88.4%
10 year		83.4%		81.0%
15 year		78.4%		75.5%
20 year		74.3%		71.3%
30 year		68.3%		65.3%
Non-fatal stroke	**KM**	**Log-logistic**	**KM**	**Log-logistic**
1 year	99.5%	99.4%	99.4%	99.3%
2 year	99.2%	98.9%	98.8%	98.7%
3 year	98.8%	98.5%	98.4%	98.1%
4 year		98.0%		97.5%
5 year		97.6%		97.0%
10 year		95.7%		94.6%
15 year		94.0%		92.5%
20 year		92.4%		90.6%

Time to event	Ticagrelor 60 mg		ASA	
30 year		89.6%		87.3%
Fatal CV	**KM**	**Log-logistic**	**KM**	**Log-logistic**
1 year	99.3%	99.6%	99.2%	99.5%
2 year	98.2%	99.1%	98.2%	98.8%
3 year	97.6%	98.5%	96.9%	98.1%
4 year		97.8%		97.3%
5 year		97.2%		96.5%
10 year		93.8%		92.3%
15 year		90.4%		88.2%
20 year		87.2%		84.4%
30 year		81.3%		77.8%
Fatal other	**KM**	**Log-logistic**	**KM**	**Log-logistic**
1 year	99.6%	99.4%	99.5%	99.4%
2 year	99.1%	98.4%	99.1%	98.4%
3 year	98.3%	97.3%	98.4%	97.3%
4 year		96.0%		96.0%
5 year		94.6%		94.6%
10 year		87.3%		87.3%
15 year		80.4%		80.4%
20 year		74.4%		74.4%
30 year		65.3%		65.3%

Footnotes: [a] See Figures 35-42 of the CS for a graphical presentation
ASA = acetylsalicylic acid; CS = company submission; CV = cardiovascular; KM = Kaplan-Meier estimate; mg = milligram; MI = myocardial infarction

Time to subsequent events

The time to subsequent non-fatal event was not explicitly incorporated in the model structure, but only used to incorporate costs and disutilities for the duration of one cycle (three months).

The time to subsequent events was assumed to be independent of initial treatment (i.e. the 'pMI_Tic60' covariate was not used in the model). Also, the company assumed (based on statistical testing) that the risk of a subsequent non-fatal stroke was influenced by the type of first non-fatal event (i.e. non-fatal MI or non-fatal stroke as first event). The other subsequent events were assumed to be independent of the type of non-fatal first event.

Estimates of time to subsequent event were calculated using similar procedures used to estimate time to first event. According to the company there was no evidence to suggest that adjusting for the label population was significant (using an alpha of 0.05), hence the time to subsequent event was not adjusted to represent the label population. In addition, for subsequent events more than one year after the first event (events occurring in the 'sTable phase'; the last tunnel state post non-fatal myocardial information and post non-fatal stroke), an exponential (time-to-event) model was used by the company (instead of selecting the most appropriate model based on AIC).

An overview of the final models is provided in Tables 5.12 (time to subsequent event occurring less than one year after the first event, termed acute phase by the company) and 5.13 (time to subsequent event occurring more than one year after the first event, termed sTable phase by the company). The estimated time to subsequent events occurring more than one year after the first event is presented in Table 5.14.

Table 5.12: Overview of parametric time-to-event models for time to subsequent event less than one year after the first event (i.e. 'acute phase')

Subsequent event	**Non-fatal MI**	**Non-fatal stroke**	**Fatal CV**	**Fatal other**
First event dependent[a]	Independent	Dependent	Independent	Independent
Distribution	Log-logistic	Weibull	Log-normal	Weibull
Variable[b]	**Coefficient**	**Coefficient**	**Coefficient**	**Coefficient**
Tic60 * MI as first event[c]	-0.3394		0.3329	
Tic90 * MI as first event[c]	-0.1234		0.2025	-0.4136
Age		-0.0372	-0.0843	
Angina pectoris	0.4770			
BMI	-0.1395			
CABG history	-0.6892			
Congestive heart failure			-1.1951	0.8622
Creatinine clearance rate ≥60 ml/min				-0.7205
Diabetes			-1.5140	
Family history of premature coronary heart disease		0.6390		
MI history			-0.6498	
North America	-0.8491			1.0939
Peripheral arterial disease history	-0.7820	0.9746		
Qualifying event was STEMI	-0.7776		0.7976	
Smoker current		1.2319	-0.6152	1.8924
Smoker former	-0.5257	1.5596		1.2643
South America		0.7490		
Stent (ever received)			0.7044	
Stroke as first event		1.6432		
Supine DBP (mm Hg)	0.0473			-0.0634
Supine SBP (mm Hg)	-0.0250			0.0450
Transient ischaemic attack history		1.2766	-1.4353	
Weight	0.0350			
_cons	10.3937	-7.8999	15.3756	-9.0586
Shape[d]	0.1828	-0.3010	0.6877	-0.5875

Source: Based on Tables 68, 70, 72 and 74 of the CS[1]
Footnotes: [a] If dependent, a different probability is calculated for patients with MI and stroke as first event in the economic model; [b] Baseline characteristics unless stated otherwise see Table 58 of the CS for more detailed variable descriptions; [c] This parameter is not used in the economic model; [d] Shape variables take the following form: Log Logistic – ln(gamma); Weibull – ln(p); Log Normal – ln(sigma)
BMI = body mass index; CABG = coronary artery bypass graft; CV = cardiovascular; DBP = diastolic blood pressure; Hg = mercury; MI = myocardial infarction; ml = millilitre; mm = millimetre; SBP = systolic blood pressure; STEMI = ST segment elevation myocardial infarction

Table 5.13: Overview of parametric time-to-event models for time to subsequent event more than one year after the first event (i.e. 'sTable phase')

Subsequent event	**Non-fatal MI**	**Non-fatal stroke**	**Fatal CV**	**Fatal other**
First event dependent[a]	Independent	Dependent	Independent	Independent
Distribution	Exponential	Exponential	Exponential	Exponential
Variable[b]	**Coefficient**	**Coefficient**	**Coefficient**	**Coefficient**
Tic60 * MI as first event[c]	0.0838		-1.4561	
Tic90 * MI as first event[c]	0.5930		-0.2784	-17.3358
Age			0.0656	
ASA dose	-0.0379		0.0080	
CABG history	1.0828	2.0910		
Congestive heart failure			1.1984	
Diabetes	0.8120		1.1836	
Hypertension				-2.5369
North America	0.7444			2.9332
Qualifying event was STEMI			-1.3193	
Smoker current		1.4197		
Stroke as first event		2.4285		
Transient ischaemic attack history		1.6552	2.0922	
_cons	-6.3340	-12.0598	-14.4348	-8.8021

Source: Based on Tables 69, 71, 73 and 75 of the CS[1]
Footnotes: [a] If dependent, a different probability is calculated for patients with MI and stroke as first event in the economic model; [b] Baseline characteristics unless stated otherwise see Table 58 of the CS for more detailed variable descriptions; [c] This parameter is not used in the economic model
ASA = Acetylsalicylic acid; CABG = coronary artery bypass graft; CV = cardiovascular; STEMI = ST segment elevation myocardial infarction

Table 5.14: Estimated time to subsequent event more than one year after the first event (parametric survival models)

	Non-fatal MI	**Non-fatal stroke**	**Non-fatal stroke**	**Fatal CV**	**Fatal other**
Distribution	Exponential	Exponential	Exponential	Exponential	Exponential
First event	NA	MI	Stroke	NA	NA
1 year	93.9%	99.1%	90.6%	96.6%	92.2%

	Non-fatal MI	Non-fatal stroke	Non-fatal stroke	Fatal CV	Fatal other
Distribution	Exponential	Exponential	Exponential	Exponential	Exponential
First event	NA	MI	Stroke	NA	NA
2 year	88.1%	98.3%	82.0%	93.3%	84.9%
3 year	82.7%	97.4%	74.3%	90.1%	78.3%
4 year	77.6%	96.6%	67.3%	87.0%	72.1%
5 year	72.8%	95.7%	60.9%	84.0%	66.5%
10 year	53.0%	91.6%	37.1%	70.6%	44.2%
15 year	38.6%	87.7%	22.6%	59.4%	29.4%
20 year	28.1%	84.0%	13.8%	49.9%	19.5%
30 year	14.9%	76.9%	5.1%	35.2%	8.6%
CV = cardiovascular; MI = myocardial infarction; NA = not applicable					

ERG comment: The company only (partly) adjusted two time-to-event models to reflect the label population since the 'label' covariate (with or without interaction term) was not statistically significant for the other time-to-event models. The time to first non-fatal MI was adjusted using a covariate representing the label population and the time to fatal CV event was adjusted using a covariate and interaction term representing the label population. It is unclear to the ERG whether the PEGASUS-TIMI 54 trial was sufficiently powered or designed to be able to detect a difference between the label population and patients who experienced their qualifying MI more than two years before inclusion in the trial, particularly considering that the stringent alpha of 0.05 that was used to select variables. Therefore, the ERG would have preferred to estimate the time-to-event models based on the label population only, instead of partly adjusting the time-to-event models estimated based on the ITT population. Despite the fact that these analyses were requested by the ERG, the company did not provide them (Clarification Question B6[26]). The company preferred to use the ITT population *"to maintain the level of precision of the model"*.[26] The ERG considers this to be a specious argument and strongly disagrees with the line of reasoning: even a perfectly precise model is useless if it is not valid. The ERG would consider it to be more valid to use the label population to estimate the time-to-event models despite the fact that it would potentially result in a decrease in precision. It might be argued that using the ITT population is a conservative approach (slides 14 and 15 of the PowerPoint presentation provided with the clarification letter[26]). However, as the company did not explore this scenario and not all 'label' specific estimates are known (e.g. time to treatment discontinuation is unknown), it is unclear to what extent and in which direction the company's approach would bias the estimated ICER for the label population.

The log-logistic distribution was used for all time-to-event models for first event and one time-to-event model for subsequent event. However, the parameterisation for the log-logistic distribution used by the company was considered unusual by the ERG:

$$TP_{LogLog.} = 1 - exp\left(\frac{\lambda(t-u)^{\frac{1}{\gamma}}}{1+\lambda(t-u)^{\frac{1}{\gamma}}} - \frac{\lambda(t)^{\frac{1}{\gamma}}}{1+\lambda(t)^{\frac{1}{\gamma}}}\right)$$

It was unclear how this parameterisation was derived and why this deviated from the standard parameterisations. Therefore, the ERG used an alternative parameterisation in its base-case:

$$TP_{LogLog.} = 1 - \frac{\left[\frac{1}{1+(\lambda t)^{\frac{1}{\gamma}}}\right]}{\left[\frac{1}{1+[\lambda(t-u)]^{\frac{1}{\gamma}}}\right]}$$

For both equations: λ=β0+xjβx; γ=shape parameter; t=time from randomisation; and u= cycle length. See Table 5.15 for the updated time to first event (using the corrected parameterisation for the log-logistic distribution).

Table 5.15: Estimated time to first event; parametric survival models and the accompanying Kaplan-Meier estimates (estimates using the corrected parameterisation for the log-logistic distribution)

Time to event	**Ticagrelor 60 mg**		**ASA**	
Non-fatal MI	**KM**	**Log-logistic**	**KM**	**Log-logistic**
1 year	98.3%	97.5%	97.8%	97.5%
2 year	96.9%	95.3%	96.0%	95.3%
3 year	95.4%	93.3%	94.8%	93.3%
4 year		91.2%		91.4%
5 year		89.3%		89.6%
10 year		81.8%		81.9%
15 year		76.3%		75.6%
20 year		72.1%		70.3%
30 year		66.0%		61.9%
Non-fatal stroke	**KM**	**Log-logistic**	**KM**	**Log-logistic**
1 year	99.5%	99.4%	99.4%	99.4%
2 year	99.2%	98.9%	98.8%	98.9%
3 year	98.8%	98.5%	98.4%	98.5%
4 year		97.9%		98.0%
5 year		97.4%		97.6%
10 year		95.0%		95.6%
15 year		92.9%		93.8%
20 year		91.0%		92.1%
30 year		87.6%		89.0%
Fatal CV	**KM**	**Log-logistic**	**KM**	**Log-logistic**
1 year	99.3%	99.6%	99.2%	99.6%
2 year	98.2%	99.1%	98.2%	99.1%
3 year	97.6%	98.5%	96.9%	98.5%
4 year		97.7%		97.8%

Time to event	Ticagrelor 60 mg		ASA	
5 year		96.9%		97.2%
10 year		92.7%		93.6%
15 year		88.6%		89.9%
20 year		84.8%		86.3%
30 year		78.1%		79.3%
Fatal other	**KM**	**Log-logistic**	**KM**	**Log-logistic**
1 year	99.6%	99.4%	99.5%	99.4%
2 year	99.1%	98.4%	99.1%	98.4%
3 year	98.3%	97.2%	98.4%	97.2%
4 year		95.9%		95.9%
5 year		94.4%		94.4%
10 year		86.4%		86.4%
15 year		78.2%		78.2%
20 year		70.5%		70.5%
30 year		57.3%		57.3%

ASA = acetylsalicylic acid; CV = cardiovascular; KM = Kaplan-Meier estimate; mg = milligram; MI = myocardial infarction

The ERG considered the parameterisations of the other time-to-event distributions used in the economic model to be appropriate.

The treatment effect of ticagrelor 60 mg was not included in the time-to-event model for 'fatal other' as first event (see Table 5.11), in contrast with the other time-to-event models for the first event. The impact of this is explored by the ERG by using the coefficient ticagrelor 90 mg for ticagrelor 60 mg.

The treatment effect of ticagrelor 60 mg was not included in the time-to-event models for subsequent events. In response to clarification question B8, the company explored the impact of this assumption and concluded that this was conservative.[26]

For the time to subsequent event, more than one year after the first event (Table 5.15), the company used the exponential distribution without exploring different parametric distributions. In line with the NICE DSU on survival analyses,[61] the company should have considered different parametric distributions for these time-to-event models. Moreover the ERG could not find Kaplan-Meier curves to compare the estimated time-to-event based on the exponential distribution with the observed time-to-event. Also, the ERG was unable to explore different parametric distributions. It is unclear to what extent and in which direction the company's approach, using an exponential distribution, would bias the estimated ICER. However, if it is assumed that the time to event is underestimated (i.e. probability of an event is overestimated), which might be the case if the probability of an (non-)fatal events decreases further 12 month after the first event, the ICER is most likely underestimated as well.

The approach to incorporate other fatal events in the economic model, using a maximum function for other fatal events from the PEGASUS-TIMI 54 trial and UK life tables (excluding CV-specific mortality) was considered reasonable by the ERG. The ERG noted that the company used 2005 statistics where 2014 statistics were available.[62] Nevertheless, this is probably not an influential issue.

Time to treatment discontinuation

In the economic model, it is assumed that patients will be treated with ticagrelor 60 mg for a maximum of three years. For this period, the time to treatment discontinuation is estimated using a parametric time-to-event model.

A similar procedure was used to estimate the time-to-event models as described above for time to first event. Additionally, the company considered interaction terms between ticagrelor treatment (i.e. Tic60 and Tic90) and the following baseline characteristics:

- Patients with spontaneous bleeding requiring hospitalisation (prior to baseline)
- Age
- Sex
- Weight
- Time from pervious ADP blocker (>12 months prior to baseline or not)

The Weibull distribution was preferred according to the AIC, however according to the company: *"none [of the distributions] fitted the first period well. When compared with observed events the Weibull function underestimates the risk during years 2 and 3, but overestimates the risk in subsequent years"*. The company preferred a piecewise exponential model, splitting the time periods into the first 91 days (during which the greatest number of treatment discontinuations occurred) and thereafter up to 3.5 years (during which the total number of patients at risk became very low). Coefficients for the piecewise exponentials are presented in Table 90 of the CS.[1] The company explored the impact of using this piecewise exponential model instead of the Weibull model in a scenario analysis. Based on Figure 56 of the CS[1], using the piecewise exponential model seems conservative compared to using the Weibull model.

ERG comment: The company provided no data supporting their argument that no distribution was a reasonable fit for the first period. Nevertheless, the ERG does not consider this to be a priority issue, as using the piecewise exponential model seems conservative compared to using the Weibull model (model with lowest AIC).

As time to treatment discontinuation was estimated based on the ITT population (without adjustment for the label population), it is unclear to what extent and in which direction the company's approach would bias the estimated ICER for the label population. Moreover, it is unclear to the ERG how competing risks (i.e. (non-)fatal events for which treatment discontinuation was assumed) were dealt with in the economic model. The treatment discontinuation seems however reasonably in line with treatment discontinuation reported in Table 32 of the clinical study report.[31] Nevertheless, the ERG explored this issue assuming all patients would receive ticagrelor 60 mg treatment until three years or occurrence of first (non-)fatal event.

Hospitalisation

Hospital admissions were incorporated in the economic model using a Poisson regression model as the numbers of admissions are count (Poisson) data that can be represented as rates per unit of patient exposure.

The hospitalisation rate was incorporated as treatment independent in the economic model. The Poisson regression model (Table 86 in the CS[1]) was used to predict hospitalisations for patients:

- Staying in the "no event" health state (hospitalisation probability: 2.6% per cycle)

- Experiencing a fatal CV event or other fatal event (hospitalisation probabilities: 3.2% and 12.3% per cycle respectively)
- Previously experienced a dyspnoea Grade 3-4 (increased hospitalisation probability: 2.0% per cycle)
- Previously experienced a non-fatal stroke or MI (increased hospitalisation probabilities: 4.4% and 4.4% per cycle respectively)

For patients experiencing a non-fatal stroke or MI (either first or subsequent), dyspnoea grade 3-4 or bleeding (major or minor) it is assumed that 100% will be hospitalised.

ERG comment: In the request for clarification, the ERG inquired whether the Poisson regression was over-dispersed and/or zero-inflated. The response from the company reassures the ERG on these two issues (clarification question B11[26]). However, in the same clarification question, the ERG inquired how the variables were selected and why ticagrelor 60 mg was not incorporated as a covariate in the Poisson regression. The company did not respond to these issues. Hence, the validity of the Poisson regression model could not be completely examined by the ERG. Particularly, given that the validation of the Poisson model was done using a simple version of the Poisson model without any covariates (see Table 84 of the CS[1]). Moreover, the hospitalisation probabilities reported in the CS (Table 87 in the CS[1]) and above for staying in the "no event" health state and experiencing a fatal CV event or other fatal event health state are incorrect (i.e. inconsistent with values used in the model) and should be:

- Staying in the "no event" health state (hospitalisation probability: 1.6% per cycle)
- Experiencing a fatal CV event or other fatal event (hospitalisation probabilities: 2.5% and 9.7% per cycle respectively)

The impact of not including ticagrelor 60 mg as a covariate in the Poisson regression for the "no event" health state was explored by the ERG (using the coefficient for ticagrelor 90 mg).

As the probability of hospitalisation was estimated based on the ITT population (without adjustment for the label population) and the validity of the Poisson model could not be fully examined, it is unclear to what extent and in which direction the company's approach would bias the estimated ICER for the label population.

5.2.7 Adverse events

The short-term impact (three months) of four adverse events is considered in the economic model: minor bleeding, major bleeding (according to the TIMI bleeding criteria), and dyspnoea grade 1-2 and dyspnoea grade 3-4. The additional risk of an adverse event, associated with ticagrelor 60 mg treatment, was estimated conditional on the patient remaining on treatment

A similar procedure was used to estimate the time-to-event models for adverse events as described above for time to first event. No adjustments to reflect the label population were incorporated. In addition, an exponential (time-to-event) model was used by the company (instead of selecting the most appropriate model based on AIC) to incorporate adverse events in the cost effectiveness model. See CS Tables 77, 79, 81 and 83 for an overview of the final models.[1] The predicted adverse event probabilities are reported in Table 5.16.

Table 5.16: Estimated adverse event probabilities per cycle (retrieved from economic model)

	Grade 1/2 Dyspnoea	Grade 3/4 Dyspnoea	Minor bleeding	Major bleeding
Distribution	**Exponential**	**Exponential**	**Exponential**	**Exponential**
Ticagrelor 60 mg	0.726%	0.008%	0.167%	0.353%
ASA	0.393%	0.002%	0.052%	0.139%
ASA = acetylsalicylic acid; mg = milligram				

ERG comment: The company used the exponential distribution without exploring different parametric distributions to estimate the probability of adverse events. In line with the NICE DSU on survival analyses[61], the company should have considered different parametric distributions for these time-to-event models. Different parametric distributions were however considered by the company in response to Clarification Question B10 and the distribution with the lowest AIC was adopted in an updated version of the company's base-case.[26] This approach is also adopted in the ERG's base-case.

The company did not include gout in the economic model, which could not be considered conservative. Gout was considered by the company in response to Clarification Question B10 and included in an updated version of the company's base-case.[26] This approach was also adopted in the ERG's base-case.

The company estimated the occurrence of adverse events based on time-to-event models. It is, however, unclear to the ERG whether repeated events are considered in the analysis. If this is not the case, the occurrence of AE might possibly be underestimated, if it is assumed that patients who experienced an AE have a higher probability of experiencing it again compared with patients that never experienced the AE.

As the probability of adverse events was estimated based on the ITT population (without adjustment for the label population) and it is unclear how repeated adverse events are handled, it is unclear to what extent and in which direction the company's approach would bias the estimated ICER for the label population.

5.2.8 Health-related quality of life

Utility inputs in the model were based on health-related quality of life data collected in the PEGASUS-TIMI 54 clinical trial.[20] Utility values were elicited in the PEGASUS-TIMI 54 trial through the EQ-5D-3L at set intervals. Table 5.17 (CS, Table 97) provides an overview of the number of participants which filled in the questionnaire at each measurement point.

Table 5.17: EQ-5D questionnaire response rate

Approx month	Completed EQ-5D questionnaire				Total
	Yes (n, %)	No (n, %)	Cognitively incapable	Refused	
0	20,573 (97.4)	558 (2.6)	5	18	21,131
8	19,097 (91.9)	1,685 (8.1)	23	352	20,782
12	17,815 (88.0)	2,418 (12.0)	15	312	20,233
18	17,147 (87.4)	2,477 (12.6)	15	289	19,624
24	15,941 (86.3)	2,527 (13.7)	14	283	18,468
30	13,755 (86.6)	2,132 (13.4)	13	209	15,887

Approx month	Completed EQ-5D questionnaire				Total
	Yes (n, %)	No (n, %)	Cognitively incapable	Refused	
36	9,779 (85.9)	1,609 (14.1)	13	150	11,388
42	4,162 (81.6)	937 (18.4)	5	76	5,099
48	464 (63.1)	271 (36.9)	0	30	735
54	12 (50.0)	12 (50.0)	0	0	24
Total	**118,745 (89.0)**	**14,626 (11.0)**	**103**	**1,719**	**133,371**

Source: Based on Table 97 of the CS[1]
EQ-5D = European Quality of Life-5 Dimensions

Based on PEGASUS-TIMI 54 EQ-5D collection, a linear random effect panel data analysis model has been used to calculate utility decrements associated with patients' characteristics and events. The panel data method determines utility decrements as being equal to the difference in utilities before and after the occurrence of an event in a pre-determined time period. This methodology was chosen because utilities were not elicited directly after the occurrence of events but at set intervals. The coefficients obtained from this analysis, which represent the utility increment or decrement for each characteristic and event, are presented in Table 5.18. The linear random effect panel data analysis allowed for utility values above 1 when applied to individual patient in the model.

Table 5.18: Linear random effect panel data analysis results

Variable	Coef.*	p-value	Lower 95% CI	Upper 95% CI
cd30_minorBld	-0.0393	0.1000	-0.0861	0.0075
cd91_majorBld	-0.0466	<0.0001	-0.0649	-0.0283
SAEdys	-0.0253	0.1160	-0.0569	0.0063
cd91_AEdys	-0.0154	<0.0001	-0.0233	-0.0075
cd91_MI	-0.0474	<0.0001	-0.0590	-0.0358
cd91_prevMI	-0.0342	<0.0001	-0.0416	-0.0267
cd91_Stroke	-0.0934	<0.0001	-0.1130	-0.0737
cd91_prevStroke	-0.0665	<0.0001	-0.0803	-0.0526
sex	0.0627	<0.0001	0.0576	0.0677
age	-0.0018	<0.0001	-0.0021	-0.0015
bmi	-0.0040	<0.0001	-0.0044	-0.0035
dmtype	-0.0141	<0.0001	-0.0186	-0.0096
MI_HIST	-0.0163	<0.0001	-0.0218	-0.0108
smk_his1	-0.0059	0.0150	-0.0106	-0.0011
smk_his2	-0.0338	<0.0001	-0.0402	-0.0275
anpect	0.0400	<0.0001	0.0344	0.0457
pci	-0.0346	<0.0001	-0.0392	-0.0300
qevtyp2	0.0052	0.0150	0.0010	0.0094
MEDTDDOS_n	-0.0001	0.0200	-0.0003	0.0000
dbpsup	-0.0003	0.0020	-0.0006	-0.0001
hyp	0.0048	0.0620	-0.0002	0.0098

Variable	Coef.*	p-value	Lower 95% CI	Upper 95% CI
hypchol	-0.0180	<0.0001	-0.0231	-0.0128
cohdhist	-0.0070	0.0020	-0.0116	-0.0025
stroke	-0.0553	<0.0001	-0.0851	-0.0254
tria	-0.0489	<0.0001	-0.0673	-0.0305
chf	-0.0521	<0.0001	-0.0576	-0.0467
spbleed	-0.0227	0.0120	-0.0404	-0.0050
Asia_Australia	0.0600	<0.0001	0.0526	0.0674
NthAmerica	-0.0052	0.0730	-0.0109	0.0005
histPAD	-0.0444	<0.0001	-0.0534	-0.0355
creatinine_cl	0.0189	<0.0001	0.0130	0.0247
_cons	1.0692	<0.0001	1.0356	1.1029
sigma_u	0.1394			
sigma_e	0.1174			
rho	0.5851			

Source: Based on Table 98 of the CS[1]
Footnote: * Coefficients = utility increment or decrement for each characteristic and event. A value of 1 represents perfect health for 1 year. minorBld=TIMI minor bleed, majorBld=TIMI major bleed; SAEdys=grade 3–4 dyspnoea; AEdys=grade 1–2 dyspnoea
CI = confidence interval; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions

The coefficients from the linear random effect model were used in order to calculate baseline utility values (utilities for the 'no event' health state) for each patient, based on their respective characteristics. The coefficient associated with age was excluded from this calculation and an age-specific utility matrix was used to adjust the utilities to age. Since several patients reached utility values above 1, the company capped the maximal baseline utility value to 1. The calculated baseline utility values, based on patients' characteristics from PEGASUS-TIMI 54, were higher than the general UK population utility values. This seemed improbable to the company. Therefore, UK general population utility values of Kind et al.[63] were used for the 'no event' health state (Table 5.19).

Table 5.19: Utility by age in the UK general population

Age Group	Male utilities	SE	Female utilities	SE
<25	0.94	0.011	0.94	0.009
25–34	0.93	0.009	0.93	0.007
35–44	0.91	0.011	0.91	0.007
45–54	0.84	0.018	0.85	0.014
55–64	0.78	0.020	0.81	0.015
64–75	0.78	0.019	0.78	0.016
>75	0.75	0.027	0.71	0.019

Source: Kind et al.[63] and Table 101 of the CS[1]
CS = company submission; SE = standard error; UK = United Kingdom

Utility decrements for (post) non-fatal MI and (post) non-fatal stroke were calculated if an event occurred in a pre-determined time period of 91 days (three months) before utility elicitation. This time window was chosen because it equals the cycle time of the cost effectiveness model and because these

events were also assumed to be associated with significant utility decrements for this period of time (CS, Table 98).

Acute and long-term consequences on quality of life of non-fatal events (MI or stroke) were represented in the cost effectiveness model. During the acute phase of the event, the utility value of patients undergoing a non-fatal event was reduced for a period of three months (one cycle; Table 5.20), according to the type of event. After this acute phase, the long-term consequences of non-fatal MI or non-fatal stroke were characterised by the post non-fatal MI and post non-fatal stroke utility decrements, respectively. These utility decrements were applied to all patients having undergone a non-fatal event, from the second tunnel state onwards (three months post first event and further). Different utility decrements were not assigned to non-fatal disabling and non-disabling strokes even though the company emphasised in the CS that their impact on quality of life is different.

Patients undergoing subsequent non-fatal MI's or strokes experienced a decrease in quality of life for one cycle (three months). No long-term quality of life consequences of subsequent events (MI's and strokes) were incorporated in the cost effectiveness model (Section 5.2.2).

Four AEs incurred a utility decrement for one cycle (three months) in the company's cost effectiveness model: TIMI (major and minor) bleeds, and dyspnoea (grade 1-2 and grade 3-4) (Table 5.20). Utility decrements four these events were also calculated based on the panel data approach.

Utility major TIMI bleeds were assumed to have the same (three months) quality of life impact as a non-fatal MI. This was justified by the argument that it also requires inpatient hospitalisation. Long-term consequences of major TIMI bleeds were not incorporated in the cost effectiveness model. Furthermore, the impact on quality of life of certain types of non-fatal bleedings (i.e. ICH and other major bleedings) (CS, Table 41) were not incorporated in the cost effectiveness model. ICH occurred 28 (0.4%) and 23 (0.3%) in the ticagrelor 60 mg BID and placebo groups respectively (HR: 1.33; 95% CI: 0.77, 2.31) and other major bleedings occurred 83 (1.2%) and 25 (0.4%) the ticagrelor 60 mg BID and placebo groups respectively (HR: 3.61, 95% CI: 2.31, 5.65).

Minor TIMI bleeds were not associated with a statistically significant three month (91 days) utility decrement, therefore, a shorter time window (30 days) before utility elicitation was applied to determine their disutility value (based on the panel data approach). On the other hand, a time window of 174 days (average time interval between two EQ-5D elicitation points) was applied to determine grade 3-4 dyspnoea utility decrement because of the low number of events. Utility decrements calculated on a period of 30 days or 174 days before utility elicitation where then adjusted to match the three months cycle time.

The impact of gout on the quality of life of patients was not incorporated in the company base-case analysis.

Table 5.20: Summary of utility values for cost effectiveness analysis

State	Utility	Justification
Baseline	UK population norm (age and gender specific)[63]	Baseline utility in PEGASUS-TIMI 54 is considerably higher than UK general population
Non-fatal MI	-0.0474*	Taken from PEGASUS-TIMI 54 in line with NICE reference case

State	Utility	Justification
Non-fatal stroke	-0.0934*	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Post MI	-0.0342*	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Post stroke	-0.0665*	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Dyspnoea (Grade 3-4)	-0.0481*	Taken from PEGASUS-TIMI 54 in line with NICE reference case
Dyspnoea (Grade 1-2)	-0.0154*	Taken from PEGASUS-TIMI 54 in line with NICE reference case
TIMI minor bleed	-0.0129	Taken from PEGASUS-TIMI 54 in line with NICE reference case
TIMI major bleed	-0.0466*	Taken from PEGASUS-TIMI 54 in line with NICE reference case

Source: Based on Table 102 of the CS[1]
Footnote: * 95% upper and lower bounds are provided in Table 98 of the CS
CS = company submission; MI = Myocardial infarction; NICE = National Institute for Health and Care Excellence; TIMI = Thrombolysis in Myocardial Infarction; UK = United Kingdom

Utility decrements obtained from the PEGASUS-TIMI 54 analysis were compared with utility decrements identified in the health-related quality of life literature review and in previous TA's (Section 5.1) (Table 5.21).[1]

Table 5.21: Comparison of the utility decrements taken from literature and those collected in PEGASUS-TIMI 54 trial

Health state/ Event	Value from trial	Value from literature	Difference	Literature reference
Non-fatal MI	-0.0474	-0.0626	+0.0152	Sullivan et al. 2011[50]
		-0.0524	+0.0050	TA182
		-0.0820	+0.0346	TA210
		-0.0630	+0.0156	TA236
		-0.0370	-0.0104	TA317
		-0.0630	+0.0156	TA335
Non-fatal stroke	-0.0934	-0.0524	-0.0410	TA182[45]
		-0.2480	+0.1546	TA210[46]
		-0.1390	+0.0456	TA236[47]
		-0.1390	+0.0456	TA335[49]
Post non-fatal MI	-0.0342	-0.0600#	+0.0258#	Lewis et al.[52]
		-0.1390	+0.1048	Stafford et al.[54]
		-0.0368	+0.0026	Sullivan et al.[50]
		0	-0.0342	TA210[46]
		-0.0210	-0.0132	TA236[47]
		0	-0.0342	TA317[48]

Health state/ Event	Value from trial	Value from literature	Difference	Literature reference
		-0.0210	-0.0132	TA335[49]
Post non-fatal stroke	-0.0665	-0.1800#	+0.1135#	Lewis et al.[52]
		-0.1600	+0.0935	Stafford et al.[54]
		-0.1009	+0.0344	Sullivan et al.[50]
		-0.1390	+0.0725	TA236[47]
		-0.2600	+0.1935	TA317[48]
		-0.0500##	-0.0165##	TA335[49]
Dyspnoea (Grade 3-4)	-0.0481	N/A	N/A	N/A
Dyspnoea (Grade 1-2)	-0.0154	N/A	N/A	N/A
TIMI minor bleed	-0.0129	-0.0010	-0.0119	TA210[46]
		-0.0400*	+0.0271#	TA335[49]
TIMI major bleed	-0.0466	-0.0070	-0.0396	TA182[45]
		-0.3000	+0.2534#	TA210[46]
		-0.1100*	+0.0634#	TA335[49]

Source: Based on Table 96 of the CS[1]
Footnotes: * Value corrected in the response to the clarification letter[25]; # Value corrected by the ERG;
These values are incorrect and should be equal to the values reported for post non-fatal stroke from TA 236 since the same values are reported in both assessments
CS = company submission; ERG = Evidence Review Group; MI = myocardial infarction; TA = technology appraisal; TIMI = Thrombolysis in Myocardial Infarction

ERG comment: The ERG agrees that using UK general population utility values for the 'no event' health state is appropriate for the current decision problem. However, several issues are raised by the ERG concerning the utility decrements for the different events and health states.

1. The choice of a linear random effect panel data analysis did not seem to be the most appropriate method of analysis. The model did not distinguish between the quality impact of non-fatal disabling and non-disabling stroke. There is uncertainty around the utility decrement associated with TIMI (major) bleeds. Long-term consequences of subsequent event and adverse events are not included in the company's base-case analysis. The quality of life impact of gout was not included. The comparison of the obtained utility decrements with previous literature was not transparent and incomplete. The company was not entirely transparent about how variables were selected and coefficients were obtained in the linear random effect panel data analysis (Table 5.21). Furthermore, the methodology used by the company to determine utility increments and decrements for patients' characteristics and events allowed for utility values above 1. The ERG did not consider this in line with good practices, and requested that the company re-calculate baseline utility values and utility increments and decrements based on a model which naturally provides values between 0 and 1. In its response to the clarification letter, the company re-calculated baseline utility values by using a distribution which naturally capped utility values to 1 and could reach negative values, which is possible when using the EQ-5D. The newly calculated baseline utility values were used by the company in a sensitivity analysis (Section 5.2.11). Utility decrements for events and health states were not re-calculated in the response to the clarification letter. However, the scale on which utility decrements are based is not bound to 0 and 1, since this method allow for utility values above 1. This might lead to biased utility decrements for

events and health states. The ERG does not consider the method used by the company to determine utility decrements as appropriate. This amplifies the uncertainty around the obtained estimates.

The company claimed that non-fatal disabling and non-disabling had different quality of life impact but implemented one utility decrement for stroke without distinguishing between disabling and non-disabling strokes. The ERG agrees that using the same estimate for non-fatal disabling and non-disabling strokes is conservative (Section 5.2.2). The ERG was, however, unable to assess whether the estimate is representative for both types of non-fatal stroke since it takes no account of the number of patients who filled in the EQ-5D questionnaire by type of non-fatal stroke (patients undergoing a non-fatal disabling stroke might be less able to fill in the EQ-5D questionnaire and consequently be under-represented in the non-fatal stroke group).

Because bleeding events are rare events, the number of observations on which utility decrements for these events were based is small (CS, Table 41). Consequently, uncertainty around the utility decrement of major TIMI bleeds remains and, when compared to previous TA's (TA210 and TA335), the utility decrement for major bleeding used by the company seems to be underestimated (Table 5.21). Furthermore, the quality of life impact of other bleeding events (e.g. intracranial bleeds) reported in the PEGASUS-TIMI 54 trial[20] were not incorporated in the cost effectiveness model (Section 5.2.2). Accordingly, the ERG preferred to use an alternative utility decrement for major TIMI bleeds in its base-case analysis: -0.1426.[59] This value was calculated by the ERG of TA210 and was based on two studies.[64, 65]

The model does not include long-term consequences of subsequent events and bleeds. A discussion of the impact of this simplification of the model structure on the results is provided in Section 5.2.2. The ERG considers that this simplification underestimates the impact of subsequent events and adverse events on quality of life, but agrees that (except for bleeding) it is likely to be a conservative assumption.

Since gout was not included in the original cost effectiveness model of the company, the ERG requested that the company include this adverse event in its analysis. The company included the quality of life consequences of gout in its revised cost effectiveness analysis in its response to the clarification letter (Sections 5.2.2 and 5.2.7). As a working assumption, gout was assumed to have the same quality of life impact as dyspnoea (grade 1-2). The ERG used this amendment in its base-case analysis.

The ERG requested that the company clarified how utility decrements from other assessments, shown in Table 96 of the CS, had been calculated (Table 5.21). The company provided the calculations in its response to the clarification letter.[25] Several utility decrements were not reported correctly from the primary source and calculation mistakes were present in the table provided in the response to the clarification letter (Table 19[26]). The company did not provide the primary sources of these estimates which hampered the ERG in its verification of these estimates. Furthermore, the ERG was not able to retrieve all reported estimates. The table from the company also seems to be incomplete. For example, Stafford et al. report a utility decrement of -0.160[54], which is not reported in the company's table. This points towards a selective reporting of utility decrements from the literature by the company.

The ERG investigated the impact of alternative utility decrements on the results of the cost effectiveness analysis. In this analysis, the ERG used the most conservative utility decrements as reported in Table 5.22. The ERG emphasises that these estimates might not be the most accurate. However, this analysis provides an idea of what the outcome of the cost effectiveness analysis could

be under less favourable utility decrements in the perspective of ticagrelor 60 mg BID + ASA. Table 5.22 provides an overview of the utility decrements used in this explorative sensitivity analysis (Section 5.3.2).

Table 5.22: Conservative utility decrements used in the explorative analysis by the ERG

Health state/event	Utility decrement	Source (as reported in the CS)	Justification
Non-fatal MI	-0.0370	TA317[48]	Most conservative estimate
Non-fatal stroke	-0.0524	TA182[45]	Most conservative estimate
Post non-fatal MI	-0.0210	TA236[47] & TA335[49]	Most conservative estimate
Post non-fatal stroke	-0.0665	-	Same as company's base case since other estimates are less conservative
Dyspnoea (Grade 3-4)	-0.0481	-	Same as company's base case since other estimates are less conservative
Dyspnoea (Grade 1-2)	-0.0154	-	Same as company's base case since other estimates are less conservative
TIMI minor bleed	-0.0400	TA335[49]	Most conservative estimate
TIMI major bleed	-0.1426	TA210[46]	Value from the ERG base-case, as -0.3000 was considered too high and improbable

CS = company submission; ERG = Evidence Review Group; MI = myocardial infarction; TA = technology appraisal; TIMI = Thrombolysis in Myocardial Infarction

In general, the quality of life impact of several events was oversimplified in the company's cost effectiveness model and the CS was not always transparent in terms of choices made (e.g. model variable choice and utility decrement calculation from previous assessments). However, most of the assumptions appear to be conservative.

5.2.9 Resources and costs

Treatment costs

Ticagrelor 60 mg was administrated at a list price of £54.60 for a 28 days' supply (£1.95 per day) and the generic cost for aspirin was £0.03 per day[66] in the cost effectiveness model. Costs of each treatment per cycle is displayed in Table 5.23. Ticagrelor 60 mg BID + ASA was administered for a maximum of 36 months from the start of the modelling (i.e. between one and two years since the index myocardial infarction).

Table 5.23: Unit costs associated with the technology in the economic model

Technology	Daily dose	Cost per day	Cost per cycle*
ASA	75 mg	£0.03	£2.64
Ticagrelor 60 mg	120 mg	£1.95	£178.06

Source: Based on Table 96 of the CS[1]
Footnote: The cycle length is 3 months, or 91.3125 days.
ASA = acetylsalicylic acid; CS = company submission; mg = milligram

ERG comment: The company did not model the use of ticagrelor 90 mg BID + ASA 12 months after a subsequent non-fatal myocardial infarction, and ticagrelor 60 mg BID + ASA between one and two years after subsequent non-fatal myocardial infarction. The ERG asked the company to incorporate these treatments in the cost effectiveness model. The company provided this in scenario analyses in its response to the clarification letter (see Section 5.2.11 for more details).[25]

Health state costs

Sources of health state cost estimates
The ERG report of TA317[57] was the principal source for health state cost estimates. TA210[59] and NHS reference costs 2014/15[60] also provided cost estimates because TA317 did not provide cost estimations for all health states of the cost effectiveness model (Section 5.1).

Health state costs were subdivided in the following categories (Table 5.24):

- Inpatient costs
- Outpatient and maintenance costs
- Adverse event costs

Table 5.24: List of resource use and associated costs in the economic model

Resource use	Value	Source
Inpatient		
Non-fatal MI	£4,476.18	ERG TA317[57]
Non-fatal stroke	£4,925.76	ERG TA317[57]
Fatal events (CAD and non-CAD)	£2,497.83	ERG TA317[57]
'No event'	£2,497.83	Assumption (=fatal non-CAD event costs)
Outpatient and maintenance		
Post non-fatal MI (0-3 months)	£639.45	ERG TA317[57]
Post non-fatal MI (3-6 months)	£639.45	ERG TA317[57]
Post non-fatal MI (6-9 months)	£319.73	ERG TA317[57]
Post non-fatal MI (9-12 months)	£319.73	ERG TA317[57]
Post non-fatal MI (12+ months, every cycle)	£160.31	ERG TA317[57]
Post non-fatal stroke (0-3 months)	£1,343.39	ERG TA317[57]
Post non-fatal stroke (3-6 months)	£1,119.49	ERG TA317[57]
Post non-fatal stroke (6-9 months)	£877.57	ERG TA317[57]
Post non-fatal stroke (9-12 months)	£689.71	ERG TA317[57]

Resource use	Value	Source
Post non-fatal stroke (12+ months, every cycle)	£689.71	ERG TA317[57]
'No event' (every cycle)	£160.31	Assumption (= post-non fatal MI)
Adverse events		
Grade 3-4 Dyspnoea	£732.98	NHS reference costs[60]
Major TIMI bleed	£2,206.87	TA210 ERG model[59]
Minor TIMI bleed	£122.48	TA210 ERG model[59]

Source: Based on Tables 103 and 106 of the CS[1]
CAD = coronary artery disease; CS = company submission; ERG = Evidence Review Group; MI = myocardial infarction; NHS = National Health Service; TA = technology appraisal; TIMI = Thrombolysis in Myocardial Infarction

The cost of one year treatment with clopidogrel after experiencing a non-fatal MI was incorporated in the model (£5.57 per cycle[66]). The initiation of ticagrelor 60 mg BID did not incur any health care costs. This assumption was investigated by the company in scenario analyses (Section 5.2.11).

ERG comment: The CS lacked transparency concerning the cost estimates used in the cost effectiveness model. Cost estimates were sourced from previous TAs and NHS reference costs 2014-15 [60], but the company did not provide the primary sources of, and the uncertainty around, these estimates. The ERG requested the company to provide the primary source of all cost estimates. The company responded that the primary sources for stroke-related events and health states was Youman et al.[67] and UKPDS[68] for MI-related endpoints, "*i.e. NHS reference costs were not used"*.[25]

The ERG further requested the company to base its cost estimates on NHS reference costs, to provide the NHS cost codes on which original costs estimates were based along with the lower and upper quartile unit costs for each recalculated cost estimate. The company met this request for revised inpatient costs for non-fatal MI, non-fatal stroke and adverse event costs (dyspnoea (grade 3-4) and TIMI bleeds (major and minor). The company's recalculation of non-fatal MI and non-fatal stroke inpatient costs and adverse event costs was based on relevant NHS cost codes from the NHS reference costs 2014/15.[60] The weighted average costs was calculated as the total volume of activity for each cost code multiplied by associated unit cost; these were summed up and then divided by total activity volumes (Table 5.25).

Following requests, details on some of the NHS currency codes, activity volumes and weighted averages were provided in Tables 21 and 22 of the response to the Clarification Question B14.[25] For the non-fatal MI costs estimates, the costs of PCI and CABG were added for 60% and 12% of the patients respectively. These figures were neither mentioned explicitly in the company submission, nor supported by a justification or evidence, so it is not possible to determine whether they are reasonable or not.

Table 5.25: List of resource use and associated costs in the economic model (original and revised)

Resource use	Value in CS (original)	Value in revised base case (revised)	National Average Unit Cost, 2014/15 schedule	Lower Quartile Unit Cost, 2014/15 schedule	Upper Quartile Unit Cost, 2014/15 schedule	HRG code from NHS reference costs, 2014/15 schedule
Inpatient						
Non-fatal MI	£4,476.18	£4,593.13	£4,593.13	£3,520.53 (sensitivity)	£5,341.93	EB10A-E, ED22A-C, ED23A-C, ED26A-C, ED27A-C, ED28A, ED28C
Non-fatal stroke	£4,925.76	£3,239.44	£3,239.44	£2,223.49 (sensitivity)	£3,929.59	AA35A-F
Fatal events (CAD and non-CAD)	£2,497.83	£2,497.83	N/A			
'No event'	£2,497.83	£2,497.83	N/A			
Outpatient and maintenance						
Post non-fatal MI (0-3 months)	£639.45	£720.56	N/A			
Post non-fatal MI (3-6 months)	£639.45	£540.42	N/A			
Post non-fatal MI (6-9 months)	£319.73	£360.28	N/A			
Post non-fatal MI (9-12 months)	£319.73	£180.14	N/A			
Post non-fatal MI (12+ months, every cycle)	£160.31	£160.31	NA			
Post non-fatal stroke (0-3 months)	£1,343.39	£2,000.77	NA			
Post non-fatal stroke (3-	£1,119.49	£1,714.94	NA			

Resource use	Value in CS (original)	Value in revised base case (revised)	National Average Unit Cost, 2014/15 schedule	Lower Quartile Unit Cost, 2014/15 schedule	Upper Quartile Unit Cost, 2014/15 schedule	HRG code from NHS reference costs, 2014/15 schedule
6 months)						
Post non-fatal stroke (6-9 months)	£877.57	£1,143.40	NA			
Post non-fatal stroke (9-12 months)	£689.71	£857.47	NA			
Post non-fatal stroke (12+ months, every cycle)	£689.71	£689.71	NA			
'No event' (every cycle)	£160.31	£160.31	NA			
Adverse events						
Grade 3-4 Dyspnoea	£732.98	£732.98	£732.98	£518.68	£846.10 (sensitivity)	DZ19H, DZ19J-N
Major TIMI bleed	£2,206.87	£2,824.81	£2,824.81	£1,923.36	£3,285.13 (sensitivity)	FZ38G-H, FZ38J-L
Minor TIMI bleed	£122.48	£942.19	£942.19	£728.49	£1,049.82 (sensitivity)	FZ38M-N, FZ38P

Source: Based on Table 26 of the response to the request for clarification[25]

CAD = coronary artery disease; CS = company submission; HRG = Health care resource group; MI = myocardial infarction; NA = not available; NHS = National Health Service; TIMI = Thrombolysis in Myocardial Infarction

Health care costs of the first non-fatal event (non-fatal MI, non-fatal stroke)
Health care costs for the first non-fatal event (MI or stroke) were based on the ERG report of TA317.[57] The health care costs associated with strokes were based on a weighted average of the health care costs associated with non-fatal disabling and non-disabling stroke as reported in TA317. The distribution of non-fatal disabling and non-disabling strokes in PEGASUS-TIMI 54 was used to calculate this weighted average (Table 5.26).[20]

Table 5.26: Non-fatal stroke cost (annual cost)

Year of Event	Cost	Events (%)
Non-fatal non-disabling stroke	£7,115.99	77.1
Non-fatal disabling stroke	£15,150.62	22.9
Non-fatal stroke (weighted average)	£8,955.92	
Source: Based on Table 107 of the CS[1] CS = company submission		

Health care costs for the first non-fatal event (MI or stroke) were divided in terms of inpatient costs, outpatient and maintenance costs. Inpatient costs were considered as a discrete cost when the event occurred and outpatient and maintenance costs were accrued in each tunnel state.

The inpatient costs for non-fatal MI and non-fatal stroke were assumed to be equal to 70% of the annual treatment costs of a non-fatal MI and 55% of the annual treatment costs non-fatal stroke, respectively (Table 5.27). No evidence was provided by the company to support the assumption of cost proportions attributable to inpatient care. The cost figures were based on the annual costs of non-fatal MI and non-fatal stroke, as reported in the ERG report of TA317[57], respectively £6,394.54 and £8,995.92 (inflated to 2015 values).

Outpatient and maintenance costs were equal to 30% of the annual treatment costs for non-fatal MI's and 45% of the annual treatment costs of non-fatal strokes. These costs were assumed to decrease during the first year after experiencing the first non-fatal event (MI or stroke). The company did not provide evidence to support these calculations (Table 5.27).

Table 5.27: Distribution of inpatient and outpatient and maintenance costs for the 1st non-fatal event

Cycle	Proportion of annual non-fatal MI cost value	Non-fatal MI cost	Proportion of annual non-fatal stroke cost value	Non-fatal stroke cost
Inpatient costs for first non-fatal event	70%	£4,476.18	55%	£4,925.76
Outpatient and maintenance costs 0–3 months after first non-fatal even	10%	£639.45	15%	£1,343.39
Outpatient and maintenance costs 3–6 months after first non-fatal even	10%	£639.45	12.5%	£1,119.49

Cycle	Proportion of annual non-fatal MI cost value	Non-fatal MI cost	Proportion of annual non-fatal stroke cost value	Non-fatal stroke cost
Outpatient and maintenance costs 6–9 months after first non-fatal even	5%	£319.73	9.8%[#]	£877.57
Outpatient and maintenance costs 9–12 months after first non-fatal even	5%	£319.73	7.7%*	£689.71
Total	100%	£6,394.54	100%	£8,995.92

Source: Based on Tables 109 and 110 of the CS[1]
Footnotes: * same as long term cost; # residual of annual cost from TA317
CS = company submission; MI = myocardial infarction; TA = technology appraisal

ERG comment: The ERG was concerned by the implementation of a unique cost estimate for non-fatal disabling and non-disabling strokes. Not implementing specific cost estimates for each type of non-fatal stroke (disabling and non-disabling) is likely to be a conservative assumption (Section 5.2.2). However, the company was not fully transparent about the primary source of these estimates. In its revised cost effectiveness model, the company used a weighted average based on weighted average of relevant NHS reference costs (Table 5.25) which is probably a representative cost estimate for inpatient stroke care in the UK. This amendment has been included in the ERG additional analyses.

Another area of concern for the ERG was the lack of justification for the distribution of inpatient, outpatient and maintenance costs in the tunnel states for first non-fatal event (MI or stroke). In the CS, respectively 70% and 55% of the annual costs (retrieved from TA317[57]) of non-fatal MI and non-fatal stroke were attributed to inpatient costs while the remainder of the cost was allocated as outpatient and maintenance costs to the tunnel states following the events. No justification was provided for this calculation. Hence, the ERG asked the company to justify the rationale behind the percentage attributed to inpatient costs. The company did not provide an explanation but recalculated its inpatient costs for first non-fatal event (MI and stroke) based on NHS reference costs which is acceptable to the ERG.

The adaptation of inpatient costs for the first non-fatal event did not influence the total costs of the first non-fatal event (still equal to TA317 annual costs, adapted to 2015 values) but it influenced the distribution of outpatient and maintenance costs over the following post-MI and post-stroke tunnel states in the revised model (Table 5.25).

More clarity from the company concerning the distribution of maintenance and outpatient costs for the post non-fatal MI and post non-fatal stroke health states would have been desirable. However, these estimates seemed reasonable after further investigation (based on cost estimates derived from PSSRU 2014 page 127 (Section 8.1.1) where a total weekly cost of health and social care package of £95 per week i.e. £4,950 per annum is quoted).

'No event' inpatient costs

Patients remaining in the 'no event' health state and post first non-fatal event had a probability of being hospitalised for events other than the ones incorporated in the cost effectiveness model. The Poisson distribution representing the probability of hospitalisation for these events is described in Section 5.2.6. Patients undergoing hospitalisation consequently accrued inpatient costs. These costs were assumed to be equal to the inpatient costs incurred by fatal events (Tables 5.24 and 5.25).[1] No details were provided about the types of events which required hospitalisation in the 'no event' health state.

ERG comment: The inpatient costs of the 'no event' health state were assumed to be equal to the inpatient costs accrued by fatal events. The ERG asked the company to clarify this assumption by providing an overview of the events which required hospitalisation. The company provided an overview of the causes of hospitalisation in the 'no event' health state for both treatment arms (Table 1, part 2 of clarification letter).[69] Because of the "*range of hospitalised events observed*" and also "*for pragmatic purposes*"[25], the company kept the inpatient costs for the 'no event' health state equal to the inpatient costs of fatal events in its revised cost effectiveness model. The company further emphasised that "*the model is highly insensitive to the choice of inpatient costs for the 'no event' health state*".[25]

The ERG does not think this assumption is reasonable since fatal events and the events from the 'no event' health state might incur different health care resource use and costs. Moreover, this assumption is not conservative. In the absence of a best estimate for 'no event' inpatient costs, the ERG recalculated 'no event' inpatient costs based on NHS reference costs 2014/15.[60] The ERG used a weighted average of non-elective short stay costs, excluding the cost codes relating to the following categories: cerebrovascular accident, nervous system infections or encephalopathy, transient ischaemic attack, stroke, actual or suspected myocardial infarction, neonatal and paediatric interventions. This resulted in a weighted average of £1,164.92 for the inpatient costs of the 'no event' health state. This estimate was considered more representative of UK clinical practice and was used in the ERG analyses.

Adverse event costs

The costs of TIMI bleeds (major and minor) and dyspnoea (grade 3-4) were included in the cost effectiveness model. Dyspnoea (grade 3-4) costs were based on a weighted average of DZ19 'Other respiratory disorders' from the NHS reference costs 2014/15.[60] The costs of TIMI (major and minor) bleeds were taken from TA210 (Table 5.24).[59] It was assumed that dyspnoea (grade 1-2) did not incur health care costs. Gout was not included in the costing of AEs.

ERG comment: Because the calculation of the costs incurred by dyspnoea (grade 3-4) was not clear to the ERG, clarification was sought. The company provided the exact cost code used to calculate the weighted average for dyspnoea (grade 3-4).[25] Furthermore, costs incurred by TIMI (major and minor) were recalculated in the response to the clarification letter. TIMI (major and minor) health care costs were based on a weighted average of relevant NHS reference costs.[60] The revised health care cost estimates (Table 5.25) for TIMI bleeds (major and minor) are probably more representative of UK practices. This amendment has been included in the ERG additional analyses.

The economic consequences of gout were also included in the revised cost effectiveness model of the company after the ERG requested this (Section 5.2.10). Gout was assumed to incur two GP visits per year (£22 per cycle). This amendment has been included in the ERG additional analyses.

5.2.10 Cost effectiveness results

Deterministic results of the cost effectiveness model are provided for the individual patient simulation (named 'complete' analysis by the company) and the cohort analysis (named 'simple' analysis by the company). In the individual patient simulation, all patients of the 'label population' (n=10,779) go through the model one at a time, hence risk equations are applied to each patient individually. Results are then averaged for each treatment arm. In the cohort analysis, a cohort with the average patient characteristics (based on PEGASUS-TIMI 54[20]), goes through the model simultaneously, i.e. all patients in the cohort at a time. A comparison of the average cohort characteristics reported in the CS with the characteristics of the cohort taken from the cost effectiveness model is provided in Table 5.32.

Ticagrelor 60 mg BID + low dose ASA compared to low dose ASA was associated with an ICER of £20,098 in the individual patient simulation. The ICER reported in the CS for the cohort analysis was £24,378 (deterministic results) while the ICER of the cohort analysis, as reported in the model, was £24,070 (Table 5.28). The discrepancy between the results of these analyses (individual patient simulation and cohort analysis) is due to the non-linearity of the cost effectiveness model. The company states that the deterministic ICER of the cohort simulation is an overestimation. The company also provided disaggregated results of QALYs by health state and costs per cost category (Table 5.29 and Table 5.30). No disaggregated results for LY by health state were provided.

Table 5.28: Deterministic base-case results of the individual patient analysis and the cohort analyses

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) per inc QALY
Individual patient simulation							
Low-dose ASA	£13,019	12.2453	9.2034	-	-	-	-
Ticagrelor 60 mg BID + low-dose ASA	£14,443	12.3363	9.2742	£1,434	0.0909	0.0708	£20,098
Cohort analysis							
Low-dose ASA	£14,264	13.4590	9.7949	-	-	-	-
Ticagrelor 60 mg BID + low-dose ASA	£15,689	13.5361	9,8541	£1,425	0.0771	0.0592	£24,070*

Source: Based on the original cost effectiveness model and Table 114 of the CS[1]

Footnotes: * The ICER reported in the CS for the cohort analysis was £24,378 (deterministic results)

ASA = acetylsalicylic acid; BID = twice daily; CS = company submission; ICER = incremental cost effectiveness ratio; Inc = incremental; LYG = life years gained; QALY = quality-adjusted life year

Table 5.29: Summary of QALY and LY gain by health state (individual patient simulation)

Health state	QALY intervention (ticagrelor 60 mg BID + LD ASA)	QALY comparator (Low-dose ASA)	Increment	Life years intervention (ticagrelor 60 mg BID + LD ASA)*	Life years comparator (Low-dose ASA)*	Increment*
No event	8.414	8.296	0.117	11.119	10.963	0.156
First event						
Post non-fatal MI	0.022	0.023	-0.001	0.031	0.032	-0.001
Post non-fatal stroke	0.007	0.007	0.000	0.010	0.010	-0.001
Subsequent events						
No event	0.819	0.864	-0.044	1.155	1.217	-0.062
Post non-fatal MI	0.011	0.012	-0.001	0.017	0.018	-0.001
Post non-fatal stroke	0.003	0.004	0.000	0.006	0.006	0.000
Adverse events						
Dyspnoea	-0.001	-0.001	0.000	-	-	-
TIMI Bleeds	-0.001	0.000	0.000	-	-	-
Total	**9.274**	**9.203**	**0.071**	**12.336**	**12.245**	**0.091**

Source: Based on PBAC guidelines[70], Table 115 of the CS[1] and Table 27 of the response to the request for clarification[25].

Footnotes: * provided in the response to the clarification letter[25]

ASA = acetylsalicylic acid; BID = twice daily; LD = low dose; MI = myocardial infarction; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life year; TIMI = Thrombolysis in Myocardial Infarction

Table 5.30: Summary of costs by cost category (individual patient analysis)

Health state	Cost intervention (ticagrelor 60 mg BID + LD ASA)	Cost comparator (Low-dose ASA)	Increment
Drug acquisition	£1,571	£132	£1,439
Outpatient costs	£8,683	£8,672	£12
Inpatient: MI events	£790	£826	-£36
Inpatient: stroke events	£227	£240	-£13
Inpatient: Fatal events	£143	£143	£0
Inpatient: other/ No Event	£2,928	£2,930	-£2
Dyspnoea	£9	£6	£3
TIMI Bleeds	£91	£71	£19
Total	**£14,443**	**£13,019**	**£1,424**

Source: Based on Table 116 of the CS[1] and PBAC guidelines[70]
ASA = acetylsalicylic acid; BID = twice dailyLD = low dose; MI = myocardial infarction; PBAC = Pharmaceutical Benefits Advisory Committee; TIMI = Thrombolysis in Myocardial Infarction

ERG comment: Because disaggregated results for the LY estimates were missing, the ERG asked the company to provide these results; these were provided in the clarification letter (Table 5.29). Furthermore, in its response to the clarification letter, the company provided a revised base-case cost effectiveness analysis wherein the following changes were included:

1. Inpatient and AE costs based on NHS reference costs (Section 5.2.9)
2. Parametric models for AEs were selected based on the AIC (Section 5.2.7)
3. Gout was included as an AE of the cost effectiveness model (both quality of life and economic impact) (Section 5.2.8 and Section 5.2.9)

In this revised base-case analysis, ticagrelor 60 mg BID + low dose ASA was associated with a deterministic ICER of £20,636 in the individual patient simulation, which is an increase of £538 compared to the company original base-case analysis (Table 5.31). Based on the company's revised base-case model, the ERG was not able to reproduce the ICER from the cohort simulation reported in the company's original cost effectiveness model (i.e. £24,070). When attempting to reproduce the company's cohort base-case analysis, the ERG obtained an ICER of £24,200 (deterministic results).

Table 5.31: Deterministic base-case results of the revised individual patient analysis and the revised cohort analyses

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) per inc QALY
Low-dose ASA (individual patient simulation)	£13,086	12.2453	9.1951	-	-	-	-
Ticagrelor 60 mg BID + low-dose ASA (individual patient simulation)	£14,518	12.3363	9.2645	£1,432	0.0909	0.0694	£20,636

Source: Based on Table 114 of the response to the request for clarification[25] and the revised cost effectiveness model

ASA = acetylsalicylic acid; BID = twice daily; Inc = incremental; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life years

5.2.11 Sensitivity analyses

Because of the intensive computation needed to perform sensitivity analyses on an individual patient level simulation, the company performed its sensitivity analyses on a single patient. The single patient profile was chosen because the resulting ICER was closest to that derived from the complete analysis. The individual patient profile (used for the sensitivity analyses) is compared with the average patient characteristics of the cohort in Table 5.32.

Using an individual patient avoids dealing with *"averages for dichotomous outcomes (i.e. a patient who is 76% male, 32% diabetic, with 76% hypertension)"*[1], according to the company. The company further justifies this methodology by the following: *"Given that the sensitivity analyses relate to parameter values rather than to covariates, we would not expect the use of the average characteristics (in place of the representative patient) to change the impact on the results in any meaningful way. Therefore, the impact of the sensitivity analyses on the representative patient selection should reflect the impact for the average patient."*[1]

The company emphasised that probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (DSA) results should be compared to the results of this individual patient instead of being compared to the results based on the individual patient simulation of the entire population.

Table 5.32: Baseline characteristics (average of the cohort, average of the cohort as used in the cost effectiveness model vs. the individual chosen for PSA and DSA)

Baseline characteristics	Patient characteristics for the cohort simulation reported in CS	Patient characteristics for the cohort simulation reported in the cost effectiveness model	Individual selected for DSA and PSA based on the individual patient simulation (Average ICER)
Mean age (years)	65.3	65.22	69
Male (%)	75.8	76.05	No
Mean weight (kg)	81.6	81.64	57
Mean BMI (kg/m^2)	28.3	28.36	22.1
Diabetes (%)	31.6	32.32	No
≥1 prior MI (%)	16.2	16.55	No
Multi-vessel CAD (%)	59.9	61.35	Yes
Non-smoker (%)	35.1	35.25[2]	No
Previous smoker (%)	48.1	48.01	No
Current smoker (%)	16.8	16.74	No
Previous stent (%)	83.8	84.80	Yes
Angina history (%)	30.3	30.59	No
Time from prior MI (days)	505.4	581.00	375
NSTEMI (%)	40.8	40.69	Yes
ASA dose (mg)	90.3	90.33	81
Supine SBP (mmHg)	132.6	132.29	140
Supine DBP (mmHg)	77.8	77.63	71
Hypercholesterolemia (%)	76.1	77.01	Yes
Hypertension (%)	77.3	77.54	Yes
Family history of CHD (%)	29.6	29.40	No
Prior CABG (%)	4.9	4.95	No

Baseline characteristics	Patient characteristics for the cohort simulation reported in CS	Patient characteristics for the cohort simulation reported in the cost effectiveness model	Individual selected for DSA and PSA based on the individual patient simulation (Average ICER)
Prior stroke (%)	0.5	0.45	No
Prior TIA (%)	1.2	1.20	No
Prior revascularisation (%)	0.4	0.42	No
CHF (%)	19.5	19.02	No
Spontaneous bleed requiring hospitalisation (%)	1.5	1.48	No
Europe and South Africa (%)	59.8	56.40[3]	No
Asia and Australia (%)	11.3	12.30	No
North America (%)	17.9	20.32	Yes
South America (%)	11.0	10.98	No
ADP blocker: <30 days	41.5	52.04[4]	Yes
ADP blocker: 30 days to <12 months	40.9	41.39	No
ADP blocker: >12 months	8.2	6.58	No
Clopidogrel: >7 days	55.2	54.29	No
History of PAD (%)	5.5	5.73	No
Creatinine clearance (≥60 mL/min)	79.2	79.17	-

Source: Based on Table 117 of the CS[1] and the cost effectiveness model

Footnotes: [1] Retrieved from 'Control Panel'-sheet, cells M166:M248, and rounded to 2 decimals; [2] Calculated based on the % of current and former smokers (rounded to 2 decimals); [3] Calculated based on the % of patients from outside Europe and South Africa (rounded to 2 decimals); [4] Calculated based on the % of patients from the following categories: ADP blocker: 30 days to <12 months, ADP blocker: >12 months (rounded to 2 decimals)

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; BMI= body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = chronic heart failure; CS = company submission; DBP = diastolic blood pressure; DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; MI = myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction; PAD = peripheral arterial disease; PSA = probabilistic sensitivity analysis; SBP = systolic blood pressure; TIA = transient ischaemic attack

The company carried out a probabilistic sensitivity analysis (PSA) including the following parameters:

- event-based risk equations
- time to first event
- time to subsequent event
- dyspnoea
- TIMI bleeds
- background mortality (from standardised mortality rates from life tables)
- utility
- utility decrements from the PEGASUS-TIMI 54 trial
- baseline utility (UK population norms)
- risk of hospitalisation (post-event)
- treatment discontinuation

A variance co-variance Cholesky decomposition matrix was used to incorporate correlations between parameters. Costs were considered certain (i.e. not subject to uncertainty) and were consequently not included within the company's PSA. Resources use parameters were however included in the PSA. Base-case PSA results are provided in Table 5.33. PSA simulation results were used to draw the PSA scatterplot and the cost effectiveness acceptability curve (CEAC) (Appendix 4). The CEAC shows that ticagrelor 60 mg BID + ASA has a 64.6% and a 100% probability of being cost effective at £20,000 and £30,000 per QALY gained thresholds, respectively.

Table 5.33: Base-case PSA results, patient simulation

	PSA performed on an individual patient (avg. ICER)
Incremental costs	£1,289
95% CI around costs	£1,249 to £1,323
Incremental QALYs	0.0669
95% CI around QALYs	0.537 to 0.0806
Change in costs (%)	-3.16 to 2.59
Change in QALYs (%)	-19.15 to 21.45
ICER	£19,275*

Source: Based on Table 118 of the CS[1]
Footnote: * deterministic ICER for individual patient £19,436
ICER = incremental cost effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Deterministic sensitivity analyses

The DSAs were performed on the same individual patient profile as used in the PSA and are presented in a tornado diagram (Appendix 4). The most influential parameters were the choice of the distribution to extrapolate the risk of a first non-fatal MI and non-CVD death beyond trial time horizon.

Scenario analyses

Structural uncertainty was investigated by the company through seven scenario analyses. These scenario analyses concerned the following:

A. Inclusion of an initiation cost (ICER range: £20,098-£21,810;CS, Table 119);

In these scenario analyses, ticagrelor 60 mg BID was initiated by GPs and/or cardiologists. Each scenario had different rates of GP and cardiologist initiating ticagrelor 60 mg BID treatment (CS, Table 119).[1]

B. Using costs and utilities from the rivaroxaban technology appraisal(ICER range: £20,366-£21,524; CS, Table 123);

In the first scenario analysis of this category, only costs of the rivaroxaban technology appraisal were used, in the second only the utilities and in the third, both utilities and costs were used.

C. Using utilities derived from the systematic review of HRQoL (ICER: £19,889; CS, Table 125);
D. Using PEGASUS-TIMI 54 trial mortality (ICER: £14,544; CS, Table 126);
E. Including subsequent treatment effects (ICER: £18,817; CS, Table 127);
F. A two-way analysis assessing the 'no event' maintenance cost (range ICER: £21,442-£28,586; CS, Table 128);
G. A one-way analysis assessing the impact of starting age, based on the cohort simulation(range ICER: approximately £22,000 – approximately £30,000; CS, Table 129).[1]

Subgroup analyses

The company also performed subgroup analyses. A description of the subgroups is provided in Table 130 of the CS.[1] In order to select patients for each subgroup, filters were applied in the cost effectiveness model to select the desired patient subpopulation. In the NICE scope, a subgroup analysis based on the 'prior revascularisation' was requested. This analysis could not be provided since stratification in PEGASUS-TIMI 54 was based on 'history of PCI'. This latter was therefore used in the subgroup analysis as a proxy for prior revascularisation.

As for the PSA of the base-case cost effectiveness analysis, the PSA of each subgroup was performed on the individual patient simulation of a single individual patient profile. This patient profile was the patient with the ICER which was the closest of the subgroup deterministic ICER. The probabilistic results of the different subgroup analyses are provided in Table 5.34.

Table 5.34: Probabilistic results for the subgroup analyses (individual patient simulation)

Subgroups	Incremental costs	Incremental QALY	ICER
Recent ADP inhibitor therapy (ADP < 30 days)	£1,589	0.074	£21,476
Diabetes (yes)	£1,491	0.1033	£14,433
Diabetes (no)	£1,443	0.0582	£24,813
History of PCI (yes)	£1,437	0.0639	£22,488
History of PCI (no)	£1,126	0.1021	£11,026

Source: Based on Tables 132, 134, 136, 138 and 140 of the CS[1]
ADP = adenosine diphosphate; CS = company submission; ICER = incremental cost effectiveness ratio; PCI = percutaneous coronary intervention; QALY = quality-adjusted life year

ERG comment: There are several issues of concern for the ERG regarding the company's sensitivity and subgroup analyses. Firstly, the method used to obtained probabilistic results was incorrect. Secondly, the non-inclusion of the uncertainty around NHS reference costs in the company's PSA.

Thirdly, the absence of probabilistic results for the deterministic and scenario analyses. Furthermore, this section provides an overview of the scenario analyses requested by the ERG and furnished by the company in the response to the clarification letter. Finally, the ERG remarks that one subgroup analysis was not performed as determined in the NICE scope.

The ERG does not think that the method for the single individual patient selection on which the PSA and DSAs are conducted was appropriate. The ERG agrees that performing a PSA on an individual patient simulation is computationally intensive. This does however not justify the selection of an individual patient to perform PSA instead of all patients. The ERG asked the company to perform PSA based on all patients of the individual patient simulation since running the PSA based on a single patient profile does not reflect the uncertainty in the output.[71]

In its response to this request, the company performed the PSA on 11 patient profiles instead of one patient profile. These 11 patients were also selected based on their ICER: the individual patient with the closest ICER to the ICER of the individual patient simulation and the five patients having the closest ICER below or above the ICER of the individual patient simulation (the '11 typical ICER patients'). The ICER of ticagrelor 60 mg BID + low dose ASA, based on the individual patient simulation of the 11 typical ICER patients, equals £20,604. The ERG think this PSA is still not appropriate and should be based on the individual patient simulation including the entire patient population of 10,799 patients, or whatever number would produce sTable results in order to reflect the uncertainty in the output.[71] The company also used this methodology to provide probabilistic results of its subgroup analyses. The ERG does not consider that these analyses provide reliable probabilistic estimates.

Since the PSA of the company, based on the individual patient simulation, does not provide reliable probabilistic estimates, the ERG preferred to provide probabilistic results of base-case and additional analyses based on the cohort analysis.

The company further emphasises that using a single patient profile for sensitivity analyses instead of the whole patient population would not affect the results of the sensitivity analyses. This statement was however not supported by any sensitivity analysis.

Costs were not incorporated within the company's PSA. According to the ERG this is incorrect. Prices are most often fixed and resource use may stochastically vary. Hence, prices should not be included in the PSA and resource use should be included in the PSA. In this case, costs were based on NHS reference costs, which are the product of prices and resource use estimates, and as a result may stochastically vary, and should be included in the PSA. The ERG incorporated the cost estimates (i.e. the ones based on NHS reference costs[60]) independently in the PSAs of its base-case and additional analyses (based on the cohort simulation).

In addition, no probabilistic results of the deterministic and scenario analyses were provided in the CS, while *"probabilistic methods provide the best estimates of mean costs and outcomes"*, according to NICE guidance.[72] The ERG asked the company to provide these but this request was not met in the response to the clarification letter. The ERG notes that none of the scenario analyses reached ICERs above the £30,000 per QALY threshold.

In its response to the clarification letter, the company provided additional scenario analyses:

A. Ticagrelor 60 mg treatment, starting 12 months after a subsequent MI

B. Ticagrelor 90 mg treatment, 1-12 months after a subsequent MI
C. Impact of not including the treatment effect variable for "non-fatal stroke"
D. Baseline utilities informed by PEGASUS-TIMI 54 – capped at 1
E. Baseline utilities informed by PEGASUS-TIMI 54 – uncapped
F. Baseline utilities informed by PEGASUS-TIMI 54 – gamma model (using a log-link)
G. Tunnel state costs as per original submission
H. Inpatient costing - lower quartile NHS ref cost for efficacy events, upper quartile for AEs

Deterministic results of these scenario analyses, based on the individual patient simulation are presented in Table 5.35.

Table 5.35: Results of the sensitivity analyses H-O

Scenario	Incremental costs	Incremental QALYs	ICER
Company base-case*	£1,434	0.0708	£20,098
H	£1,402	0.0694	£20,202
I	£1,429	0.0694	£20,585
J	£1,487	0.0606	£24,533
K	£1,432	0.0744	£19,253
L	£1,432	0.0744	£19,253
M	£1,432	0.0725	£19,749
N	£1,435	0.0694	£20,680
O	£1,448	0.0694	£20,860

Source: Based on Tables 13, 14, 15, 16, 17, 18, 19, 21 of the response to the request for clarification[25]
Footnote: * Deterministic results, individual patient simulation
ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

Scenarios J and K provide the same results because of the low number of patients impacted by baseline utility capping. The most influential scenario is scenario J where the treatment effect of ticagrelor BID 60 mg on the first non-fatal stroke is removed. The company does not consider this scenario as plausible. All of the presented scenario analyses provide ICER below the £30,000 threshold. No probabilistic results of these scenario analyses were provided.

The NICE scope requested subgroup analyses for *"people who have or have not had prior revascularisation"* (Table 3.1).[17] However, the pivotal trial PEGASUS-TIMI 54[20] did not include this as a pre-specified subgroup. The company provided subgroup analyses based on 'history of PCI' as proxy for 'prior revascularisation'. This is not in accordance with the NICE scope.

5.2.12 Model validation and face validity check

Face validity
In section 5.10 of the CS, the company describes different endeavours which aimed at validating model outcomes. However, there was no description of how face validity was assessed.

Internal validity
The company explains that *"Tests were performed to check for errors that may have occurred in programming or during the incorporation of data into the model."* For example, *"transition probabilities, costs and QALYs were set equal for both treatment strategies in the model"*.[1] This

analysis provided no difference in the estimation of costs and health benefits, which was expected. No further details were provided on the internal validation process.

Cross validation

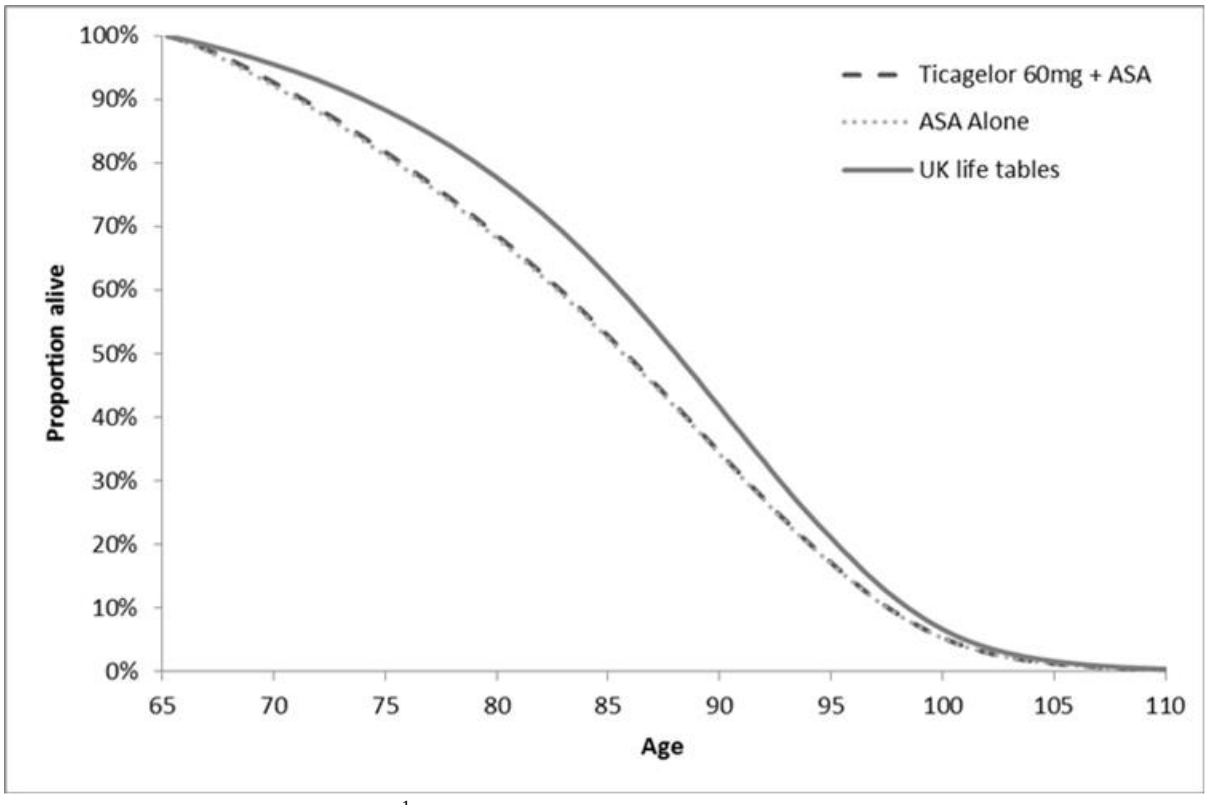
Cross validation was not performed by the company, presumably because of the absence of another relevant cost effectiveness analysis for the current decision problem.

External validity

The cost effectiveness model contains a comparison of observed events in PEGASUS-TIMI 54 with the modelled events in the model. The company notes that the model *"slightly underestimates the total number of observed subsequent events"* (Table 5.37). The company further emphasises that the model provides a conservative estimate of the cost effectiveness of ticagrelor 60 mg BID because AEs for ticagrelor 60 mg BID+ASA are overestimated and TIMI major bleeds for low dose ASA are underestimated.[1] No comparison of the number of MI's, strokes or other CV events occurring in PEGASUS-TIMI 54 with external sources (e.g. UK databases) was provided in the CS.

Furthermore, the company compared survival obtained from the cost effectiveness model with survival estimates from UK life tables (Figure 5.3).

Figure 5.3: Comparing the proportion of survival modelled for ticagrelor 60 mg BID + low-dose ASA and low-dose ASA with UK life tables



Source: Based on figure 67 of the CS[1]

ASA = acetylsalicylic acid; BID = twice daily; CS = company submission; mg = milligram; UK = United Kingdom

ERG comment:

Transparency
The company quoted previous TAs as (potential) sources for model input parameters for costs and utilities, but did not reference the primary sources of the identified values. Moreover, the ERG was unable to find several utility values in the primary sources identified in previous TAs. This hampered transparency.

Face validity
In its response to the clarification letter, the company explains that model structure has been informed through a systematic literature review. The company further justify the choice of a competing risk approach to model the different events of the composite endpoints by the following: *"The principal advantage of using a competing risks framework is that it allows for different coefficients for each separate endpoint. […] Additionally, as the risk equation approach models events directly, as opposed to a composite event and assessing the probability of that event being of a certain type, far fewer assumptions need to be made."*[25] Additionally, two experts [redacted] "*agreed that the competing risk approach was preferable."*

The ERG agrees that the competing risk approach might be valid to model the different events of the composite endpoints, however, the original cost effectiveness model did not contain long-term consequences of subsequent events which may decrease the face validity of the model.

Internal validity
The internal validation efforts seem to be adequate.

Cross validation
Since no cross validation was performed in the CS, the ERG asked the company to provide a comparison of the model structure, input parameters, key model assumptions and model outcomes of the current assessment with the five studies identified in the cost effectiveness literature review (Section 5.1) and the following TA's: TA182, TA210, TA236, TA317, TA335. The company provided these comparison in its response to the clarification letter and concluded that *"there is no consensus on modelling approach undertaken between the studies"* and that *"Some consistency, as expected, was found in the use of tunnel and transient-event states to model acute and follow-on phases of specific events."* Furthermore, *"No assumptions were adopted from other studies or appraisals for the current submission."* and *"The comparison of model outcomes […] should be interpreted with caution"*.[25]

External validity
Minor TIMI bleeds and grade 1-2 dyspnoea were not included in the comparison of observed versus modelled events in the CS. The ERG requested that the company include these events.[26] This was provided in the response to the request for clarification.[25] Discrepancies in the estimation of the number of dyspnoea grade 1-2 by the model against the number of observed dyspnoea grade 1-2 should be noted.

The company further claims that adverse events were overestimated for ticagrelor 60 mg BID+ASA and that major TIMI bleeds are underestimated for low-dose ASA. According to the company, this bias provides a conservative estimate of the cost effectiveness of ticagrelor 60 mg BID+ASA. This argument is wrong since the number of major TIMI bleeding events is also overestimated in the low dose ASA group (Table 5.36).

The underestimation of the following events in the ticagrelor 60 mg BID + low dose ASA might lead to an overestimation of the effect of ticagrelor: non-fatal MI (first event), fatal CV (first event), non-fatal MI (subsequent event), non-fatal stroke (subsequent event), TIMI minor bleeds and dyspnoea (grade 1-2). On the other hand, the underestimation of the following events in the low dose ASA treatment arm leads to a conservative cost effectiveness estimate: non-fatal MI (first event), fatal CV (first event), non-fatal stroke (subsequent event), fatal CV (subsequent event), TIMI minor bleeds and dyspnoea (grade 3-4). Based on these observations, it is difficult to assess whether the cost effectiveness estimate is conservative.

Table 5.36: Comparison of the number of observed vs. modelled events, during a period of the PEGASUS-TIMI 54 ('Label' population, derived from complete analysis)

	Ticagrelor 60 mg BID + low-dose ASA		Low-dose ASA		Modelled vs. observed		Modelled vs. observed (%)*		Comments($)
	Observed	Modelled	Observed	Modelled	Ticagrelor 60 mg BID + LD ASA	Low-dose ASA	Ticagrelor 60 mg BID + LD ASA	Low-dose ASA	
[redacted]									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

	Ticagrelor 60 mg BID + low-dose ASA		Low-dose ASA		Modelled vs. observed		Modelled vs. observed (%)*		Comments($)
	Observed	Modelled	Observed	Modelled	Ticagrelor 60 mg BID + LD ASA	Low-dose ASA	Ticagrelor 60 mg BID + LD ASA	Low-dose ASA	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 141 of the response to request for clarification[25]

Footnotes: * Calculated by the ERG; ($) added after clarification phase

ASA = acetylsalicylic acid; BID = twice daily; CV = cardiovascular; ERG = Evidence Review Group; mg = milligram; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction

The ERG further requested the company to provide a comparison of the number of MI's, strokes and other CV events from PEGASUS-TIMI 54 with external, preferably UK, database (e.g. http://www.isdscotland.org/Health-Topics/[73], https://indicators.hscic.gov.uk/webview/[74], https://www.ucl.ac.uk/nicor/audits/minap[75]).[26] The company deemed such a comparison inappropriate because the population of the current decision problem is highly specific and not represented in these sources. Requesting the data needed for such a comparison would however require more time than allowed by the NICE procedure.[25] Since model outcomes were not compared with UK databases, the ERG was unable to assess whether outcomes of the model were representative for the UK setting.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from Section 5.2, the ERG defined a new base-case (see Table 6.1). This base-case included multiple adjustments to the original base-case presented in the CS.[1] The ERG used the cohort simulation to obtain a probabilistic estimate of the ICER, as the probabilistic sensitivity analysis of the patient level simulation was not implemented correctly. Hence, all of the following adjustments were performed on the cohort analysis. These adjustments were subdivided into three categories (derived from Kaltenthaler et al.[76]):

1. Fixing errors (correcting the model were the company's submitted model was unequivocally wrong)
2. Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
3. Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred)

The combination of these corrections/amendments resulted in the ERG base-case (Table 5.37). Additionally, several explorative sensitivity analyses were performed based on the ERG base-case to test uncertainties within the model.

Fixing errors

1. Corrected parameterisation of the log-logistic models for first and subsequent non-fatal MI or stroke and first fatal event (CVD-related or non-CVD related) (see Section 5.2.6)

Fixing violations

2. Include the quality of life and economic consequences of gout (see Section 5.2.8 and 5.2.9)
3. Base the choice of AEs distributions on AIC (see Section 5.2.7)
4. Adjusted health care costs (see Section 5.2.9)
5. Uncertainty of costs, based on NHS reference costs[60], in PSA (see Section 5.2.11)

Matters of judgment

6. Alternative disutility for major bleeds (see Section 5.2.8)
7. Alternative inpatient costs for the 'no event' health state (see Section 5.2.9)

Table 5.37: Deterministic company base-case and probabilistic ERG base-case – results of the cohort simulation

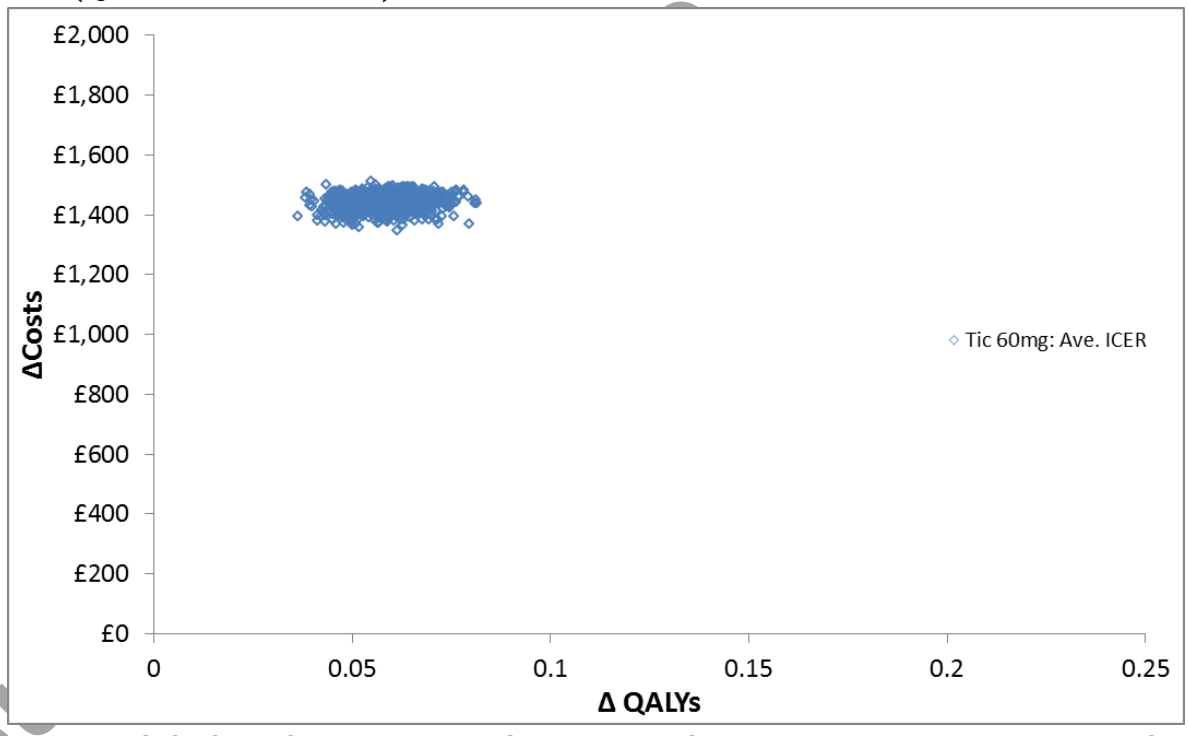
	Ticagrelor 60 mg BID + low-dose ASA		Low dose ASA				
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
Company base-case	£15,689	13.5361	9,8541	£1,425	0.0771	0.0592	£24,070*
ERG base-case	9.768	£14,113	9.709	£12,674	0.058	£1,439	£24,711

Footnote: * The ICER reported in the CS for the cohort analysis was £24,378 (deterministic results)
ASA= acetylsalicylic acid; BID= twice per day; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

5.3.1 Probabilistic sensitivity analyses (ERG base-case)

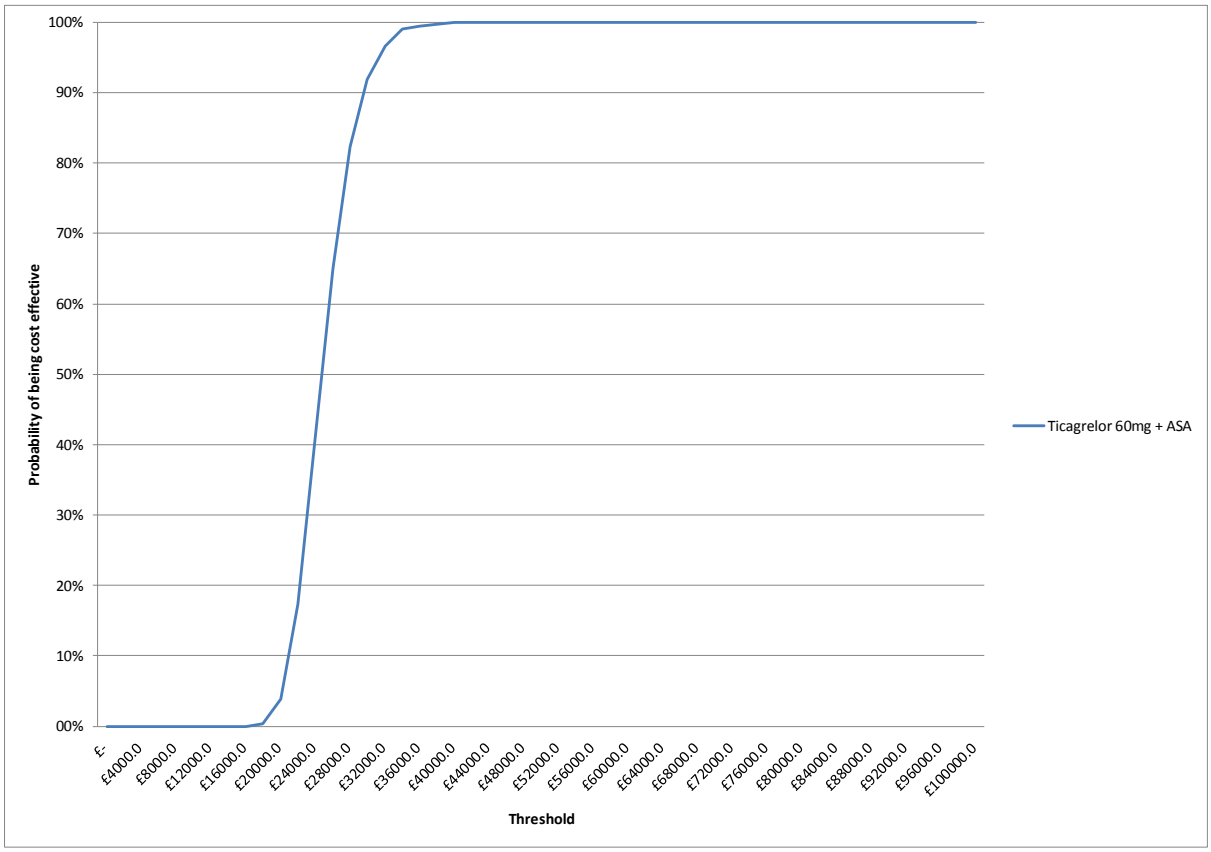
A PSA was performed to capture the parameter uncertainty in the ICER. The scatterplot and CEAC of this analysis are presented in Figures 5.4 and 5.5 respectively. Ticagrelor 60 mg BID + low-dose ASA has a 3.9% and 91.9% probability of being cost effective at the £20,000 and £30,000 thresholds respectively, based on the ERG base-case analysis.

Figure 5.4: Cost effectiveness plane for ticagrelor 60 mg BID + low dose ASA vs low dose ASA (QALYs; ERG base case)



ASA= acetylsalicylic acid; BID= twice per day; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; mg = milligram; QALY = quality-adjusted life year

Figure 5.5: CEAC ERG base-case



ASA= acetylsalicylic acid; CEAC = cost effectiveness acceptability curve; ERG = Evidence Review Group; mg = milligram

5.3.2 Additional exploratory analyses performed by the ERG base-case

Additional exploratory sensitivity analyses were performed by the ERG to examine the potential impact of various alternative assumptions on the cost effectiveness estimates. These analyses were performed on the ERG base-case and investigated the impact of the following adjustments (Table 6.2):

1. The probability of hospitalisation for 'no event' health state was made treatment dependent;
2. The time to fatal other (first event) was made treatment dependent;
3. Treatment discontinuation was assumed to be caused by non-fatal events or after a three year treatment period;
4. More conservative utility values were used for health states and events (Table 5.22).

Assuming treatment discontinuation was caused by non-fatal events or after a three year treatment period was the most influential explorative analysis performed by the ERG and increased the ICER to £33,675. The other explorative analyses did not substantially influence the ICER, which remained under the £30,000 threshold (Table 6.2).

5.4 Conclusions of the cost effectiveness section

Regarding cost effectiveness, the ERG used the cohort simulation to obtain a probabilistic estimate of the ICER, as the probabilistic sensitivity analysis of the patient level simulation was not implemented correctly (ICER £22,316). The majority of the time-to-event model used by the company in the economic modelling were not adjusted for the label population (the *MI<2 years subgroup* in the PEGASUS TIMI 58 trial) and the ERG was unable to determine the impact on the ICER. Besides this

issue the ERG fixed an error in the parameterisation of the log-logistic models for first and subsequent non-fatal MI or stroke and first fatal event. Violations were fixed with regard to:

- Including the quality of life and economic consequences of gout (see Section 5.2.8 and 5.2.9)
- Choice of AEs distributions on AIC (see Section 5.2.7)
- Adjustment of health care costs (see Section 5.2.9)
- Inclusion of uncertainty of costs, based on NHS reference costs, in PSA (see Section 5.2.11)

In addition, the ERG judged that an alternative, larger disutility for major bleeds was more plausible (see Section 5.2.8). The ERG also judged that alternative, larger inpatient costs for the 'no event' health state were more plausible. (see Section 5.2.9)

These adjustments by the ERG resulted in an ICER of £24,711; higher than the probabilistic estimate of the cohort simulation base case from the company. The explorative analyses with alternative assumptions underlying time to treatment discontinuation resulted in an ICER of £33,676.

It should be noted that the ERG additional analyses are based on the cohort simulation, which may be an overestimation as this analysis does not take into account nonlinearity in the model. It should also be noted that all ERG additional analyses are conditional upon the time-to-event models that are unadjusted for the ‘label population’. Although this may be conservative, the ERG was unable to determine the magnitude and direction of the bias this may have caused.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Tables 6.1 and 6.2 show how each individual change impacts the ICER plus the combined effect of all changes simultaneously. The analyses numbers in Table 6.1 correspond to the analyses numbers reported in Section 5.3. Moreover, the exploratory sensitivity analyses are presented in Table 6.2 (both conditional on the ERG base case). Appendix 3 and the economic model sent by the ERG contains technical details on the analyses performed by the ERG.

Table 6.1: ERG base-case, incorporating corrections and amendments identified by the ERG – probabilistic results of the cohort simulation

	Ticagrelor 60 mg BID + low-dose ASA		Low-dose ASA				
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔQALY**	**ΔCosts**	**ICER**
Company base-case (deterministic, cohort analysis)	£15,689	13.5361	9,8541	£1,425	0.0771	0.0592	£24,070[#]
Company base-case[*]	9.846	£15,686	9.787	£14,262	0.059	£1,425	£24,072
1. Correction of the log-logistic parameterisation	9.771	£15,749	9.711	£14,326	0.060	£1,424	£23,826
2. Include gout	9.846	£15,745	9.788	£14,314	0.058	£1,431	£24,639
3. AEs distributions choice based on AIC	9.832	£15,683	9.773	£14,259	0.059	£1,424	£23,983
4. Adjusted health care costs	9.847	£15,721	9.788	£14,288	0.059	£1,433	£24,108
5. Include uncertainty around NHS costs in PSA	9.849	£15,687	9.789	£14,263	0.059	£1,424	£24,022
6. Alternative disutility for major bleeds	9.851	£15,688	9.792	£14,264	0.059	£1,424	£24,231
7. Alternative inpatient costs for the 'no event' health state	9.850	£13,973	9.791	£12,543	0.059	£1,431	£24,193
ERG base-case	9.768	£14,113	9.709	£12,674	0.058	£1,439.10	£24,711

Footnotes: [*] Reproduced by the ERG; [#] The ICER reported in the CS for the cohort analysis was £24,378 (deterministic results)

AE = adverse event ; AIC= Akaike Information Criterion; BID= twice per day; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; mg = milligram; NHS= National Health Service; PSA= probabilistic sensitivity analysis; QALY = quality-adjusted life year

Table 6.2: Exploratory sensitivity analyses based on ERG base-case – probabilistic results

	Ticagrelor 60 mg BID + low-dose ASA		Low-dose ASA				
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔQALY**	**ΔCosts**	**ICER**
ERG base-case	9.768	£14,113	9.709	£12,674	0.058	£1,439	£24,711
Hospitalisation probability for 'no event' state treatment dependent	9.766	£14,171	9.708	£12,671	0.058	£1,499	£25,834
Time to fatal other (1st event) treatment dependent	9.767	£14,115	9.710	£12,678	0.058	£1,437	£24,989
TTD because of non-fatal event or after 3years	9.760	£14,609	9.703	£12,680	0.057	£1,929	£33,676
Use of more conservative utilities	9.790	£14,116	9.732	£12,676	0.057	£1,440	£25,091

BID= twice per day; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; PSA= probabilistic sensitivity analysis; QALY = quality-adjusted life year; TTD= Time to treatment discontinuation

7 END OF LIFE

The CS does not discuss issues regarding end of life criteria and the ERG considers this intervention does not meet the end of life criteria.

8 OVERALL CONCLUSIONS

8.1 Statement of principal findings

The evidence regarding clinical effectiveness was based on a large randomised controlled trial comparing ticagrelor 60 mg BID + ASA versus placebo + ASA in patients who experienced an MI 1-three years ago. The CS also reported results from subgroup of patients who had an MI <2 years ago which was consistent with the final scope of the appraisal and the licensed indication for ticagrelor. Subgroup data were also reported for patients who had an MI <2 years ago with/without diabetes and patients with an MI <2 years ago with/without a prior history of PCI.

There was evidence that the effectiveness of ticagrelor was different in different patient populations. In the full analysis set from PEGASUS-TIMI 54 the treatment effect of ticagrelor on STEMI was greater than the effect on STEMI. In patients with an MI <2 years ago the effect of ticagrelor on the risk of MI was greater in patients without diabetes than those with diabetes. Conversely, the effect of ticagrelor on the risk of stroke was greater in patients with diabetes than those without diabetes within the population of patients with an MI <2 years ago. The history of PCI in patients with an MI <2 years ago did not influence the effect of ticagrelor on the risk of MI however the effect of ticagrelor on the risk of stroke was greater in patients with PCI than those without PCI.

The increased risk of TIMI major bleeds associated with ticagrelor treatments was greater in those with diabetes or with a history of PCI compared to patients without diabetes or without PCI respectively.

It should be noted that the results from PEGASUS-TIMI 54 are based on small numbers of events for each outcome compared to the total number of patients in each arm, therefore, although there are differences in the relative risk of events the absolute risk remains quite low.

The final scope specified clopidogrel + ASA as a comparator however the CS did not present evidence for the comparison of ticagrelor + ASA versus clopidogrel + ASA. There were no studies that directly compared these two treatments and the company argued that an indirect comparison was not possible due to differences in the design and patient characteristics of the available studies. As a result there is a lack of evidence regarding the relative effectiveness of ticagrelor compared to clopidogrel.

Regarding cost effectiveness, the ERG used the cohort simulation to obtain a probabilistic estimate of the ICER, as the probabilistic sensitivity analysis of the patient level simulation was not implemented correctly (ICER £22,316). The ERG was unable to determine the impact on the ICER of the fact that the majority of the time-to-event model used by the company in the economic modelling were not adjusted for the label population (the *MI<2 years subgroup* in the PEGASUS TIMI 58 trial). Besides this issue the ERG fixed an error in the parameterisation of the log-logistic models for first and subsequent non-fatal MI or stroke and first fatal event. Violations were fixed with regard to:

- Including the quality of life and economic consequences of gout (see Section 5.2.8 and 5.2.9)
- Choice of AEs distributions on AIC (see Section 5.2.7)
- Adjustment of health care costs (see Section 5.2.9)
- Inclusion of uncertainty of costs, based on NHS reference costs, in PSA (see Section 5.2.11)

In addition, the ERG judged that an alternative, larger, disutility for major bleeds was more plausible (see Section 5.2.8). The ERG also judged that alternative, larger, inpatient costs for the 'no event' health state were more plausible. (see Section 5.2.9)

These adjustments by the ERG resulted in an ICER of £24,711; higher than the probabilistic estimate of the cohort simulation base case from the company. The explorative analyses with alternative assumptions underlying time to treatment discontinuation resulted in an ICER of £33,676.

It should be noted that the ERG additional analyses are based on the cohort simulation, which may be an overestimation as this analysis does not take into account nonlinearity in the model. It should also be noted that all ERG additional analyses are conditional upon the time-to-event models that are unadjusted for the 'label population'. Although this may be conservative, the ERG was unable to determine the magnitude and direction of the bias this may have caused.

8.2 Strengths and limitations of the assessment

The model approach was generally state of the art. The company developed a patient level state transition model, allowing for non-linearity. In addition a competing risk framework was used to estimate the time to the multiple first events in the model.

Subsequent and adverse events were not modelled explicitly and, as a consequence, only had a three month impact. In case of the adverse events, this model simplification is not conservative.

The majority of the time-to-event models used in the economic modelling were based on the ITT population from PEGASUS TIME 58, and not adjusted for the 'label population'. Although this may be conservative, the ERG was unable to determine the magnitude and direction of the bias this may have caused. The modelling of time to treatment discontinuation was unclear and may be incorrect. Alternative assumptions increased the ICER.

The company quoted previous TAs as (potential) sources for model input parameters for costs and utilities, but did not reference the primary sources of the identified values. This hampered transparency.

The probabilistic sensitivity analysis for the patient level simulation was not programmed correctly. As a result, the ERG based its base-case and additional analyses on the cohort simulation. The probabilistic ICER from the cohort simulation may be an overestimation of the ICER due to ignoring non-linearity in the model.

9 REFERENCES

[1] AstraZeneca. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]: AstraZeneca evidence submission to National Institute of Health and Clinical Excellence. Single technology appraisal (STA)*: AstraZeneca, 2016

[2] Rapsomaniki E, Thuresson M, Yang E, Blin P, Hunt P, Chung S-C, et al. Outcomes among 140,887 survivors of acute myocardial infarction: comparison of health system data in 4 countries [JAMA submitted manuscript]. 2014.

[3] Kern DM, Mellström C, Hunt PR, Tunceli O, Wu B, Westergaard M, et al. Long-term cardiovascular risk and costs for myocardial infarction survivors in a US commercially insured population. *Curr Med Res Opin* 2016;32(4):703-11.

[4] Yang E, Stokes M, Johansson S, Mellstrom C, Magnuson E, Cohen D, et al. Clinical and economic outcomes among elderly myocardial infarction survivors in United States [submitted manuscript, not yet approved]. 2014.

[5] Rapsomaniki ESD, Emmas C, Chung S, Pasea L, Denaxas S, Shah AD, et al. Health outcomes in patients with stable coronary artery disease following myocardial infarction; construction of a PEGASUS-TIMI-54 like population in UK linked electronic health records. 2013.

[6] Gulliksson M, Wedel H, Koster M, Svardsudd K. Hazard function and secular trends in the risk of recurrent acute myocardial infarction: 30 years of follow-up of more than 775,000 incidents. *Circ Cardiovasc Qual Outcomes* 2009;2(3):178-85.

[7] Figueras J, Missorici M, Lidon RM, Cortadellas J, Soler Soler J. Coincidental annual distribution of first and second acute myocardial infarction. *Am J Cardiol* 2002;89(12):1416-20.

[8] Health & Social Care Information Centre (HSCIC). *Hospital Episode Statistics, Admitted Patient Care - England, 2014-15 [Internet]*: HSCIC, 2015 [accessed 22.4.16] Available from: http://www.hscic.gov.uk/hesdata

[9] Grime JAA. *Prescribing of oral antiplatelet therapy: results from a representative patient records survey into cardiologist prescribing intentions for high risk post-MI patients at hospital discharge. Data on File*, 2016

[10] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60(16):1581-98.

[11] National Institute for Clinical Excellence. *MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE guidelines 48 [Internet]*. London: National Institute for Clinical Excellence, 2007 [accessed 24.5.16] Available from: https://www.nice.org.uk/guidance/cg48

[12] National Institute for Health and Care Excellence. *Myocardial infarction: cardiac rehabilitation and prevention of further MI. NICE clinical guideline 172 [Internet]*. London: National Institute for Health and Care Excellence, 2013 [accessed 18.4.16] Available from: https://www.nice.org.uk/guidance/cg172

[13] Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients

Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37(3):267-315.

[14] Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33(20):2569-619.

[15] AstraZeneca. *Real world study into post MI prescribing to support NICE submission: 27th May 2015. Data on File*: AstraZeneca, 2015

[16] Scottish Intercollegiate Guidelines Network (SIGN). *Acute coronary syndromes. A national clinical guideline. SIGN 93 [Internet]*. Edinburgh: SIGN, 2013 [accessed 18.4.16] Available from: http://www.sign.ac.uk/guidelines/fulltext/93/

[17] National Institute for Health and Care Excellence. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]. Final scope [Internet]*. London: National Institute for Health and Care Excellence, 2016 [accessed 18.4.16] Available from: https://www.nice.org.uk/guidance/GID-TA10016/documents/final-scope

[18] Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF, et al. Design and rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. *Am Heart J* 2014;167(4):437-444.e5.

[19] European Medicines Agency. *Brilique (ticagrelor): EPAR - Product Information. Annex I. Summary of product characteristics [Internet]*. London: European Medicines Agency, 2011 [accessed 18.4.16] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf

[20] Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372(19):1791-800.

[21] electronic Medicines Compendium (eMC). Clopidogrel 75 mg Film-coated Tablets - Summary of Product Characteristics (SPC) [Internet]. 2015 [accessed 24.5.16]. Available from: https://www.medicines.org.uk/emc/medicine/24272

[22] United Kingdom Clinical Pharmacy Association (UKCPA) – Cardiac Group. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]: UKCPA professional organisation submission to National Institute of Health and Clinical Excellence. Single technology appraisal (STA)*: United Kingdom Clinical Pharmacy Association (UKCPA), 2016

[23] Canadian Agency for Drugs and Technologies in Health. *CADTH peer review checklist for search strategies [Internet]*. Ottawa: CADTH, 2013 [accessed 14.4.16] Available from: http://www.cadth.ca/en/resources/finding-evidence-is

[24] National Institute for Health and Care Excellence. *Single Technology Appraisal: company evidence submission template [Internet]*. London: NICE, 2015 [accessed 14.4.16] Available from: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/specification-for-company-submission-of-evidence-2015-version.docx

[25] AstraZeneca. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]. Response to request for clarification from the ERG*: AstraZeneca, 2016. 76p.

[26] National Institute for Health and Care Excellence. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]. Clarification letter*. London: National Institute for Health and Care Excellence, 2016

[27] Scottish Intercollegiate Guidelines Network. Search filters [Internet]. Edinburgh: Scottish Intercollegiate Guidelines Network, 2015 [accessed 14.4.16]. Available from: http://www.sign.ac.uk/methodology/filters.html

[28] AstraZeneca. Prevention of cardiovascular events (eg, death from heart or vascular disease, heart attack, or stroke) in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin (PEGASUS). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010-2014 [cited 2016 Apr 18]. Available from: http://clinicaltrials.gov/show/NCT01225562. NLM Identifier: NCT01225562

[29] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 14.4.16] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[30] Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions [Internet]*. Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011 [accessed 14.4.16]. Available from: http://www.cochrane-handbook.org/

[31] AstraZeneca. *A randomised, double-blind, placebo controlled, parallel group, multinational trial, to assess the prevention of thrombotic events with ticagrelor compared to placebo on a background of acetyl salicylic acid (ASA) therapy in patients with history of myocardial infarction [PEGASUS: PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome - Thrombolysis In Myocardial Infarction Study Group]. Clinical study report. 14th February 2015. Data on File. [Confidential]*: AstraZeneca, 2015

[32] Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007;49(19):1982-8.

[33] Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, et al. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. *J Am Coll Cardiol* 2015;65(20):2211-21.

[34] Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Am Heart J* 2004;148(2):263-8.

[35] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357(20):2001-15.

[36] Fuentes QE, Fuentes QF, Andrés V, Pello OM, de Mora JF, Palomo GI. Role of platelets as mediators that link inflammation and thrombosis in atherosclerosis. *Platelets* 2013;24(4):255-62.

[37] Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol* 2015;12(1):30-47.

[38] Bonaca MP, Bhatt DL, Steg PG, Budaj A, Bansilal S, Storey RF, et al. TCT-78: Efficacy of long-term ticagrelor in stented patients in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2015;66(15 Suppl B):B36.

[39] AstraZeneca. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]: AstraZeneca evidence submission: Appendices*: AstraZeneca, 2016. 165p.

[40] Banerjee S, Brown A, McGahan L, Asakawa K, Hutton B, Clark M, et al. Clopidogrel versus other antiplatelet agents for secondary prevention of vascular events in adults with acute coronary syndrome or peripheral vascular disease: clinical and cost-effectiveness analyses. *CADTH Technol Overv* 2012;2(1):e2102.

[41] Begum N, Stephens S, Schoeman O, Fraschke A, Kirsch B, Briere JB, et al. Cost-effectiveness analysis of rivaroxaban in the secondary prevention of acute coronary syndromes in Sweden. *Cardiol Ther* 2015;4(2):131-53.

[42] Chen J, Bhatt DL, Dunn ES, Shi C, Caro JJ, Mahoney EM, et al. Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone for secondary prevention of cardiovascular events: results from the CHARISMA trial. *Value Health* 2009;12(6):872-9.

[43] Chen J, Shi C, Mahoney EM, Dunn ES, Rinfret S, Caro JJ, et al. Clinical research economic evaluation of clopidogrel plus aspirin for secondary prevention of cardiovascular events in Canada for patients with established cardiovascular disease: results from the CHARISMA trial. *Can J Cardiol* 2011;27(2):222-31.

[44] Gaspoz JM, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink MG, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 2002;346(23):1800-6.

[45] National Institute for Health and Care Excellence. *Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance 182 [Internet]*. London: National Institute for Health and Care Excellence, 2009 [accessed 22.4.16] Available from: https://www.nice.org.uk/guidance/ta182

[46] National Institute for Health and Care Excellence. *Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. NICE technology appraisal guidance 210 [Internet]*. London: National Institute for Health and Care Excellence, 2010 [accessed 18.4.16] Available from: https://www.nice.org.uk/guidance/ta210

[47] National Institute for Health and Care Excellence. *Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisal guidance 236 [Internet]*. London: National Institute for Health and Care Excellence, 2011 [accessed 18.4.16] Available from: https://www.nice.org.uk/guidance/ta236

[48] National Institute for Health and Care Excellence. *Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes. NICE technology appraisal guidance 317 [Internet]*. London: National Institute for Health and Care Excellence, 2014 [accessed 18.4.16] Available from: https://www.nice.org.uk/guidance/ta317

[49] National Institute for Health and Care Excellence. *Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. NICE technology appraisal guidance 335 [Internet]*. London: National Institute for Health and Care Excellence, 2015 [accessed 18.4.16] Available from: https://www.nice.org.uk/guidance/ta335

[50] Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making* 2011;31(6):800-4.

[51] De Smedt D, Clays E, Annemans L, De Bacquer D. EQ-5D versus SF-12 in coronary patients: are they interchangeable? *Value Health* 2014;17(1):84-9.

[52] Lewis EF, Li Y, Pfeffer MA, Solomon SD, Weinfurt KP, Velazquez EJ, et al. Impact of cardiovascular events on change in quality of life and utilities in patients after myocardial infarction: a VALIANT study (valsartan in acute myocardial infarction). *J Am Coll Cardiol* 2014;2(2):159-65.

[53] Nam J, Briggs A, Layland J, Oldroyd KG, Curzen N, Sood A, et al. Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction (FAMOUS-NSTEMI) developmental trial: cost-effectiveness using a mixed trial- and model-based methods. *Cost Eff Resour Alloc* 2015;13:19.

[54] Stafford M, Soljak M, Pledge V, Mindell J. Socio-economic differences in the health-related quality of life impact of cardiovascular conditions. *Eur J Public Health* 2012;22(3):301-5.

[55] van Stel HF, Busschbach JJ, Hunink MG, Buskens E. Impact of secondary cardiovascular events on health status. *Value Health* 2012;15(1):175-82.

[56] Centre for Reviews and Dissemination. About the databases: search strategies [Internet]. University of York: Centre for Reviews and Dissemination, 2015 [accessed 14.4.16]. Available from: http://www.crd.york.ac.uk/crdweb/searchstrategies.asp

[57] Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Fleeman N, et al. Prasugrel (Efient®) with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182): systematic review and economic analysis. *Health Technol Assess* 2015;19(29):1-130.

[58] Curtis L, Burns A, eds. *Unit Costs of Health and Social Care 2015 [Internet]*. Canterbury: Personal Social Services Research Unit, University of Kent, 2015 [accessed 14.4.16]. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php

[59] Greenhalgh J, Bagust A, Boland A, Martin Saborido C, Oyee J, Blundell M, et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis. *Health Technol Assess* 2011;15(31):1-178.

[60] Department of Health. *Reference costs 2014-15 [Internet]*. London: Department of Health, 2015 [accessed 14.4.16] Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015

[61] Latimer N. *NICE DSU Technical Support Document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Report by the Decision Support Unit [Internet]*. Sheffield: School of Health and Related Research (ScHARR), 2013 [accessed 6.6.16] Available from: http://www.nicedsu.org.uk/

[62] Office for National Statistics. Dataset: deaths registered in England and Wales (Series DR) [Internet]. Office for National Statistics, 2015 [accessed 6.6.16]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables

[63] Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;316(7133):736-41.

[64] Jansen JP, Pellissier J, Choy EH, Ostor A, Nash JT, Bacon P, et al. Economic evaluation of etoricoxib versus non-selective NSAIDs in the treatment of ankylosing spondylitis in the UK. *Curr Med Res Opin* 2007;23(12):3069-78.

[65] Quinn RR, Naimark DM, Oliver MJ, Bayoumi AM. Should hemodialysis patients with atrial fibrillation undergo systemic anticoagulation? A cost-utility analysis. *Am J Kidney Dis* 2007;50(3):421-32.

[66] Joint Formulary Committee. *British National Formulary. 70*. London: BMJ Group and Pharmaceutical Press, 2015.

[67] Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003;21 Suppl 1:43-50.

[68] Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabet Med* 2003;20(6):442-50.

[69] AstraZeneca. *Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]. Response to request for clarification from the ERG: part 2*: AstraZeneca, 2016. 38p.

[70] Pharmaceutical Benefits Advisory Committee. *Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3)*. Canberra: Pharmaceutical Benefits Advisory Committee 2008

[71] Halpern EF, Weinstein MC, Hunink MG, Gazelle GS. Representing both first- and second-order uncertainties by Monte Carlo simulation for groups of patients. *Med Decis Making* 2000;20(3):314-22.

[72] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [Internet]*. London: NICE, 2013 [accessed 14.4.16] Available from: http://publications.nice.org.uk/pmg9

[73] ISD Scotland. Topics: Information Services Division's Major Work Programmes [Internet]. ISD Scotland, 2016 [accessed 6.6.16]. Available from: http://www.isdscotland.org/Health-Topics/

[74] Health & Social Care Information Centre (HSCIC). *Indicator portal [Internet]*: HSCIC, 2016 [accessed 6.6.16] Available from: https://indicators.hscic.gov.uk/webview/

[75] NICOR: National Institute for Cardiovascular Outcomes Research. *MINAP (Myocardial Ischaemia National Audit Project) [Internet]*: NICOR: National Institute for Cardiovascular Outcomes Research, 2016 [accessed 6.6.16] Available from: https://www.ucl.ac.uk/nicor/audits/minap

[76] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

Appendix 1: Further critique of searches in the company submission

Clinical effectiveness

- The animal/human limit included in the Embase search strategy was incorrect, as the terms used were from MEDLINE (search lines #69 and #70). However, the search strategy was limited to human studies by applying the Ovid database limits (search lines #92 and #93).

- The RCT search filter included 'Review of reported cases.pt.' and 'Review, multicase.pt.': neither term identifies any records; neither term is included in the SIGN RCT filter[27] from which this was derived; and neither term is actually a publication type (pt) in MEDLINE (Ovid).

- Reporting the exact date span of the database searches would have been more transparent than using 'to present' for MEDLINE. This would allow others to replicate the search more accurately. In the list of databases given in the main CS for each of the searches conducted, the date span was given as '1980 to present' for Embase, but it was then reported more specifically with the search strategies in the appendices: Embase 1980 to 2015 Week 48; Searched on 1st December 2015.

- The Cochrane Library database results would have been better reported per database rather than as a total.

Cost effectiveness

- In the MEDLINE search strategy it appears that search line #35 was inadvertently combined with search line #34. Search line #34 comprises search terms for economic evaluation, whilst the facet which includes line #35 is comprised of search terms for 'models': these facets were then combined using Boolean AND. Search line #35 consists of a set of acronyms for economic analyses (CEA, CBA, CUA, etc.) and should have been included in that facet of search terms (search line #34). In the Embase search strategy the corresponding search lines were line #42 (economic evaluation) and #41 (economic analyses acronyms).

- There are redundant search terms where hyphenated phrases have been replicated: the databases searched do not recognise hyphens, and so the same results are achieved with or without hyphens. e.g., 'cost benefit analysis' retrieves the same as 'cost-benefit analysis'.

- The results from the Cochrane Library search would have been better reported per database rather than as a total.

Measurement and valuation of health effects

- There were no MeSH or EMTREE subject heading terms in the HRQoL facet of search terms.

- The date limits used were different in MEDLINE to those used in Embase: 'dd' (date delivered) was used in Embase, whilst 'ed' (entry date) was used in MEDLINE.

- There was a misspelling in search line #8 in both MEDLINE and Embase, 'short form thiry' instead of 'short form thirty'.

- There were no proximity operators in the HRQoL facet of search terms. This would have increased sensitivity, and improved the search strategy.

- There was a mistake in search line #37, ‘ora nonSTEMI’ instead of ‘or nonSTEMI’

- Incorrect EMTREE index terms were used in the Embase search strategy, e.g., the MeSH term ‘myocardial infarction/’ was used instead of ‘heart infarction/’. Similarly, the MeSH term ‘unstable, angina/’ was used instead of ‘unstable angina pectoris/’, and the MeSH term ‘Coronary Thrombosis/’ was used instead of the EMTREE term ‘coronary artery thrombosis/’.

Cost and healthcare resources use identification, measurement and valuation

MEDLINE was misspelt as MELDINE (Table 25).

Appendix 2: Phillips et al. Checklist

Question(s)	*Response (Y, N or NS)*	*Comments*
Is there a clear statement of the decision problem?	Y	
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Partly	The scope requested clopidogrel + ASA to be considered a comparator for this appraisal, which was not included.
Is the primary decision-maker specified?	Y	
Is the perspective of the model stated clearly?	Y	
Are the model inputs consistent with the stated perspective?	Y	
Has the scope of the model been stated and justified?	Y	
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Partly	Subsequent event are not explicitly considered in the model.
Are the sources of data used to develop the structure of the model specified?	Y	
Are the causal relationships described by the model structure justified appropriately?	Y	
Are the structural assumptions transparent and justified?	Y	
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	
Is there a clear definition of the options under evaluation?	Y	
Have all feasible and practical options been evaluated?	N	The scope requested clopidogrel + ASA to be considered a comparator for this appraisal, which was not included.
Is there justification for the exclusion of feasible options?	Y	
Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Y	
Is the time horizon of the model sufficient to reflect all important differences between options?	Y	
Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and	Y	

Question(s)	*Response (Y, N or NS)*	*Comments*
justified?		
Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	
Is the cycle length defined and justified in terms of the natural history of disease?	Y	
Are the data identification methods transparent and appropriate given the objectives of the model?	Y	
Where choices have been made between data sources, are these justified appropriately?	N	It is unclear why previous technology appraisals are preferred above other alternative sources (e.g. NHS reference prices).
Has particular attention been paid to identifying data for the important parameters in the model?	Y	
Has the quality of the data been assessed appropriately?	Y	
Where expert opinion has been used, are the methods described and justified?	NA	
Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	
Is the choice of baseline data described and justified?	Y	
Are transition probabilities calculated appropriately?	N	The parameterisation of the log-logistic distribution is unusual. It is unclear how this parameterisation was derived and why this deviated from the standard parameterisations
Has a half-cycle correction been applied to both cost and outcome?	Y	
If not, has this omission been justified?	NA	
If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Y	
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	
Have alternative extrapolation assumptions been explored through sensitivity analysis?	Y	

Question(s)	*Response (Y, N or NS)*	*Comments*
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Y	
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	N	
Are the costs incorporated into the model justified?	Partly	Not all assumptions were justified
Has the source for all costs been described?	N	Primary sources were not always described.
Have discount rates been described and justified given the target decision-maker?	Y	
Are the utilities incorporated into the model appropriate?	Y	
Is the source for the utility weights referenced?	Y	
Are the methods of derivation for the utility weights justified?	Y	
Have all data incorporated into the model been described and referenced in sufficient detail?	Y	
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Y	
Is the process of data incorporation transparent?	Y	
If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	Y	
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Y	
Have the four principal types of uncertainty been addressed?	Y	
If not, has the omission of particular forms of uncertainty been justified?	NA	
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Y	

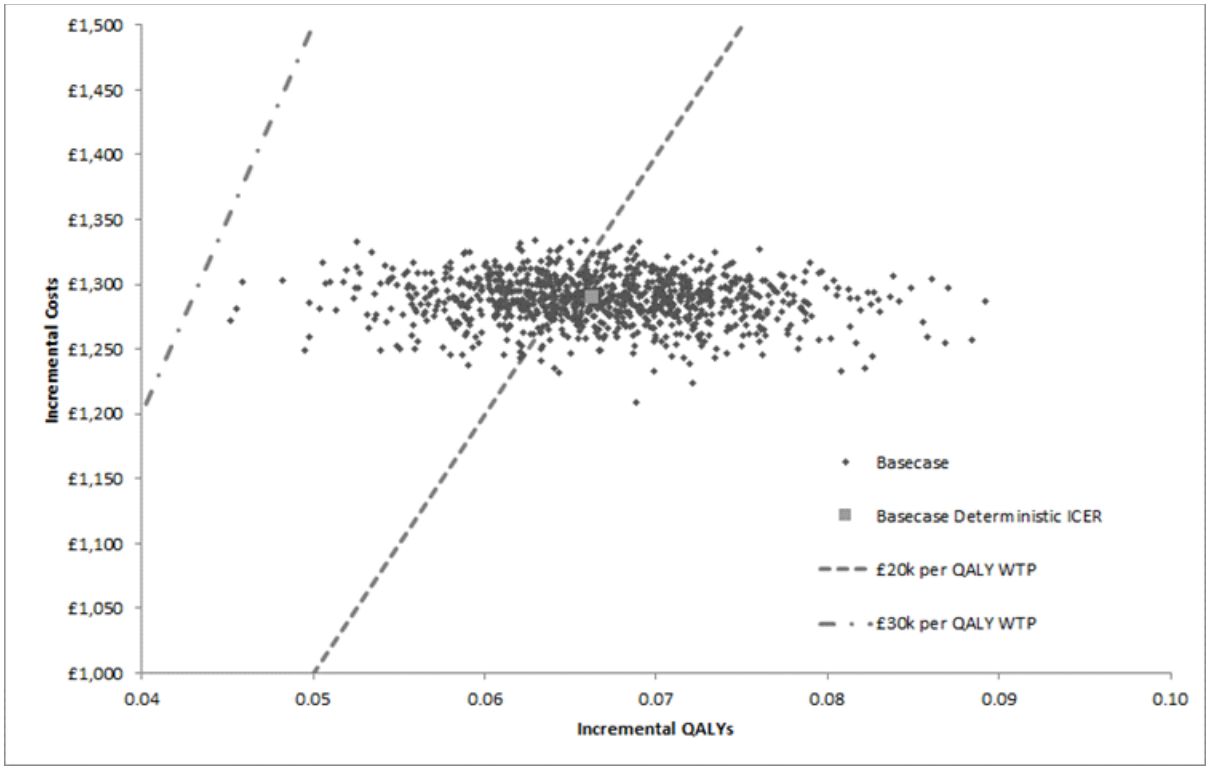
Question(s)	***Response (Y, N or NS)***	***Comments***
Has heterogeneity been dealt with by running the model separately for different subgroups?	Y	
Are the methods of assessment of parameter uncertainty appropriate?	Y	
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	
Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Y	
Are any counterintuitive results from the model explained and justified?	NA	
If the model has been calibrated against independent data, have any differences been explained and justified?	NA	
Have the results of the model been compared with those of previous models and any differences in results explained?	NA	

Appendix 3: Details and deterministic ICER of ERG analyses (for validation purposes)

Item	Adjusted cell(s)	Deterministic ICER
Fixing errors		
Parameterisation Log-logistic models	ASA only P11:S211, V11:V14, X11:X14; Ticagrelor 60 mg + ASA P11:S210, V11:V14, X11:X14	£24,092.91
Fixing violations		
Select cohort simulation (=1 in all ERG analyses)	Control panel G7	
Add Gout	Serious AEs X5	£24,822.83
Alternative distributions for AEs	Bleeds O10, O11; Serious AEs F11, X11	£24,173.43
Adjust Health care costs	Health care costs H28:H31, H39:H42, H91, H96, H110, H112, M28:M31, M39:M42	£24,337.73
Uncertainty of costs in PSA	Health care costs H91, H96, H104, H110, H112	£24,200.13
Matters of judgement		
Alternative disutility major bleeds	HRQoL N46	£24,276.00
Alternative inpatient costs for 'no event' state	Health care costs H120	£24,310.23
ERG base case		£24,940.29
Exploratory sensitivity analyses (conditional on ERG base case)		
Hospitalisation probability for 'no event' state treatment dependent	Ticagrelor 60 mg + ASA BX11:BX210	£25,945.40
Time to fatal other (1st event) treatment dependent	l.tic60.D.LogL EJ152	£24,940.29
TTD because of non-fatal event or after 3years	Ticagrelor 60 mg + ASA U10:U22	£33,738.36
Use of conservative utilities	HRQoL N39:N42, N45, N46	£25,295.04

Appendix 4: Scatterplot and CEAC of the company base-case analysis and tornado diagram of the DSAs

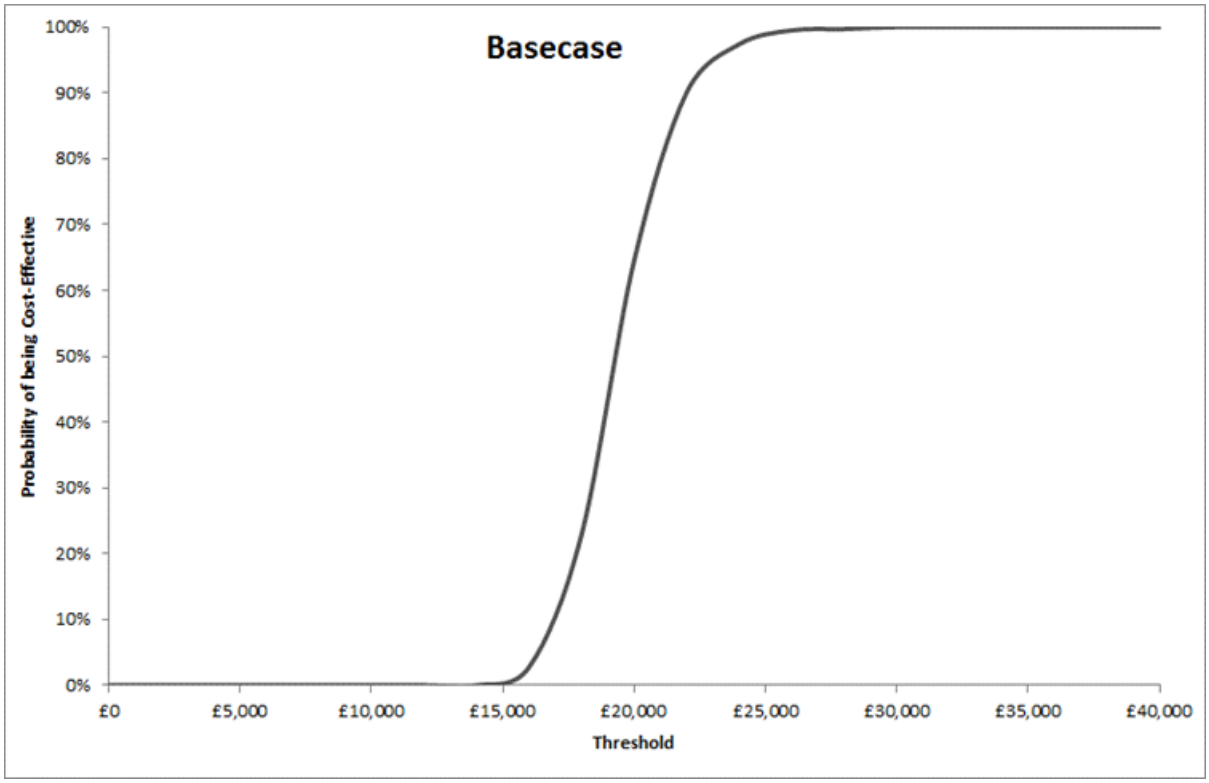
Figure A4.1: Base-case PSA scatterplot



Source: Based on figure 54 of the CS1

CS = company submission; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; WTP = willingness-to-pay

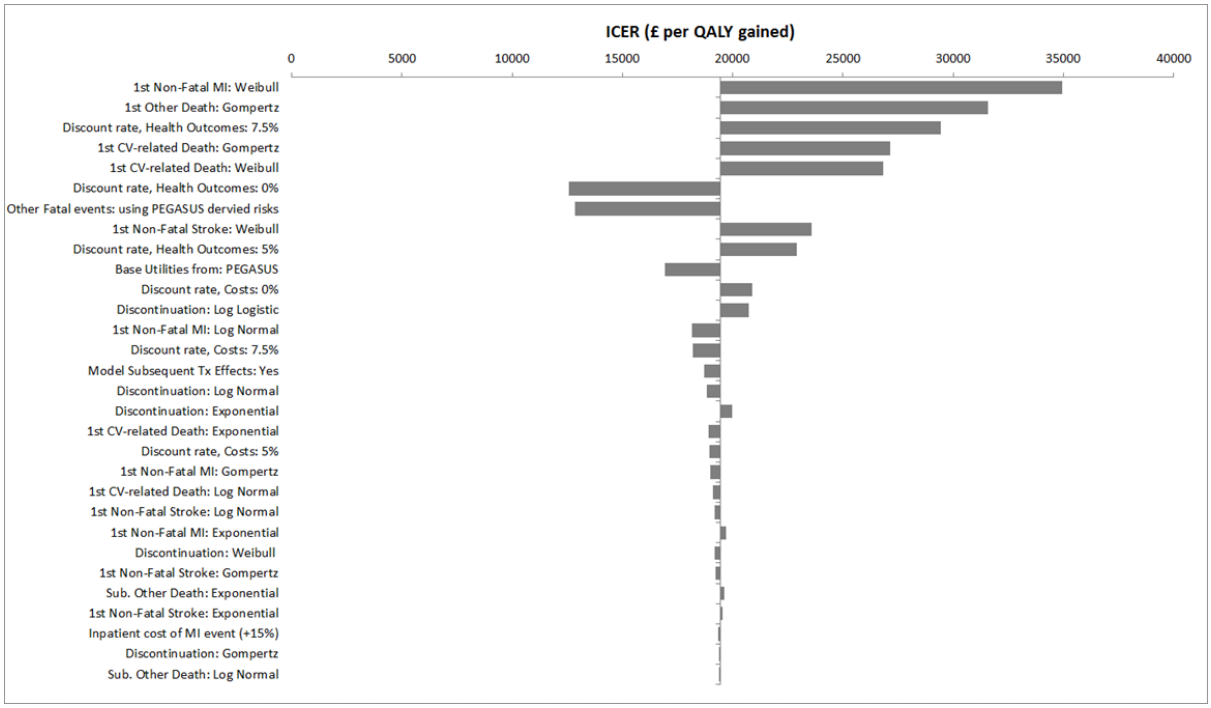
Figure A4.2: Base-case PSA CEAC



Source: Based on figure 55 of the CS1

CS = company submission; CEAC = cost effectiveness acceptability curve; PSA = probabilistic sensitivity analysis

Figure A4.3: DSA for base-case



Source: Based on figure 56 of the CS1

CS = company submission; CV = cardiovascular; DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; MI = myocardial infarction; QALY = quality-adjusted life year

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday, 23 June 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Exclusion of Primary outcome from Table I

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 14. Table I presents the outcomes for the populations defined in the final scope, but omits the primary endpoint of the pivotal trial (PEGASUS-TIMI 54).	Table I should be amended to include the composite of CV death, MI or stroke for the patient populations described.	The primary endpoint of the pivotal clinical trial is relevant to the decision problem and its omission from this table is important.	Not a factual order Table I presents all outcomes defined in the final scope which includes all components of the composite endpoint, i.e. is more informative than the single composite endpoint.

Issue 2 Opinion of UK Clinical Pharmacy Association (UKCPA)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 17 The ERG present advice received from the UKCPA regarding the relevance of the PEGASUS-TIMI 54 study to the UK. "(PEGASUS-TIMI 54) *is not reflective of current UK practice, since we do not actively seek out patients post-event to restart or redefine treatment durations. [...] However, in view of an increasingly aging population (who are increased risk of bleeding) and with co-morbidities that may warrant treatment with anticoagulation, the results of PEGASUS may not be applicable to the general 'real world' population that present with an ACS* [acute coronary syndrome]"	We ask that it is made clear that these comments refer to the overall ITT population in the PEGASUS-TIMI 54 study and that this is in agreement with our position (MI <2 years) which was stated throughout the original submission. E.g. Chapter 1: Executive Summary, Chapter 2.3: Administration and costs of the technology, Chapter 3: Health condition and position of the technology in the treatment pathway, Chapter 4.13: Interpretation of clinical effectiveness and safety evidence. It is also important to note that the misuse of ACS at the end of this statement is likely to lead to confusion and uncertainty and should be corrected accordingly (it is suspected that this was intended to refer to MI patients, rather than	The current wording of this paragraph implies that none of the results from PEGASUS-TIMI 54 are applicable to UK practice. The use of "ACS" at the end of the paragraph is likely to cause confusion given that this study (and appraisal) focusses only on patients with a history of MI.	Not a factual error Text in the ERG is an accurate reproduction of the UKCPA submission.

	ACS patients).		

Issue 3 Description of submitted data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 17 ERG states: "*The primary outcome in PEGASUS-TIMI 54 was time to first occurrence after randomisation of any event from the composite of cardiovascular (CV) death, MI or stroke. However, the CS presented results for the individual components of the composite primary outcome."*	Please correct as follows: *"The primary outcome in PEGASUS-TIMI 54 was time to first occurrence after randomisation of any event from the composite of cardiovascular (CV) death, MI or stroke. However, the CS **also** presented results for the individual components of the composite primary outcome."* Further to this, the results for the primary endpoint are missing in the text on p.17 and should be reported.	This is incorrect since both composite and individual components were provided in the submission (p79-83).	The word "also" was added, as suggested. For presentation of primary endpoint, please see reply to issue 1.

Issue 4 Effect of ticagrelor on STEMI/NSTEMI events

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 17 The ERG states "*It should be noted that in the full analysis set the effect was larger in patients with STEMI (HR: 0.62, 95% CI 0.45 to 0.86) than those with NSTEMI (HR: 0.91, 95% CI 0.76 to 1.09)."* This implies that the effect was in patients who had experienced a STEMI or NSTEMI as the qualifying event (i.e. the MI that occurred 1 – 3 years prior to study entry). In fact it	Please amend this sentence so the meaning is clear. Suggested wording is: *"It should be noted that in the full analysis set the effect was larger **on the outcome of** STEMI (HR: 0.62, 95% CI 0.45 to 0.86) than **on the outcome of** NSTEMI (HR: 0.91, 95% CI 0.76 to 1.09)."*	The current wording is ambiguous and may cause confusion.	Changes were made accordingly.

refers to the effect on subsequent STEMI/NSTEMI events during the course of the study itself.			

Issue 5 Impact of a scenario analysis miscalculated

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 20 It is stated that "*When assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI, the deterministic ICER of the patient simulation* ***increased with*** *approximately* ***£500****"*	This should be amended to read: "*When assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI, the deterministic ICER of the patient simulation* ***decreased by*** *approximately* ***£50****"*	In generating the statement on page 20, the ERG has compared the ICER for the scenario (£20,585) with the company base-case ICER of the original submission (£20,098), rather than the revised company base-case ICER as provided in the response to the clarification questions (£20,636). The inputs to the scenario analysis that generate the ICER of £20,585 are consistent with those of the revised company base-case ICER as provided in the response to the clarification questions, bar the scenario parameter value itself (includes NHS ref costs inpatient costing, AE functional forms selected based on AIC, gout as AE). (It is logical that this scenario would decrease the ICER, as the cost offset associated to averting an MI is being increased)	The ERG agrees that the calculation of the impact of the scenario analysis is incorrect and changed the text on page 20: "When assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI, the deterministic ICER of the patient simulation increased with approximately £500." into: "When assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI, the deterministic ICER of the patient simulation decreased by approximately £50."

Issue 6 Request for amendment to wording (clarification)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 20	We request this be amended to read "*Due to* ***software-associated computational*** *constraints,*	MS Excel is the rate limiter	The ERG agrees that it is more in line with the text

It is stated that "*Due to **time** constraints, the probabilistic sensitivity analysis (PSA) was not based on all 10,779 patients of the 'label population"*	*the probabilistic sensitivity analysis (PSA) was not based on all 10,779 patients of the 'label population"*		of the company submission to state that computational constraints were the reason to base the PSA on a single patient. The text on page 20 ""Due to **time** constraints, the probabilistic sensitivity analysis (PSA) was not based on all 10,779 patients of the 'label population" was changed into: "Due to computational constraints, the probabilistic sensitivity analysis (PSA) was not based on all 10,779 patients of the 'label population"

Issue 7 Inconsistency of the ERG's opinion on the indirect comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 20 (and other areas) There appears to be an inconsistency in	We believe the opinions expressed in the report concerning the evidence supporting our decision to not attempt	The existence of 2 apparently opposing views on the feasibility of	Not a factual error The statement that "any indirect

the ERG's opinion on the appropriateness of attempting an indirect comparison of ticagrelor + ASA with clopidogrel + ASA. On page 12, when considering the decision problem in the CS, the ERG states: "*The ERG agrees with the company that the differences in terms of design and characteristics of included patients between trials … were such that any indirect comparison would have been very difficult to interpret due to substantial heterogeneity between studies*." This opinion is repeated at several points in the report (Section 1.6.2 [p22], Section 3.3 [p35], Section 4.4 [p73] However, on P 20 (and other sections concerning the cost effectiveness evidence), the ERG states "*Clopidogrel + low dose ASA was not included in the model analyses, based on the argument that available evidence did not allow for an indirect comparison. The ERG disagrees with this argument. According to the ERG, the available evidence does allow inclusion of clopidogrel + low dose ASA as a comparator in the model based on an indirect comparison, as long as the assumptions are clearly reported and the uncertainties are propagated."*	an indirect comparison of ticagrelor + ASA with clopidogrel + ASA must be consistent in all sections and propose those expressed in the cost effectiveness sections of the report be aligned with those in the clinical effectiveness sections.	conducting an indirect comparison and/or using the results of such an attempt is likely to cause confusion.	comparison would have been very difficult to interpret due to substantial heterogeneity between studies" highlights the uncertainties surrounding this comparison which, however, is possible in principle. The statements in the cost effectiveness amend the previous statement by highlighting that modelling of results of an indirect comparison would have been possible "as long as the assumptions are clearly reported and the uncertainties are propagated".

Issue 8 Missing reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 25, 31 and others The ERG assert that the reference for the market research of prescribing intentions was not provided, despite a request to supply all missing references.	All references in the report to this should be amended appropriately. The relevant reference has been supplied separately.	We dispute this assertion as our records show that this reference was not included in the list of missing references provided by NICE on 17th May. Thus, this is factually inaccurate.	The company did not provide the relevant reference but is correct that the reference was not requested in the email of 17 May. Therefore, the phrase "despite a request by the ERG to provide all missing references" was removed on page 25. The statement on page 31 is still factually accurate.

Issue 9 Study design for PEGASUS-TIMI 54

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 34 The ERG has stated *"The stipulation that treatment is for up to three years reflects the fact that the PEGASUS-TIMI 54 study, the only study of ticagrelor in the population of interest,* ***treated patients for up to three years****"* This is inaccurate.	Please amend to the following: *"The stipulation that treatment is for up to three years reflects the fact that the PEGASUS-TIMI 54 study, the only study of ticagrelor in the population of interest,* ***had a median follow up of approximately three years****"*	The statement is incorrect. The PEGASUS-TIMI 54 study did not pre-specify a maximum treatment duration. The wording used in the EMA licence reflects the median follow-up in the study which was approximately 3 years.	Changed accordingly.

Issue 10 NICE recommendations for clopidogrel

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 35 The ERG has inaccurately reported the recommendation from NICE concerning the use of clopidogrel beyond 12 months from an MI: "*The latter recommendation indicates that clopidogrel may be used beyond 12 months post-MI in some circumstances."*	We propose this sentence is amended to clarify that this refers to clopidogrel monotherapy. "*The latter recommendation indicates that clopidogrel may be used* ***as a monotherapy option*** *beyond 12 months post-MI in some circumstances* ***instead of aspirin. It should be noted that such use of monotherapy in place of aspirin is out of scope for this appraisal (which considers the addition of a treatment to a background of aspirin****."*	The current wording is inaccurate and may cause confusion. The correction is necessary to ensure readers are aware that this is out of scope when considering the addition of a new treatment on a background of aspirin in this appraisal.	Changes were made accordingly, i.e. the first sentence was changed as suggested while the second sentence suggested by the company is unnecessary.

Issue 11 Selection criteria for systematic literature review

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 39 The ERG states: ''*The criteria relating to study population specifically excluded patients who had received <18 months dual antiplatelet therapy. The choice of 18 months treatment as a cut off appears arbitrary and* ***no justification for this decision was provided by***	We propose this sentence is amended to clarify that the choice of 18 months as a lower limit for treatment duration was justified in response to clarification questions. "*The criteria relating to study population specifically excluded patients who had received <18 months dual antiplatelet therapy. The choice of 18 months treatment as a cut off* ***was justified by the company in response to***	The current wording ignores our explanation and justification for this cut off as described in our response to the ERG's clarification questions. A11: The purpose of the systematic literature review was to compare studies exploring long-term treatment of patients who had experienced an MI at least 1 year ago. The use of a lower limit for treatment duration was employed to help exclude studies	Changes were made accordingly

the company.*"* The underlined section of this sentence is incorrect.	***clarification questions as an attempt to focus on long term use of dual antiplatelets in the relevant patient population***.*"*	investigating short-term treatment which were known to be irrelevant (e.g. PLATO; 12 months, TRITON-TIMI 38; 15 months) and was a pragmatic way of retrieving potentially useful studies which recruited patients immediately following an MI.	

Issue 12 ERG base case approach ignores the non-linearity in the model which stems from heterogeneity in patient baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Economic section (throughout) The ERG has adopted the use of the probabilistic 'average profile-based' cohort simulation to inform the ERG base case. This ignores the non-linearity in the model which stems from heterogeneity in patient baseline characteristics	We request that the ERG adopts the use of the deterministic 'individual profile-based' cohort simulation to inform the ERG base case.	We acknowledge the ERG's statement that NICE guidance advises that "*probabilistic methods provide the best estimates of mean costs and outcomes*".[1] We also recognise that the PSA approach employed in the model was not optimal, in that, owing to software-associated computational constraints, the process undertaken to complete the PSA did not utilise an individual patient simulation methodology (see Issue 6 above). Therefore, the PSA does not reflect the same level of first order uncertainty that would be expected in an individual patient simulation. Were it computationally feasible to implement a PSA with 1,000 or even 100 trials conducted in each of the 10,779 patients within the model we would employ it.	This is a matter of judgment, not a factual inaccuracy. The ERG agrees with the company that, in this case, a PSA on the 'individual profile-based' cohort simulation would have been preferred. However, the PSA of this approach was not correctly implemented by the company. The arbitrary selection of one patient (or eleven in the response to clarification questions) for the PSA leads to a bias in the ICER of unknown direction and magnitude, because this patient (group) may not reflect the average and covariance between relevant characteristics of the population of interest. Therefore, the ERG prefers to use the results from the PSA of the 'average profile-based' cohort simulation in its report.

		However we feel that, by focussing its base case on the probabilistic 'average profile-based' cohort simulation, the ERG may not have fully interpreted the intention that underlies the NICE guidance for the use of probabilistic methods. Broadly, within the current model: By comparing the results of the probabilistic 'average profile-based' cohort simulation with those of the deterministic 'average profile-based' cohort simulation, one is exploring the impact of second order uncertainty associated to parameter values for those parameters described on page 296 of the CS (which, importantly, do not include patient baseline characteristics). The impact of exploring said uncertainties on the ICER is small: Using the ERG base-case, the probabilistic 'average profile-based' cohort simulation yields an ICER of £24,711/QALY as compared with £24,940/QALY for the corresponding deterministic analysis, a difference of £229 in the mean. By comparing the results of the deterministic 'individual profile-based' cohort simulation with those of the deterministic 'average profile-based' cohort simulation, one is exploring the impact of first order patient level heterogeneity. The impact of exploring said uncertainties on the ICER is much greater in this case: As described above, the deterministic 'average profile-based' cohort simulation associated to	

		the ERG base-case yields an ICER of £24,940/QALY, whereas the corresponding deterministic 'individual profile-based' cohort simulation yields an ICER of £20,675/QALY, a difference of £4,265 in the mean. This difference demonstrates that the mean ICER calculated across all relevant patients differs materially from that calculated using only the average value for each baseline characteristic, i.e. that the outputs of the model are non-linear, in respect of heterogeneity present within patient baseline characteristics. The NICE Decision Support Unit technical support document on cost-effectiveness modelling using patient-level simulation advises that: "*If there are factors which vary between patients (e.g. age) which have a non-linear relationship with the model outcomes (e.g. costs and QALYs), then estimating the model outcomes for a cohort of patients using only average characteristics (e.g. mean age at starting treatment) will provide a biased estimate of the average outcome across the population to be*"[2]. As such we feel strongly that by focussing its base case on the probabilistic 'average profile-based' cohort simulation, the ERG is introducing a "known" bias into results, by ignoring the non-linearity in the model associated to heterogeneity in patient baseline characteristics. Or, put another way the ERG is exploring the uncertainty around the wrong	

		mean. As described above we recognise that the current model is not optimal in terms of PSA approach but we have demonstrated above that the uncertainties not explored within the deterministic 'individual profile-based' cohort simulation would not be expected to materially impact the (mean) ICER and therefore it is the deterministic 'individual profile-based' cohort simulation, rather than the probabilistic 'average profile-based' cohort simulation, which yields the more accurate reflection of the underlying ICER.	

Issue 13 Consideration of time-to-discontinuation in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5. The ERG expressed concern about the decision not to adjust the time to discontinuation function for the 'label population' in the cost effectiveness model. As a result, an exploratory analysis assuming	We strongly believe that this exploratory analysis lacks credibility, does not address uncertainty in the decision problem and we request that the ERG removes it from the report.	The concerns of the ERG are addressed in two ways: • By demonstrating that discontinuation in the MI<2 years ago subgroup is similar to that of the full PEGASUS-TIMI 54 population and • By demonstrating that the ERG's exploratory sensitivity analysis leads to drug acquisition costs (and therefore the ICER) being significantly overestimated. **Discontinuations in the MI<2 years ago subgroup is similar to that of the full PEGASUS-TIMI 54 population** In PEGASUS-TIMI 54, the percentage of patients who discontinued in the full population using the full analysis set (from randomisation until common study endpoint) was **31.4%** (ticagrelor 60mg) vs. **23.7%** (placebo) using 36 month KM estimate, as presented in Figure 1. The corresponding percentages in patients with MI <2 years ago were also very similar: **31.0%** (ticagrelor 60mg) vs. **23.8%** (placebo), as presented at Figure 2. Patients who were on study drug when they died were not counted as they premature discontinued, hence not included in	Not a factual inaccuracy. This is an exploratory analysis and should be interpreted as such. Moreover, this analysis was provided as a result of multiple concerns. New data are provided by the company to address

patients would only discontinue oral antiplatelet treatment due to non-fatal events (or the end of the three year treatment period) was conducted.		the discontinuation curve. Based on the Markov trace for the ERG's exploratory sensitivity analysis, the percentages of patients who have discontinued after 36 months are significantly lower: Of 962.6 patients still alive after 36 months in the ticagrelor arm, 46.9 have encountered a non-fatal event and of 958.5 still alive in the placebo arm, 56.8 have encountered a non-fatal event, i.e. discontinuation of **4.9%** (ticagrelor 60mg) vs. **5.9%** (placebo).	one concern (label versus ITT population), but the company did not provide clarity regarding how competing risks (i.e. (non-)fatal events for which treatment discontinuation was assumed) were dealt with in the economic model (see section 5.2.6 of the ERG report).
		Figure 1: Kaplan-Meier plot of cumulative percentage of patients with premature discontinuation of study drug – full PEGASUS-TIMI 54 population	

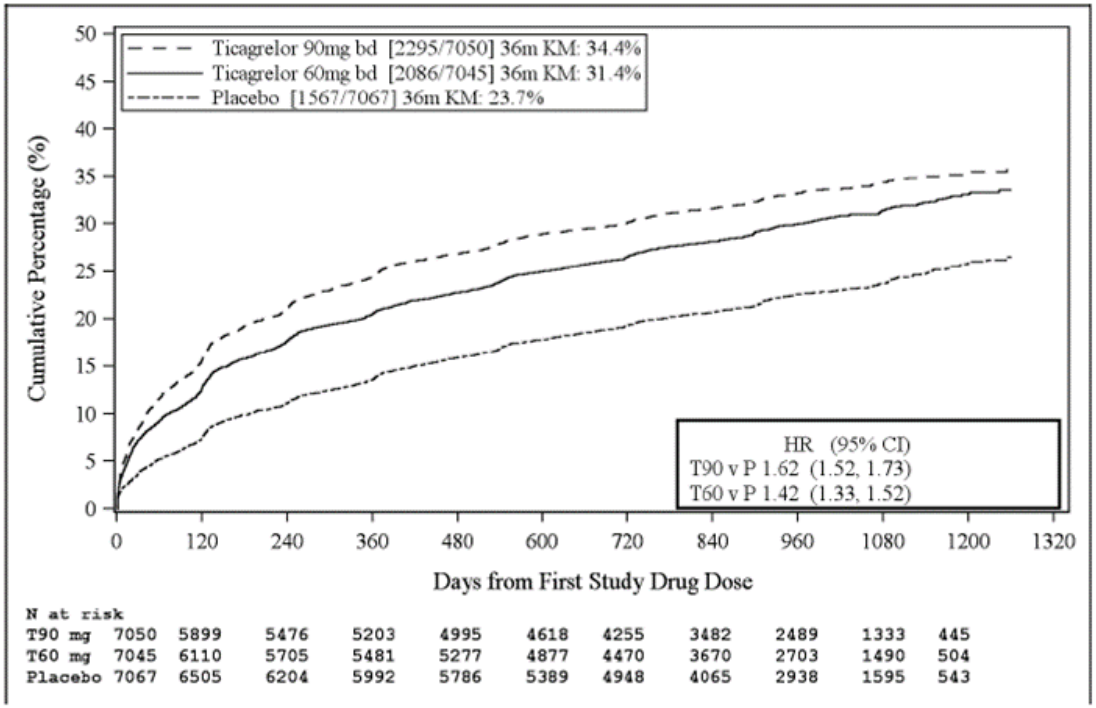
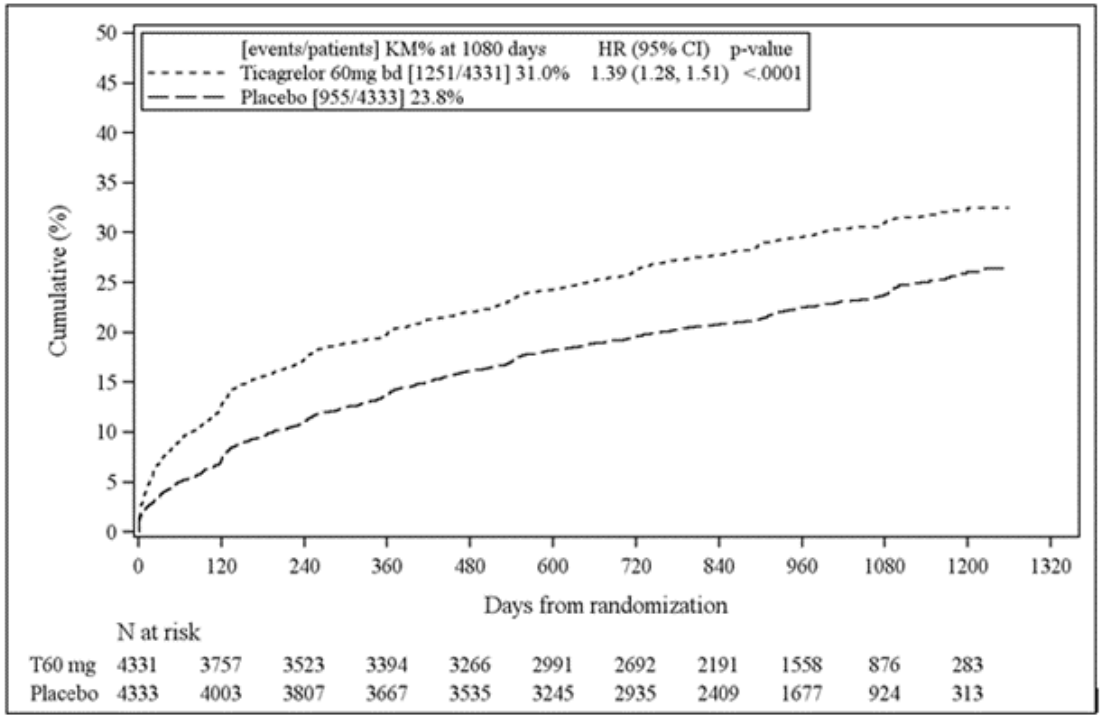

Ticagrelor 90mg bd [2295/7050] 36m KM: 34.4%
Ticagrelor 60mg bd [2086/7045] 36m KM: 31.4%
Placebo [1567/7067] 36m KM: 23.7%
Cumulative Percentage (%)
0
5
10
15
20
25
30
35
40
45
50
HR (95% CI)
T90 v P 1.62 (1.52, 1.73)
T60 v P 1.42 (1.33, 1.52)
0
120
240
360
480
600
720
840
960
1080
1200
1320
Days from First Study Drug Dose
N at risk
T90 mg 7050 5899 5476 5203 4995 4618 4255 3482 2489 1333 445
T60 mg 7045 6110 5705 5481 5277 4877 4470 3670 2703 1490 504
Placebo 7067 6505 6204 5992 5786 5389 4948 4065 2938 1595 543

		Figure 2: Kaplan-Meier plot of cumulative percentage of patients with premature discontinuation of study drug – MI<2 years ago population	



Furthermore, the average duration of study drug exposure for the full population using the full analysis set was **24.98** (ticagrelor 60 mg) vs. **27.06** months (placebo), as presented in the table below. The corresponding exposure durations in patients with MI <2 years ago were very similar: **24.76** (ticagrelor 60mg) vs. **26.65** (placebo) months.

		Ticagrelor 60mg BID	**Placebo**
Full PEGASUS-TIMI 54 population		**N=7045**	**N=7067**
Total duration of exposure (months)	**Mean**	**24.98**	**27.06**
	SD	13.28	11.89
	Median	29.17	30.30

	Total treatment years	14663	15939
Actual duration of exposure (months)	Mean	24.60	26.77
	SD	13.26	11.87
	Median	28.67	30.00
	Total treatment years	14440	15766
MI<2 years ago population		**N=4331**	**N=4333**
Total duration of exposure (months)	**Mean**	**24.76**	**26.66**
	SD	13.09	11.78
	Median	28.57	29.90
	Total treatment years	8938	9626
Actual duration of exposure (months)	Mean	24.41	26.36
	SD	13.07	11.78
	Median	28.23	29.53
	Total treatment years	8809	9518
Total duration of exposure = ((last dose date – first dose date) +1) / 30 Actual duration of exposure = Total duration of exposure, excluding prescribed temporary interruptions.			

The ERG's exploratory analysis overestimates drug costs and ICER

To illustrate that the ERG's exploratory sensitivity analysis leads to drug acquisition costs not in keeping with the trial for patients with MI<2 years ago, we have calculated trial-based drug acquisition costs and compared with the drug acquisition costs in the ERG's exploratory sensitivity analysis and base case models (where the latter follows the manufacturer's approach to modelling discontinuation):

	Ticagrelor		**Placebo**	
Trial-based drug acquisition costs, based on average duration of exposure in PEGASUS-TIMI 54, MI<2 years ago population				
Duration of treatment	24.76 months x 30,4 days	**753 days**	26.65 months * 30,4 days	810 days
Cost of treatment	753 days * £ 1.98	**£1,491**	810 days * £ 0.03	**£24**
Incremental drug acquisition cost		**£1,467**		
Model-based drug acquisition costs, based on ERG's explorative discontinuation analysis - deterministic (3 year time horizon)				

			£1,981		**£30**
Incremental drug acquisition costs			**£1,951**		
Model-based drug acquisition costs, based on ERG's base case - deterministic (3 year time horizon) – consistent with manufacturer's approach to modelling discontinuation					
			£1,497		**£30**
Incremental drug acquisition costs			**£1,467**		

The ERG's exploratory discontinuation analysis significantly underestimated the percentage of patients who discontinue, resulting in incremental drug acquisition costs being overestimated by £484 (33%), leading to the ICER being overestimated by approximately £9,000 vs. the ERG's base case.

Issue 14 The impact of gout on quality of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P 115 (and p 117) The ERG states: "The impact of gout on the quality of life of patients was not incorporated in the company base-case analysis."	We propose this sentence is amended to clarify that this was incorporated into the economic model in response to clarification questions. "The impact of gout on the quality of life of patients was not incorporated in the company base-case analysis **in the original CS, although this was subsequently provided with other corrections in response to clarification questions.**	An amended model was provided in response to the ERG's clarification questions which incorporated this, and other corrections and amendments.	This is not a factual inaccuracy. The sections in the ERG summarising the company's analyses are based on the original company submission. Any additional data or analyses received are considered in the ERG comments. This is the format the ERG used for writing our report. In this case, in the report (ERG comment section 5.2.7) it is acknowledged that gout was considered by the company in response to Clarification Question B10.

Issue 15 Disutility for TIMI major bleed employed in ERG base case has no association with the population or intervention of interest, nor is it clear that it reflects a 'TIMI' major bleed

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr>
<td>Page 117

Disutility for TIMI major bleed employed in ERG base case has no association with the population or intervention of interest, nor is it clear that it reflects a 'TIMI' major bleed.</td>
<td>ERG base case should use a value of [redacted] for the disutility of a TIMI major bleed (see justification)</td>
<td>In response to the ERG challenge on disutility (/ QALY loss) associated with a TIMI major bleed, we have explored this with an additional set of analyses. Using the original random effects panel data model that was applied in the economic model, the time period before EQ-5D collection in which TIMI major bleeding events were associated with a change in utility was adjusted from the original 91 days period (one model cycle) to a 182 days (two model cycles). Extending the duration of time between data EQ-5D data collection and TIMI major bleed occurrence beyond 182 days is complicated by the fact that these data were collected at 6 month intervals.

The utility decrement associated to a TIMI major bleed (while controlling for the original baseline characteristics and events) was statistically significant, but had a much smaller magnitude compared to the utility decrement generated using the shorter timeframe. The results of this can be seen in the table below.

Duration and magnitude of disutility associated with TIMI major bleeds
<table>
<tr><th></th><th>Coeff.</th><th>Std Err.</th><th>Z-score</th><th>95% CI Lower</th><th>95% CI Upper</th></tr>
<tr><td>91 days (original)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>182 days</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
While there is evidence of a longer duration of disutility associated with the occurrence of a TIMI major bleed, incorporating this into the economic model will have a negligible impact vs. the company base case as disutility attributable to two model cycles is just over half of the utility decrement associated with one model cycle.

Furthermore we would comment that the disutility for a TIMI major bleed</td>
<td>Not a factual inaccuracy.

This is a matter of judgement; given the uncertainty around the utility decrement of major TIMI bleeds and since the long-term impact of bleeds was neglected in the model the ERG preferred a more conservative approach (see section 5.2.8 of the ERG report).</td>
</tr>
</table>

		within the company's model has been derived directly from the trial concerned with the population and intervention of interest. The same cannot be said for the disutility used in the ERG's base case, whereby the disutility has been derived from a study of coxibs and NSAIDs in patients with ankylosing spondylitis and a study of anticoagulation in haemodialysis patients with atrial fibrillation. Furthermore, definitions of major bleed vary and it is not clear that the disutility used in the ERG's base case is consistent with a 'TIMI' major bleed. Should the ERG wish to use an alternative disutility for a TIMI major bleed to that of the company's base case, we would recommend using [redacted], which reflects the disutility over 182 days, adjusted for cycle length [redacted] x 2) and has been derived via the trial concerned with the population and the intervention of interest, based on the occurrence of 'TIMI' major bleeding events.	

Issue 16 Reporting of base-case model outputs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 5.37, Table 6.1 The ERG provides several tables comparing the results of the original model described in the submission, the updated model provided in response to clarification questions and their own base-case. The values of QALYs and costs in some of these tables have been incorrectly transcribed from the tables provided. For example, in Table 5.37, the QALYs for the TICA 60 + ASA treatment arm in the company base-case are reported as £15,689, the Costs as 13.5361 and the incremental Costs as 0.0592.	We propose these (and other) tables are amended to correctly report Costs and QALYs with appropriate units.	The accurate reporting of the results of the economic model is important in ensuring clarity and accuracy.	Table 5.37 and Table 6.1 have been corrected.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

- Erratum -

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check. It should be noted that none of these changes affect the overall conclusions of the ERG report.

The table below lists the page to be replaced in the original document and the nature of the change.

Page	Change
17	In response to item 3 of the factual inaccuracy check, the word "also" was added.
17	In response to item 4, wording was amended: "It should be noted that in the full analysis set the effect was larger on the outcome of STEMI (HR: 0.62, 95% CI 0.45 to 0.86) than on the outcome of NSTEMI (HR: 0.91, 95% CI 0.76 to 1.09)."
17	In response to item 17, relevant bits have been highlighted as commercially or academically in confidence, respectively.
18	In response to item 17, relevant bits have been highlighted as commercially or academically in confidence, respectively.
20	In response to item 6, wording was amended: "Due to computational constraints, the probabilistic sensitivity analysis (PSA) was not based on all 10,779 patients of the 'label population'".
20	In response to item 5, wording was changed to: "When assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI, the deterministic ICER of the patient simulation decreased by approximately £50."
25	In response to item 8, the phrase "despite a request by the ERG to provide all missing references" was removed.
34	In response to item 9, wording was changed to: "The stipulation that treatment is for up to three years reflects the fact that the PEGASUS-TIMI 54 study, the only study of ticagrelor in the population of interest, had a median follow up of approximately three years".
35	In response to item 10, wording was amended: "The latter recommendation indicates that clopidogrel may be used as a monotherapy option beyond 12 months post-MI in some circumstances instead of aspirin."
39	In response to item 11, wording was amended: "The criteria relating to study population specifically excluded patients who had received <18 months dual antiplatelet therapy. The choice of 18 months treatment as a cut off was justified by the company in response to clarification questions as an attempt to focus on long term use of dual antiplatelets in the relevant patient population."
143	In response to item 16, values in table 5.37 have been corrected.
147	In response to item 16, values in table 6.1 have been corrected.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and additional searches of clinical trials registers and conference proceedings were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal.

The number of reviewers who assessed studies for inclusion in the review was unclear. The text of the CS implies that one reviewer assessed titles and abstracts in the first pass and that studies identified for inclusion at the second pass were checked by a second reviewer. The use of only one reviewer for screening of titles and abstracts would not be considered best practice and increases the risk of relevant studies being missed. Furthermore, if only the included studies were checked in the second pass by a second reviewer then relevant studies could have been excluded by a single reviewer. Similarly, details on how data extraction and quality assessment were conducted are lacking. The ERG agrees with the CS that PEGASUS-TIMI 54 has low risk of bias.

Patients included in the PEGASUS-TIMI 54 trial might not be reflective of the population in the United Kingdom (UK). According to the UK Clinical Pharmacy Association, the trial "*is not reflective of current UK practice, since we do not actively seek out patients post-event to restart or redefine treatment durations. The other factors specified in the inclusion criteria could be used to define "high risk" patients; ≥ 65 years, diabetes requiring medication, second prior spontaneous MI, multivessel disease and chronic renal dysfunction. However, in view of an increasingly aging population (who are increased risk of bleeding) and with co-morbidities that may warrant treatment with anticoagulation, the results of PEGASUS may not be applicable to the general 'real world' population that present with an ACS* [acute coronary syndrome]*"*.

The primary outcome in PEGASUS-TIMI 54 was time to first occurrence after randomisation of any event from the composite of cardiovascular (CV) death, MI or stroke. However, the CS also presented results for the individual components of the composite primary outcome. In principle the individual component end points may lack sufficient power, however given the number of patients enrolled in the study it is likely that any clinically meaningful differences would be detected.

The results of PEGASUS-TIMI 54 showed that ticagrelor 60 mg BID reduced the risk of MI in both the full analysis set (HR: 0.84, 95% CI 0.72 and 0.98) and in the relevant subgroup of patients with MI <2 years ago ([redacted]). It should be noted that in the full analysis set the effect was larger on the outcome of STEMI (HR: 0.62, 95% CI 0.45 to 0.86) than on the outcome of NSTEMI (HR: 0.91, 95% CI 0.76 to 1.09). In patients with MI <2 years ago ticagrelor 60 mg BID reduced the risk of MI more in patients without diabetes (HR: 0.72, 95% CI 0.55 to 0.92) than in patients with diabetes (HR: 0.96, 95% CI 0.70 to 1.32). In patients with MI <2 years ago ticagrelor 60 mg BID reduced the risk of MI to a similar degree in patients with PCI [redacted] or without PCI (HR: 0.82, 95% CI 0.51 to 1.31).

Ticagrelor 60 mg BID reduced the risk of stroke to a similar degree in the PEGASUS-TIMI 54 full analysis set (HR: 0.75, 95% CI 0.57 to 0.98) and in the subgroup of patients with MI <2 years ago [redacted] As in the analysis of MI there was a difference in the effect of ticagrelor 60 mg BID on the risk of stroke between patients with or without diabetes however the difference was reversed compared to the analysis of MI. In patients who had MI <2 years ago ticagrelor 60 mg BID reduced the risk of stroke by more in patients with diabetes (HR: 0.59, 95% CI

0.34 to 1.02) than in patients without diabetes (HR: 0.81, 95% CI 0.52 to 1.25). In patients who had MI <2 years ago ticagrelor 60 mg BID reduced the risk of stroke more in patients without a history of PCI (HR: 0.51, 95% CI 0.26 to 1.00) than in those with a history of PCI (HR: 0.81, 95% CI 0.55 to 1.21).

Treatment with ticagrelor 60 mg BID was associated with an increase in the risk of TIMI defined major bleeds compared to placebo. This increase was smaller in patients with MI <2 years ago (HR: 1.50, 95% 1.06 to 2.11) than in the full analysis set (HR: 1.78, 95% CI 0.35 to 2.35). Among patients with MI <2 years ago those with diabetes had a greater increase in the risk of TIMI major bleeds (HR: 3.32, 95% CI 1.51 to 7.31) than those without diabetes (HR: 1.69, 95% CI 1.07 to 2.68). Similarly, patients with a history of PCI had a greater increase in the risk of bleeding (HR: 2.17, 95% CI 1.41 to 3.34) than those without a history of PCI (HR: 1.55, 95% CI 0.59 to 4.06).

There were no statistically significant differences in the risk of intracranial haemorrhage between patients receiving ticagrelor 60 mg BID and those receiving placebo in either the full analysis set or the subgroup of patients with MI < 2 years ago. In both populations the difference between treatment arms amounted to two events. There was an increase in the risk of other major bleeds for patients receiving ticagrelor 60 mg BID in both the full analysis set (HR: 2.53, 95% CI 1.74 to 3.66) and in patients with MI < 2 years ago (HR: 2.19, 95% CI 1.39 to 3.46). The risk of TIMI major or minor bleeds was also increased for patients receiving ticagrelor 60 mg BID in the full analysis set (HR: 1.91, 95% CI 1.51 to 2.42) and in patients with MI < 2 years ago (HR: 1.73 95% CI 1.30 to 2.30).

Ticagrelor 60 mg BID reduced the risk of cardiovascular death to a greater degree in patients with MI <2 years ago [redacted] than in the full analysis set (HR: 0.83, 95% CI 0.68 to 1.01). Within the group of patients with MI <2 years ago the results were similar for patients with or without diabetes and for patients with or without a history of PCI. Ticagrelor 60 mg BID also reduced the risk of all-cause mortality both in patients with MI < 2 years ago [redacted] and in the full analysis set (HR: 0.89, 95% CI 0.76 to 1.04).

Patients receiving ticagrelor 60 mg BID had an increased risk of any serious adverse event compared to placebo both in the full analysis set (HR: 2.08, 95% CI 1.07 to 4.02) and in patients with an MI <2 years ago (HR: 2.71, 95% CI 1.14 to 6.46). The risk of events leading to discontinuation of the study drug was also increased in patients receiving ticagrelor 60 mg BID compared to placebo both in the full analysis set (HR: 5.95, 95% CI 4.42 to 8.01) and in patients with MI <2 years ago (HR: 6.18, 95% CI 4.17 to 9.15).

It should be noted that the results from PEGASUS-TIMI 54 are based on small numbers of events for each outcome compared to the total number of patients in each arm and should therefore be interpreted with a degree of caution.

The annual number of incident continuation therapy ticagrelor 60 mg-eligible patients is likely to be higher than estimated by the company as the underlying figures only included England, i.e. did not include Wales.

1.4 Summary of cost effectiveness submitted evidence by the company

The company conducted systematic reviews to identify relevant cost effectiveness studies, health-related quality of life studies and resource use and costs studies. The company did not identify any

The company considered cost data from the ERG assessment of technology appraisal (TA) 317 (inflated to 2015 values) as appropriate for the current decision problem. These costs were supplemented by the ERG assessment report of TA210 and NHS references costs when unit costs were not available from TA317.

The company analysed the model both with an individual patient simulation and a cohort simulation. In the cohort simulation, a cohort of identical patients goes through the model, with risk equations applied to the 'average patient'. In the individual patient simulation, all patients in the 'label population' (n=10,779) go through the model one at a time, hence risk equations are applied to each patient individually.

Ticagrelor 60 mg BID + low dose ASA compared to low dose ASA was associated with a deterministic ICER of £20,098 in the individual patient simulation. The deterministic incremental cost effectiveness ratio (ICER) of the cohort simulation was £24,070. According to the company, the cohort simulation overestimated the results as a result of non-linearity in the model.

Due to computational constraints, the probabilistic sensitivity analysis (PSA) was not based on all 10,779 patients of the 'label population'. Instead a single patient was simulated. This patient had a profile that produces an ICER which was the closest to the mean expected ICER of the individual patient simulation. The cost effectiveness acceptability curve (CEAC) shows that ticagrelor 60 mg BID + ASA has a 64.6% and a 100% probability of being cost effective at £20,000 and £30,000 per QALY gained thresholds, respectively.

Deterministic sensitivity analyses showed that the most influential parameters were the choice of the distribution to extrapolate the risk of a first non-fatal MI and non-cardiovascular disease (CVD) death beyond the trial time horizon.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The structure of the de novo model included some simplifications that potentially influence health outcomes and costs: non-explicit modelling of subsequent events and adverse events (and hence only taking into account costs and disutility for the duration of one cycle), not including gout as an adverse event, and not distinguishing between non-fatal disabling and non-disabling stroke. In response to the ERG's request, the company provided a model with gout included as an adverse event. This amendment was used in the ERG's base-case.

In clinical practice, patients who experience a subsequent non-fatal event would probably receive ticagrelor 90 mg BID + low dose ASA for 12 months, followed by ticagrelor 60 mg BID + low dose ASA for 36 months. This was not included in the economic model. Upon request, the company provided a scenario analysis assuming ticagrelor 60 mg BID is given for remaining lifetime from 12 months following a myocardial infarction. This led to an increase of the deterministic ICER of the patient simulation of approximately £100. When assuming ticagrelor 90 mg treatment, 1-12 months after a subsequent MI, the deterministic ICER of the patient simulation decreased by approximately £50.

Clopidogrel + low dose ASA was not included in the model analyses, based on the argument that available evidence did not allow for an indirect comparison. The ERG disagrees with this argument. According to the ERG, the available evidence does allow inclusion of clopidogrel + low dose ASA as a comparator in the model based on an indirect comparison, as long as the assumptions are clearly

cumulative risk for MI, stroke or death across the countries were found (between 17.9% in France and 36.2% in US). After adjustments however, the differences in risk of MI/stroke/death across all four countries was reduced (between 16.7% in France and 21.3% in England)".[2] The observed and adjusted cumulative three year risk of MI, stroke or death reported based on 7,238 patients in England were 24.1% (95% confidence interval (CI) 22.7-25.5) and 21.3% (95% CI 18.2-24.2), respectively.[2]

The company estimated the number of patients who would be eligible for treatment with 60 mg ticagrelor twice daily (BID) as follows: *"The number of hospital admissions for 'actual myocardial infarction' (ICD10 [*10th revision of the International Statistical Classification of Diseases and Related Health Problems] *code; I21) in England in the year 2014/15 was 78,397.*[8] *Each is assumed to represent one patient. Of these patients, 90% are assumed to receive aspirin-based DAPT [*dual antiplatelet therapy] *in the first year following MI.*[9] *Of the resultant cohort, 67% are expected to remain CV [*cardiovascular] *event-free over the next year.*[2] *For the purposes of the budget impact analysis, it is assumed that all of these patients remain on DAPT for the year following MI. Of these patients, 59% are expected to meet the PEGASUS-TIMI 54 inclusion criteria and not meet the exclusion criteria.*[2] *This yields the estimate for the annual number of incident continuation therapy ticagrelor 60 mg-eligible patients to be 27,887".*

ERG comment: The description of acute coronary syndrome was based on the American College of Cardiology/American Heart Association guidelines on the management of patients with unstable angina/ Non-ST segment elevation myocardial infarction (NSTEMI).[2] The definition of MI is based on the universal definition of MI developed by joint task force of the European Society for Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA) and the World Heart Federation (WHF).[10]

The reference on the time to a second MI event from the Swedish Acute Myocardial Infarction statistics was checked and found to be correctly cited and accurately reported.[6] The paper supporting the statement that 24% of recurrent MIs occur within the first year and 29% occurred in years 2-4 was checked and found to report the results of a single study of 307 patients.[7] It was not clear from the publication when or where these patients were recruited and according to what criteria. The authors of the study which was published in 2002 were affiliated to Spanish hospitals. Therefore, one might assume that the study was conducted in Spain 15-20 years ago. As a result it is unclear whether the results of this study are applicable to 2016 and patients in the United Kingdom (UK).

The CS stated that 140,880 patients were included in the analysis however the underlying reference reported results based on 140,887 patients.[2] The reason for this discrepancy was unclear however given the large number of patients involved this is unlikely to substantially alter the estimated risk of MI, stroke or death.

The reference for the number of hospital admissions for acute myocardial infarction was checked and found to be accurate.[8] The reference to support the assumption that 90% of patients will receive aspirin-based DAPT in the first year following MI was not provided. The data reported by the APOLLO program showed that in England 41% of 7,238 patients were prescribed DAPT at one year post-MI.[2] The reference provided by the company did not report sufficient detail to evaluate the assumption that 67% of patients in England receiving DAPT would remain CV event free for one year or that 59% of those patients would meet the inclusion criteria for PEGASUS-TIMI 54.

3.1 Population

The patient population described in the final scope is *"Adults who have had a myocardial infarction and are at increased risk of atherothrombotic events"*.[17]

The definition of the patient population addressed in the CS is *"Adults who have had a myocardial infarction between 1 and 2 years ago and are at increased risk of atherothrombotic events"*.[1]

ERG comment: The patient population addressed in the CS is based on the PEGASUS-TIMI 54 trial. The overall population in this study was patients who had experienced a prior MI between one and three years ago who also had ≥1 additional atherothrombosis risk factor.[18] The patient population addressed in the CS is a subpopulation of the overall study population who had experienced a prior MI between one and two years ago who also had ≥1 additional atherothrombotic risk factor.

This subpopulation excludes patients who had an MI <1 year ago which is in line with the licensed indication which states that patients must have a history of MI of at least one year to be eligible for treatment with ticagrelor 60 mg BID.[19]

The patient population addressed in the CS also excludes those patients who had an MI between two and three years ago. The licensed indication for ticagrelor 60 mg BID states that treatment may be initiated up to two years following an MI or within one year after stopping treatment with a previous ADP receptor inhibitor.[19] In principle patients who had been treated with an ADP receptor inhibitor for the first two years following their MI would be eligible for treatment, i.e. up to three years from the initial MI. The company acknowledged this in the CS but argued that there were relatively few patients that meet these criteria in practice. Given that there are few ADP inhibitors licensed for use beyond 12 months following an MI and that most patients receive ASA monotherapy after the first 12 months the ERG agrees with the company that the subgroup specified is the CS represents the most relevant available evidence for the population requested in the final scope.

3.2 Intervention

The intervention in the CS is "*ticagrelor 60 mg BID co-administered with aspirin for up to 3 years*".[1] This is in line with the scope which specified "*ticagrelor co-administered with aspirin*".[17]

ERG comment: According to the CS, the recommended dose of ticagrelor specified in the license is 60 mg twice daily co-administered with aspirin.[1] The stipulation that treatment is for up to three years reflects the fact that the PEGASUS-TIMI 54 study, the only study of ticagrelor in the population of interest, had a median follow-up of approximately three years.[20]

3.3 Comparators

The comparators in the scope issued by NICE were aspirin monotherapy or clopidogrel in combination with aspirin.[17]

The CS only included aspirin monotherapy as a comparator.[1] The company argued that clopidogrel in combination with aspirin does not have a licensed indication in the population of interest as it is not established as clinical practice in the NHS. The company further argued that there is no evidence to support the comparison of ticagrelor plus aspirin versus clopidogrel plus aspirin as there is no head to head trial comparing these treatments and an indirect comparison was not possible.

ERG comment: The clinical indications for clopidogrel are described in the summary of product characteristics (SmPC)[21] as:

- *"Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.*

- *Patients suffering from acute coronary syndrome:*
    - *Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).*
    - *ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy."*

The population of patients with ACS includes those who have experienced an MI. The trials which supported the licensed indication of clopidogrel continued treatment for up to 12 months in these patients.[21] NICE recommends clopidogrel as a treatment option for up to 12 months in patients who have had NSTEMI or in patients who have had STEMI and received a bare metal or drug eluting stent. Clopidogrel is also recommended by NICE as a treatment option instead of aspirin in patients who have other cardiovascular disease and have either: had an MI and stopped dual antiplatelet therapy, or had an MI more than 12 months ago.[12] The latter recommendation indicates that clopidogrel may be used as a monotherapy option beyond 12 months post-MI in some circumstances instead of aspirin. This is supported by the submission from the UK Clinical Pharmacy association (UKCPA) which indicates that the duration of treatment may be extended on a case-by-case basis.[22]

The ERG agrees with the company that the differences between trials of ticagrelor plus aspirin versus placebo plus aspirin and trials of clopidogrel plus aspirin versus placebo plus aspirin were such that an indirect comparison was not feasible.

These differences are discussed in more detail in Section 4.4.

3.4 Outcomes

The outcomes reported in the CS[1] are in line with the outcomes listed in the scope specified by NICE.[17]

3.5 Other relevant factors

No other relevant factors were identified.

rivaroxaban each given in combination with aspirin. The included comparators were placebo, monotherapy or triple therapy. The CS did not specify which treatments were eligible as monotherapy or triple therapy.

The criteria relating to study population specifically excluded patients who had received <18 months dual antiplatelet therapy. The choice of 18 months treatment as a cut off was justified by the company in response to clarification questions as an attempt to focus on long term use of dual antiplatelets in the relevant patient population.

The number of reviewers who assessed studies for inclusion in the review was unclear. The text of the CS implies that one reviewer assessed titles an abstracts in the first pass and that studies identified for inclusion at the second pass were checked by a second reviewer. Only using one reviewer for screening of titles and abstracts would not be considered best practice[30] and increases the risk of relevant studies being missed.

4.1.3 Critique of data extraction

The company states that "*data extraction Table (DET) in Microsoft Excel file was developed and pilot tested for possible data extraction of eligible RCTs on prolonged (at least 18 months) dual anti-platelet therapy involving aspirin, ticagrelor, clopidogrel, vorapaxar, prasugrel or rivaroxaban*".[1]

ERG comment: The company did not specify which data were extracted or how many reviewers were involved in the data extraction process. The CS did not report sufficient information to determine whether the extracted data were assessed for accuracy.[1]

4.1.4 Quality assessment

The CS reported the assessment of methodological quality using the Cochrane risk of bias tool in the studies identified in the systematic review.[1]

ERG comment: The company did not report the number of reviewers involved in the assessment of risk of bias. The use of only one reviewer to conduct the quality assessment would not be considered best practice[30] and increases the risk of inappropriate assessment.

4.1.5 Evidence synthesis

The company did not report details of the methods of evidence synthesis for either direct or indirect comparisons.

ERG comment: The systematic review reported in the CS identified only one study directly comparing ticagrelor plus aspirin to any of the included comparators therefore no formal meta-analysis was possible.[1] The details of this study are discussed in Section 4.2

The company assessed the similarity of the three studies identified by the systematic review for potential inclusion in a network meta-analysis but concluded that the studies were not comparable therefore no methods for network meta-analysis were reported.[1] The study design and patient characteristics in these trials are discussed in Section 4.3.

Table 5.137: Deterministic company base-case and probabilistic ERG base-case – results of the cohort simulation

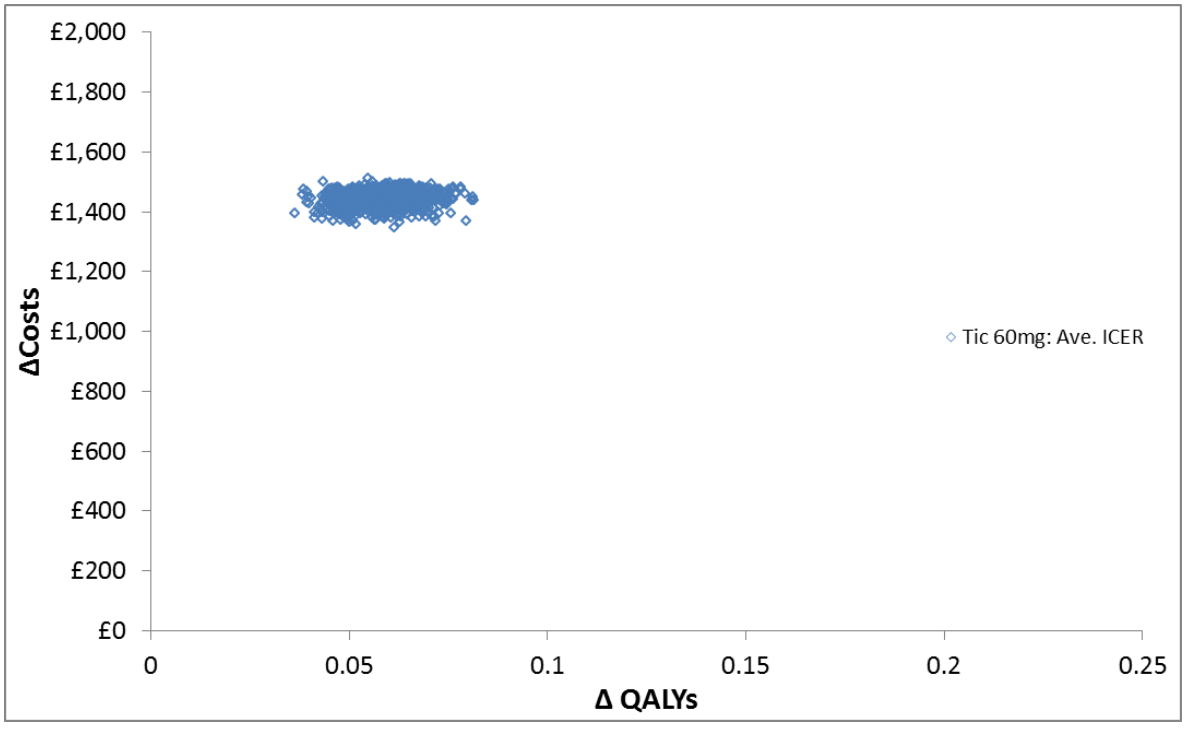
	Ticagrelor 60 mg BID + low-dose ASA		Low dose ASA				
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
Company base-case	9,854	£15,689	9.794	£14,264	0.059	£1,425	£24,070*
ERG base-case	9.768	£14,113	9.709	£12,674	0.058	£1,439	£24,711

Footnote: * The ICER reported in the CS for the cohort analysis was £24,378 (deterministic results)
ASA= acetylsalicylic acid; BID= twice per day; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

5.3.1 Probabilistic sensitivity analyses (ERG base-case)

A PSA was performed to capture the parameter uncertainty in the ICER. The scatterplot and CEAC of this analysis are presented in Figures 5.4 and 5.5 respectively. Ticagrelor 60 mg BID + low-dose ASA has a 3.9% and 91.9% probability of being cost effective at the £20,000 and £30,000 thresholds respectively, based on the ERG base-case analysis.

Figure 5.14: Cost effectiveness plane for ticagrelor 60 mg BID + low dose ASA vs low dose ASA (QALYs; ERG base case)



ASA= acetylsalicylic acid; BID= twice per day; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; mg = milligram; QALY = quality-adjusted life year

Table 6.21: ERG base-case, incorporating corrections and amendments identified by the ERG – probabilistic results of the cohort simulation

	Ticagrelor 60 mg BID + low-dose ASA		Low-dose ASA				
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔQALY**	**ΔCosts**	**ICER**
Company base-case (deterministic, cohort analysis)	9,854	£15,689	9.794	£14,264	0.059	£1,425	£24,070[#]
Company base-case[*]	9.846	£15,686	9.787	£14,262	0.059	£1,425	£24,072
1. Correction of the log-logistic parameterisation	9.771	£15,749	9.711	£14,326	0.060	£1,424	£23,826
2. Include gout	9.846	£15,745	9.788	£14,314	0.058	£1,431	£24,639
3. AEs distributions choice based on AIC	9.832	£15,683	9.773	£14,259	0.059	£1,424	£23,983
4. Adjusted health care costs	9.847	£15,721	9.788	£14,288	0.059	£1,433	£24,108
5. Include uncertainty around NHS costs in PSA	9.849	£15,687	9.789	£14,263	0.059	£1,424	£24,022
6. Alternative disutility for major bleeds	9.851	£15,688	9.792	£14,264	0.059	£1,424	£24,231
7. Alternative inpatient costs for the 'no event' health state	9.850	£13,973	9.791	£12,543	0.059	£1,431	£24,193
ERG base-case	9.768	£14,113	9.709	£12,674	0.058	£1,439.10	£24,711

Footnotes: [*] Reproduced by the ERG; [#] The ICER reported in the CS for the cohort analysis was £24,378 (deterministic results)

AE = adverse event; AIC= Akaike Information Criterion; BID= twice per day; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; mg = milligram; NHS= National Health Service; PSA= probabilistic sensitivity analysis; QALY = quality-adjusted life year