Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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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

Abdullah Pandor critiqued the clinical effectiveness data reported by the manufacturer. Daniel Pollard and Matt Stevenson critiqued the mathematical model provided and the cost-effectiveness analyses submitted by the manufacturer. Anna Cantrell undertook the literature searches run by the ERG.

Tim Chico and Robert Henderson provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final document.

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Abbreviations

ADP	adenosine diphosphate
ACS	acute coronary syndrome
CABG	coronary artery bypass graft
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CV	cardiovascular
ECG	electrocardiogram
EMA	European Medicines Agency
ERG	Evidence Review Group
ESC	European Society of Cardiology
GRACE	Global Registry of Acute Coronary Events
HR	hazard ratio
HRQoL	health-related quality of life
HS/ICH	haemorrhagic stroke or intracranial haemorrhage
ICER	incremental cost-effectiveness ratio
IS	ischaemic stroke
ITT	intention-to-treat
LY	Life Years
MI	myocardial infraction
MINAP	Myocardial Ischaemia National Audit Project
MS	Manufacturer's Submission
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NMB	net monetary benefit
NSTEMI	non-ST segment elevation myocardial infarction
PASS	post-authorisation safety study
PCI	percutaneous coronary intervention
PSA	probabilistic sensitivity analyses
PSS	Personal Social Services
QALY	quality adjusted life years
RCT	randomised controlled trial
STA	Single Technology Appraisal
STEMI	ST-segment elevation myocardial infarction
TIA	transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
UA	unstable angina

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The population considered within the manufacturer's submission (MS) is defined in accordance with the licensed indication as 'adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers' (i.e. ST segment elevation myocardial infarction [STEMI] and non-ST segment elevation myocardial infarction [NSTEMI]). The Evidence Review Group (ERG) notes that since completion of the ATLAS ACS 2-TIMI 51 trial in 2011 (the main evidence source), sensitivity of biomarker assays has increased. As a result, biomarker negative patients in the reported studies might now be biomarker positive using current more sensitive assays. In accordance with the scope the MS defines the intervention as rivaroxaban in combination with aspirin alone or with aspirin and a thienopyridine (clopidogrel). The MS considered clopidogrel with aspirin or aspirin alone for people for whom clopidogrel is considered unsuitable as the most relevant comparator, as reflected in the scope. Other dual antiplatelet regimens such as aspirin in combination with ticagrelor or prasugrel, which are recommended in NICE guidelines (Clinical Guideline 167 and 172 and Technology Appraisal Guidance 236 and 317) for the acute and maintenance phases of ACS, were absent from the scope. The outcome measures identified in the scope: death from any cause; non-fatal cardiovascular events; incidence of revascularisation procedures; adverse effects; and health related quality of life (HRQoL) were included. Additional relevant outcomes presented in the MS included rates of cardiovascular mortality and stent thrombosis. The results provided are presented in terms of cost per quality adjusted life years (QALY) with a lifetime horizon represented by a 40-year time horizon. Costs were considered from a NHS and Personal Social Services perspective.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The MS included a systematic review of the clinical effectiveness literature. The ATLAS ACS 2-TIMI 51 trial, which forms the basis of the submission, was a phase III, randomised, double blind, placebo controlled, event driven, multicentre (766 sites in 44 countries including the UK) study, which compared the efficacy and safety of oral rivaroxaban tablets (either 2.5 mg or 5 mg twice daily) with placebo in 15,526 adults with ACS (STEMI, NSTEMI and unstable angina). All patients received standard care (aspirin alone [stratum 1, n=1053] or aspirin and a thienopyridine [stratum 2, 14,473] either as clopidogrel [approx. 99%] or ticlopidine according to national or local guidelines). The higher dose of rivaroxaban (5 mg twice daily) was presented for completeness and is not part of the marketing authorisation (n=5176). The mean duration of treatment with the study drug was 13.1 months. All primary and secondary efficacy endpoint analyses were subject to a hierarchical testing strategy and were conducted according to a modified intention-to-treat (mITT) approach (the primary evaluation strategy) with sensitivity analyses using variations of the intention-to-treat analysis sets. A large number of patients discontinued from the study (15.5% (2402/15,526). Corresponding data for

the licensed population were not provided by the manufacturer. The main reasons for study discontinuation were withdrawal of consent and adverse events.

The ERG considered the hazard ratios (HR) of the efficacy results from the combined rivaroxaban dose to be more plausible than those of the individual doses as there is no clear biological mechanism that the 2.5 mg dose would be more efficacious than the 5 mg dose. This view was supported by US Food and Drug Administration briefing documents for the Cardiovascular and Renal Drugs Advisory Committee, which considered these findings to be likely spurious. Similarly, the European Medicines Agency assessment report concluded that these findings may partly have been due to chance. The manufacturer has also conceded that the two doses were likely to be 'more similar than they are different'. Hence, the combined efficacy results are presented in this summary.

As the main focus of this appraisal was based on the licensed indication, a post-hoc subgroup analysis of patients after an ACS with elevated cardiac biomarkers without prior stroke or transient ischaemic stroke i.e. the licensed population (all strata, n=12,353; 80% of total population) showed that treatment with rivaroxaban significantly reduced the primary composite efficacy endpoint of cardiovascular death, MI or stroke for the combined rivaroxaban group (2.5 mg and 5 mg twice daily) compared with the placebo group, with rates of 6.2% and 7.9%, respectively (HR 0.79, 95% confidence interval [CI]: 0.69 to 0.91, p=0.001). When the components of the primary efficacy endpoint were analysed individually, the combined rivaroxaban group (2.5 mg and 5 mg twice daily) significantly reduced the risk of death from cardiovascular causes (HR 0.72, 95% CI: 0.57 to 0.90, p=0.004) and MI (HR 0.81, 95% CI: 0.68 to 0.97, p=0.021) compared with placebo but increased (albeit non-significantly) the risk of stroke (HR 1.30, 95% CI: 0.85 to 2.01, p=0.225).

Results for secondary endpoint 1 (a composite efficacy endpoint of all-cause death, MI or stroke), mirrored those of the primary efficacy endpoint (HR 0.79, 95% CI: 0.69 to 0.91, p<0.001) as the majority of deaths [redacted] were cardiovascular in origin. [redacted]

Among patients who received at least one dose of a study drug, premature discontinuation of treatment occurred in 26.9% (1376/5115) of patients receiving the 2.5 mg dose of rivaroxaban, 29.4% (1504/5110) receiving the 5 mg dose of rivaroxaban and 26.4% (1351/5125) receiving placebo. No statistical comparisons were reported for these differences. As compared with placebo, rivaroxaban increased the rates of non-coronary artery bypass grafting (CABG) Thrombolysis in Myocardial

Infarction (TIMI) major bleeding in a dose-dependent manner. As such the bleeding rates from the licensed 2.5 mg twice daily dose were considered most appropriate: HR 3.44, 95% CI: 1.97 to 6.01, p<0.001.

[redacted]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review process followed by the manufacturer was comprehensive. Despite minor limitations in the manufacturer's search strategy, The ERG is reasonably confident that all relevant studies (published and unpublished) of rivaroxaban (in combination with aspirin or with aspirin and a thienopyridine [clopidogrel]) were included in the MS, including data from ongoing/planned studies. The specified inclusion and exclusion criteria are appropriate and generally reflect the information given in the decision problem. The validity assessment tool used to appraise the included studies was based on the minimum criteria for assessment of risk of bias in RCTs and was considered appropriate by the ERG.

Compared with standard care, the addition of rivaroxaban (2.5 mg twice daily) to existing antiplatelet therapy reduced the composite of CV mortality, MI or stroke MI but increased the risk of major bleeding and intracranial haemorrhage. There are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Due to the post-hoc mITT analyses, high dropout rates and missing vital status data inference of treatment effects (including magnitude) may be confounded. The key uncertainties in the clinical evidence relate to optimal dosing, duration of treatment, generalisability to the UK population and the possibility of bias due to informative censoring.

1.4 Summary of cost-effectiveness submitted evidence by the manufacturer

The manufacturer submitted a cohort Markov model with a time horizon of 40-years, populated with data from the ATLAS ACS 2-TIMI 51 trial. Treatment with clopidogrel and aspirin was assumed to be for a period of one year and indefinitely respectively. The manufacturer used in the deterministic analyses a yet to be confirmed acquisition cost of £58.80 per pack for 56 2.5 mg rivaroxaban tablets. In the base case, treatment with rivaroxaban was assumed to be for a period of between one and two years. The model allowed for treatment discontinuations due to further ACS events. The

manufacturer estimated that rivaroxaban plus aspirin with or without clopidogrel had an ICER of £6,205. The ICER did not rise above £10,000 per QALY in any of the sensitivity analyses undertaken.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The model had several errors which were corrected by the ERG. The ERG considered the model submitted by the manufacturer to be relatively inflexible which meant that the ERG could not conduct all the exploratory analyses which were deemed to be potentially relevant to the decision problem. The largest limitation was that there was no allowance in the model to use the pooled efficacy data of the rivaroxaban 2.5 mg twice daily and rivaroxaban 5 mg twice daily arms from the ATLAS ACS 2-TIMI 51 trial or to explore alternative HRs for efficacy and adverse events. Additionally, the impact of bias due to any informative censoring could not be evaluated.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The manufacturer undertook a comprehensive systematic review (no major limitations were noted) of rivaroxaban for the prevention of adverse outcomes in patients after the acute management of ACS. The ATLAS ACS 2-TIMI 51 study was a large, well designed, multicentre RCT of reasonable methodological quality (with some limitations, as noted in section 1.3) that measured a range of clinically relevant outcomes.

The mathematical model submitted by the manufacturer allowed patients to discontinue their drug treatment if they experienced a further ACS event. The mathematical model submitted by the manufacturer also incorporated the cost and health consequences of bleeds and revascularisations.

1.6.2 Weaknesses and areas of uncertainty

The included RCT is not an absolute reflection of the population with ACS in the UK, so the external validity may be questionable. A large area of uncertainty is that other dual antiplatelet regimens were absent from the scope and therefore the relative cost-effectiveness of rivaroxaban compared with these interventions has not been estimated. Such interventions include ticagrelor and prasugrel, which are recommended in current NICE guidelines (Clinical Guideline 167 and 172 and Technology Appraisal Guidance 236 and 317) for the acute and maintenance phases of ACS.

The model submitted by the manufacturer could not appropriately track the event history of patients with multiple events, which could cause inaccuracy in the estimated cost-effectiveness ratios presented. The manufacturer did not consider published uncertainty in the probabilistic sensitivity analysis (PSA) nor were correlations between parameters considered. Additionally some data, such as

the acquisition costs of rivaroxaban, were inappropriately incorporated into the PSA. The acquisition cost of rivaroxaban 2.5 mg has not been confirmed, the results would change were the price assumed in the modelling not equal to the confirmed price.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG adjusted the parameterisation of the uncertainty in the manufacturer's PSA using published estimates of uncertainty, if this information was available. The mean PSA ICER (£6,150) calculated by the ERG was not substantially different from the manufacturer's deterministic ICER (£6,205) allowing all further exploratory analyses to be performed using the deterministic scenario. The ERG made a small number of changes to the manufacturer's base case scenarios although this did not affect the conclusions. In none of the ERG's additional scenario analyses did the ICER rise above £10,000 per QALY; however, the impact of any informative censoring could not be evaluated. It is uncertain in what direction (and to what extent) the ICER would change should the pooled HR with respect to efficacy parameters for the 2.5 mg twice daily and 5 mg twice daily doses be used rather than the data solely from the 2.5 mg twice daily group.

2 BACKGROUND

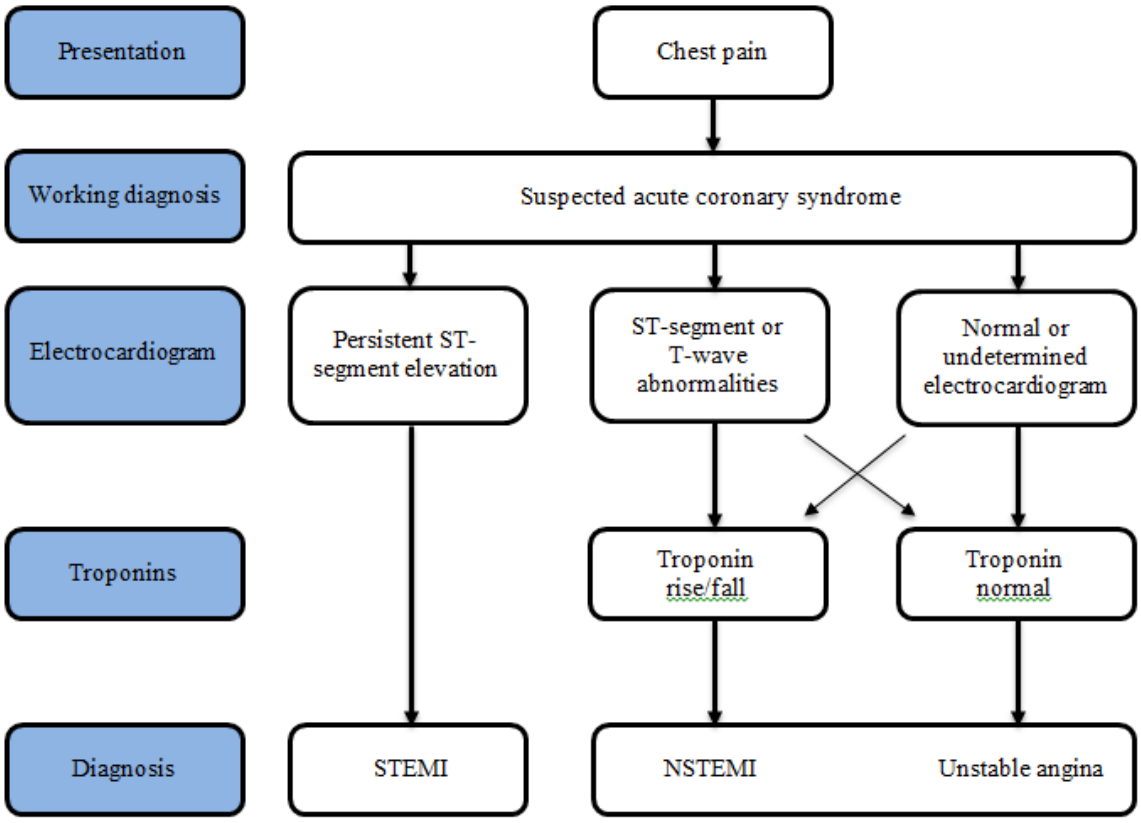
This report provides a review of the evidence submitted by Bayer in support of rivaroxaban (co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine) for the prevention of atherothrombotic events in adults after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (i.e. the licensed population). It considers both the original submission received on the 25th June 2014 and a subsequent response to clarification questions supplied by Bayer on the 31st July 2014.

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer provided a reasonable description of the underlying health problem, which is briefly summarised in this section. ACS encompasses a range of conditions including ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA), arising from thrombus formation on an atheromatous plaque (accumulation of fatty deposits within the arteries of the heart).[1]

The classification of ACS is largely based on the characteristics of the presenting electrocardiogram (ECG) and levels of cardiac biomarkers. As shown in Figure 1, the presence of acute chest pain and persistent ST segment elevation often indicates total occlusion of the affected artery, resulting in necrosis of the tissue supplied by that artery and is classified as STEMI. In contrast, ACS without persistent ST segment elevation is usually classified as either UA or NSTEMI based on the absence or presence of myocardial damage as evidenced by the detection of a rise and or fall of the blood level of a cardiac biomarker (e.g. troponin). The UK licence (based on a post-hoc analysis) of rivaroxaban for the prevention of atherothrombotic events is restricted to adult patients with recent ACS with elevated biomarkers (STEMI and NSTEMI) as this subgroup was considered to derive the greatest benefit.[2]

Figure 1: Classification of ACS (adapted)[3]



According to the Hospital Episode Statistics data for England[4] and the Patient Episode Database for Wales[5] there were a total of 81,652 hospital admissions for myocardial infarction (MI) between April 2012 and March 2013 (of these 80,150 were for acute MI and 1502 for subsequent MI). Other sources of evidence identified by the Evidence Review Group (ERG) support these findings and note that between April 2012 and March 2013 the Myocardial Ischaemia National Audit Project (MINAP) database[6] (a national clinical audit of all hospitals in England (with the exception of Scarborough Hospital), Wales and Belfast that admit patients with STEMI or NSTEMI) recorded 80,974 hospital admissions with a final diagnosis of MI. Of these, 40% were diagnosed as STEMI (32,665) and 60% were diagnosed as NSTEMI (48,309). The average age of patients with STEMI and NSTEMI was 65 years and 72 years respectively. The authors of the MINAP report[6] also acknowledged that the audit records the majority of admissions for STEMI but not all patients having NSTEMI are entered into the database. The authors believe that the true ratio of STEMI to NSTEMI could be at least 1:3 rather than 2:3, which would suggest approximately 100,000 MIs per annum.

Despite improvements in survival after the first and recurrent acute MI over the last three decades, individuals remain at high risk for recurrent events and death due to vessel occlusions from vulnerable coronary plaques. A recent record linkage study[7] of long-term prognosis in England found that 86% of patients admitted to hospital for acute MI between 2004 and 2010 survived for at least 30 days. However, the 30 day survivors of both first and recurrent acute MI were, respectively, at 2 and 3 times higher risk of death from any cause compared with the general population for at least 7 years after the event. For all survivors of a first acute MI, the risk of a second acute MI was highest during the first year and the cumulative risk increased more gradually thereafter.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer, in general, provided a reasonable overview of current service provision. However, explicit details on existing NICE guidance, particularly on prasugrel[12] and ticagrelor[9] were lacking in the MS, although the ERG are aware that neither intervention is contained in the final scope issued by NICE.[8] An overview of current service provision is provided in this section.

Dual antiplatelet regimens such as aspirin and an adenosine diphosphate (ADP) receptor antagonist are the mainstay of treatment in the pharmacological management of ACS. A summary of the relevant guidelines and guidance documents, which have been published by NICE are summarised in Table 1. Briefly, initial treatment decisions are primarily guided by the presenting diagnosis – differentiating STEMI (which requires immediate emergency restoration of blood flow to the occluded artery) from UA/NSTEMI (where a partial thrombotic obstruction leads to impaired blood flow that needs to be restored promptly but not urgently). The vast majority of patients with confirmed STEMI undergo (primary) percutaneous coronary intervention (PCI) to the occluded artery.[6] In the days preceding and following PCI, patients usually receive a loading dose of aspirin and a ADP receptor antagonist (clopidogrel, prasugrel or ticagrelor) followed by maintenance treatment with dual antiplatelet therapy for up to 12 months. Thereafter, aspirin is recommended to be taken indefinitely in people for whom aspirin is suitable.[1,9-12]

For patients with NSTEMI, treatment options in general, as recommend by NICE Clinical Guideline No. 94,[1] depend on an individual's risk score of future cardiovascular (CV) events using an established risk scoring system such as the Global Registry of Acute Coronary Events (GRACE) classification.[13] In addition to aspirin, patients with predicted 6-month mortality risk greater than 1.5% are usually offered a loading dose of one of clopidogrel, prasugrel or ticagrelor followed by maintenance treatment for up to 12 months. Beyond this, aspirin is recommended to be taken indefinitely in all patients for whom aspirin is suitable[1,9,10,12] (Figure 2).

Table 1: Summary of NICE guidelines and guidance documents for ACS

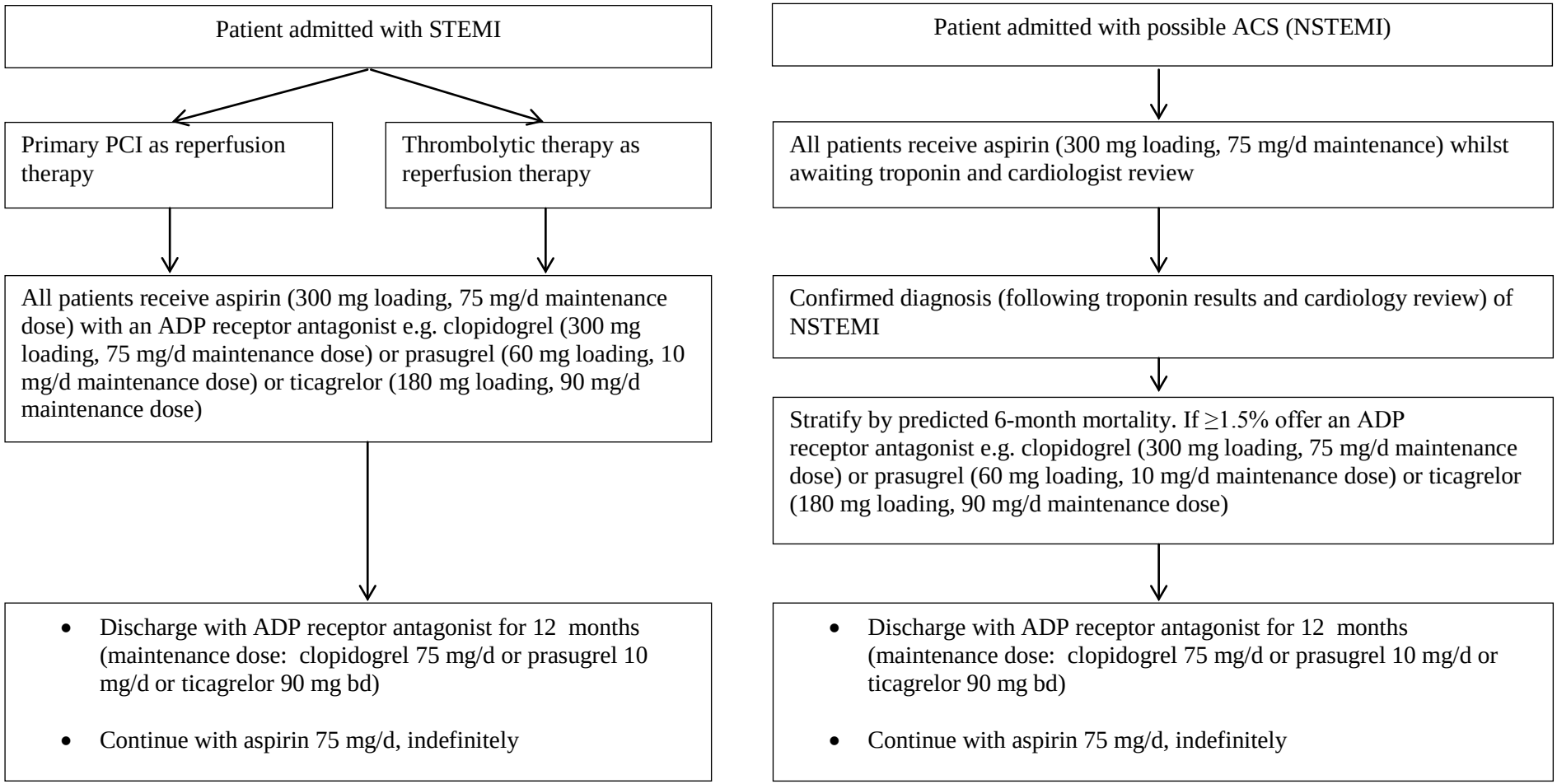
Guidance	Date	Drugs	Recommendation
NICE Technology Appraisals			
Technology Appraisal No. 317. Prasugrel with PCI (review of Technology Appraisal No. 182)[12]	2014	Prasugrel plus aspirin	Prasugrel 10 mg in combination with aspirin is recommended as an option within its marketing authorisation, that is, for preventing atherothrombotic events in adults with ACS (UA/NSTEMI or STEMI) having primary or delayed PCI.
Technology Appraisal No. 236. Ticagrelor for the treatment of ACS[9]	2011	Ticagrelor plus aspirin	Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS that is, people with: • STEMI – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary PCI or • NSTEMI or • Admitted to hospital with UA. Before ticagrelor is continued beyond the initial treatment, the diagnosis of UA should first be confirmed, ideally by a cardiologist.
NICE Clinical Guidelines			
Clinical Guideline No. 172. Secondary prevention in primary and secondary care for patients following a myocardial infarction[10] (Clinical Guideline No. 172 is an update of Clinical Guideline No. 48)	2013	Clopidogrel or ticagrelor plus aspirin	This guideline recommends: • Aspirin should be offered to all people after an MI and continue it indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. • For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment. • Clopidogrel should be considered as a treatment option for up to 12 months for: o People who have had an NSTEMI, regardless of treatment o People who have had a STEMI and received a bare-metal or drug-eluting stent. • Ticagrelor is also recommended as per Technology Appraisal No. 236 noted above • Prasugrel-prasugrel for the treatment of ACS has not been incorporated in this guidance because this technology appraisal is currently scheduled for update. • There are special recommendations for antiplatelet therapy in people with an indication for anticoagulation.
Clinical Guideline No. 167. Myocardial infarction with STEMI: the acute management of	2013	Ticagrelor plus aspirin	Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in people with STEMI – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary PCI. This

myocardial infarction with STEMI[11]			recommendation is adapted from NICE Technology Appraisal No. 236.
Clinical Guideline No. 94. Unstable angina and NSTEMI: the early management of unstable angina and non-ST segment elevation myocardial infarction[1]	2010	Clopidogrel plus aspirin	This guideline recommends: • As soon as the risk of adverse cardiovascular events has been assessed, offer a loading dose of 300 mg clopidogrel in addition to aspirin to patients with a predicted 6-month mortality risk of more than 1.5% and no contraindications (for example, an excessive bleeding risk). • Offer a 300 mg loading dose of clopidogrel to all patients with no contraindications who may undergo PCI within 24 hours of admission to hospital.[a] • In line with 'Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention' (Technology Appraisal No. 182), prasugrel in combination with aspirin is an option for patients undergoing PCI who have diabetes or have had stent thrombosis with clopidogrel treatment. • Treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of NSTEMI. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended.

ACS, acute coronary syndrome; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; UA, unstable angina

[a] The NICE technology appraisal of ticagrelor notes that current practice in the UK involves a loading dose for clopidogrel of 600 mg (unlicensed dose)

Figure 2: Simplified treatment pathway for the management of ACS (STEMI and NSTEMI) in the UK[1,9-12]



The clinical advisors to the ERG noted that in UK clinical practice the duration and choice of the ADP receptor antagonist (e.g. clopidogrel, prasugrel or ticagrelor) varies based on patient characteristics and nature of illness (STEMI or NSTEMI). In general, treatment decisions are based on a number of factors such as speed and potency of pharmacodynamic action (e.g. ticagrelor and prasugrel are rapidly available within 30 minutes after ingestion whereas clopidogrel has a delayed onset of action of several hours), poor antiplatelet response (e.g. up to 30% of patients who receive clopidogrel are low or no responders to its platelet inhibition), potential concerns with compliance to short-acting drugs (e.g. ticagrelor is dosed twice a day compared with once a day clopidogrel and prasugrel), increased bleeding risk (e.g. ticagrelor is a reversible non-competitive antagonist of the of the $P2Y_{12}$ receptors, whereas prasugrel is associated with an increased risk of major and fatal bleeding and is not recommended in patients aged over 75 years and those weighing under 60kg); and cost (e.g. generic clopidogrel is markedly cheaper than either prasugrel or ticagrelor).[14]

Despite variation in practice among clinicians in the UK, the ERG clinical advisors believe that aspirin in combination with ticagrelor or prasugrel are increasingly being used as first line treatments in the acute and maintenance phases of ACS. It is noteworthy that the current 2012 European Society of Cardiology (ESC) clinical practice guidelines for patients with STEMI recommend dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor (over aspirin and clopidogrel) for up to 12 months in patients treated with PCI.[15] ESC guidelines have similar recommendations for the long term management of patients with NSTEMI.[3] Data from the British Cardiovascular Intervention Society PCI registry[16] estimated the use of ticagrelor or prasugrel to be 30% in patients with STEMI and 6% in people with NSTEMI in 2012; however, these data are likely to be underestimates given the expected increase in frequency of use following recent NICE guidance.[10-12]

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem addressed by the MS is reproduced (with minor changes) in Table 2.

Table 2: Decision problem as issued by NICE and addressed by the MS

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale provided by the manufacturer if different from the scope**
Population	People with ACS with elevated cardiac biomarkers (STEMI and NSTEMI)	Adult patients after an ACS with elevated cardiac biomarkers	Essentially the same but wording as per the Summary of Product Characteristics[17]
Intervention	Rivaroxaban (in combination with aspirin or with aspirin and a thienopyridine [clopidogrel])	Rivaroxaban (in combination with aspirin or with aspirin and a thienopyridine [clopidogrel])	N/A
Comparator(s)	• Clopidogrel with aspirin • Aspirin alone for people for whom clopidogrel is considered unsuitable	• Clopidogrel with aspirin • Aspirin alone for people for whom clopidogrel is considered unsuitable	N/A
Outcomes	The outcome measures to be considered include: • Death from any cause • Non-fatal cardiovascular events • Incidence of revascularisation procedures • Adverse effects of treatment (including bleeding events) • Health-related quality of life.	The outcome measures included: • Death from any cause • Non-fatal cardiovascular events • Incidence of revascularisation procedures • Adverse effects of treatment (including bleeding events) • Health-related quality of life The following outcomes were also considered (subject to availability of data): • Cardiovascular mortality • Stent thrombosis	Cardiovascular mortality and stent thrombosis are considered to be important outcomes in ACS
Economic analysis	The reference case stipulates that the cost-effectiveness of	The cost-effectiveness of rivaroxaban in terms of the	N/A

	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.	incremental cost per quality-adjusted life year is presented. A lifetime time horizon was used in the base case of the model. Costs were considered from an NHS and Personal Social Services perspective.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: people with NSTEMI, people with STEMI; people with diabetes mellitus; people who received prior primary PCI and people who did not receive prior primary PCI in the acute phase of management. Guidance will only be issued in accordance with the marketing authorisation.	No subgroup data were considered in the submission	The licenced 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 conclusion about (non-pre-specified) subgroups of subgroups.
Special considerations, including issues related to equity or equality	N/A	N/A	N/A

ACS, acute coronary syndrome; N/A, not applicable; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction

3.1 Population

The manufacturer's statement of the decision problem appropriately defines the population as 'adult patients after an ACS with elevated cardiac biomarkers'. However the ERG note that the terminology 'elevated cardiac biomarkers' is less sensitive than if a patient exhibits a rise and/ or fall in their

cardiac biomarkers (preferably troponins) as many patients have persistently raised biomarkers outside the context of ACS[18] and in contemporary practice, the diagnosis of NSTEMI requires evidence of myocardial ischaemia combined with a rise and/or fall in the blood level of a cardiac biomarker (troponin). In addition, the MS does not include any details on the mean age at diagnosis in the UK against which to compare the characteristics of patients in the clinical trial.

3.2 Intervention

Rivaroxaban (Xarelto, Bayer) is a highly selective direct factor Xa inhibitor with oral bioavailability and a rapid onset of action. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.[17]

Rivaroxaban is currently licensed in the EU (including the UK)[17] for the prevention of atherothrombotic events in adults after an ACS with elevated cardiac biomarkers, co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine (an antiplatelet agent not available in the UK).[19] This indication is approved for a new 2.5 mg tablet, which is not yet available, but is due to be launched in the UK in September 2014 (p3 and 9; MS). The recommended dose is 2.5 mg twice daily (available in 56-tablet packs) with a yet to be confirmed acquisition cost of £58.80 per pack, which equates to a price of £2.10 per day (pB303, MS and further clarification response 23 July 2014).

Rivaroxaban is contraindicated in the following groups of people: those with active bleeding; those with significant risk of major bleeding (e.g. recent gastro-intestinal ulcer, oesophageal varices, recent brain, spine, or ophthalmic surgery, recent intracranial haemorrhage, malignant neoplasms, vascular aneurysm), those with prior stroke or transient ischaemic attack (TIA), those with hepatic disease associated with coagulopathy and during pregnancy and breastfeeding. In addition, treatment is not recommended in combination with other antiplatelet agents (e.g. prasugrel or ticagrelor) or in patients with creatinine clearance < 15 ml/min (to be used with caution in patients with creatinine clearance 15 - 29 ml/min).[17,19]

Additional licensed indications (not the subject of this appraisal) to the products market authorisation include the following (p8, MS and Summary of Product Characteristics):[17,19]

- Rivaroxaban (recommended dose: 10 mg per day) is indicated for preventing venous thromboembolism in adults undergoing elective hip or knee replacement surgery

- Rivaroxaban (recommended dose: 20 mg per day) is indicated for preventing stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors

(e.g. congestive heart failure, hypertension, age≥ 75 years, diabetes mellitus, prior stroke or TIA)

- Rivaroxaban (recommended dose: 15 mg twice daily for the first three weeks followed by 20 mg per day thereafter) is indicated for treating deep vein thrombosis and pulmonary embolism and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults

3.3 Comparators

The decision problem addressed in the MS states that the standard comparators considered were (1) clopidogrel with aspirin and (2) aspirin alone for people for whom clopidogrel is considered unsuitable. The ERG agrees that these interventions are appropriate and relevant comparators; however, some points need further clarification.

As discussed in section 2.2, other dual antiplatelet regimens such as aspirin in combination with ticagrelor or prasugrel are increasingly being used as treatment options in the acute and maintenance phases of ACS in the UK. In addition, these regimens are recommended in current clinical practice guidelines and guidance documents issued by NICE[9-12] and the ESC.[3,15] However, these treatment options were absent in the final scope issued by NICE.[8]

3.4 Outcomes

The NICE scope outlines five clinical outcome measures and one measure of cost-effectiveness. All of these are stated to have been addressed in the MS (p27-28). Clinical outcome measures included death from any cause, non-fatal CV events, incidence of revascularisation procedures, adverse effects of treatment (including bleeding events) and health-related quality of life. Additional outcomes (not in the final scope issued by NICE) included CV mortality and stent thrombosis. These are all appropriate and clinically meaningful outcomes, and there are no other valid outcomes which the ERG would have expected to be included.

Incremental cost per quality adjusted life years (QALYs) gained was used as a measure of cost-effectiveness, which is in accordance with the NICE reference case.[20] In addition, in the mathematical model the manufacturer used a lifetime horizon intended to be represented by a 40-year duration. Costs were considered from a NHS and Personal Social Services perspective.

3.5 Other relevant factors

The manufacturer declared that no equity issues were identified (p28 of the MS).

4 CLINICAL EFFECTIVENESS

This chapter presents a review of evidence relating to the clinical effectiveness of rivaroxaban in combination with aspirin or with aspirin and a thienopyridine (clopidogrel) in adult patients after an ACS with elevated cardiac biomarkers. Section 4.1 presents a critique of the manufacturer's systematic review and Section 4.2 provides a summary of the clinical effectiveness results (efficacy and safety) and critique of included rivaroxaban trials. Section 4.3 and 4.4 provides a critique and summary of results of any indirect comparison or mixed treatment comparison conducted, whilst Section 4.5 presents additional work on clinical effectiveness undertaken by the ERG. Finally, Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The searches undertaken by the manufacturer to identify all relevant RCTs were conducted in March 2014. The search strategy utilised appropriate free text and medical subject heading terms to identify the condition (ACS), the intervention (rivaroxaban) and the type of evidence (RCTs). Searches were further restricted to human and English language publications. Although the strategy is simple and effective, justification for adapting the published methodological RCT search filter (that was originally developed by the Scottish Intercollegiate Guidelines Network) was lacking. Several electronic bibliographic databases (MEDLINE, MEDLINE in Process, EMBASE, and the Cochrane Library) were searched from inception. Although research registers such as ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number Register were not searched, three conference proceedings (American Heart Association Scientific Sessions, European Society of Cardiology and American College of Cardiology) were reviewed for relevant abstracts presented at meetings held in 2012 and 2013. Supplementary searches such as scanning of bibliographies of included studies, existing systematic reviews, manufacturer's database of trial protocols, clinical study reports and correspondence with regulatory bodies were also undertaken. The number of hits following a repeat of the electronic database search strategies for the identification of relevant rivaroxaban intervention studies on 28 July 2014 (Section 6.1 of the MS) by the ERG, show numbers to be consistent with those reported in the MS. Whilst the ERG considers the search strategies to be comprehensive to retrieve important citations relating to all eligible studies of which the ERG and its clinical advisors are aware of, restricting the searches by English language can lead to publication bias.[21,22]

4.1.2 Inclusion criteria

The MS describes an appropriate method of identifying and screening references for inclusion in the systematic review of rivaroxaban for the prevention of atherothrombotic events in adult patients after

an ACS with elevated cardiac biomarkers. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in selection were resolved through discussion with a third reviewer (p33, MS). A summary of the inclusion and exclusion criteria, as reported in the MS (p30-32; data re-tabulated and adapted in a consistent and more transparent format), for the systematic review of rivaroxaban is summarised in Table 3.

The specified inclusion and exclusion criteria were appropriate and generally reflect the information given in the decision problem. It is noteworthy that the reporting of clinical harms is often inadequate in controlled clinical trial publications because they exclude patients at high risk from harms,[23] may be too short to identify long-term or delayed harms, or may have sample sizes too small to detect uncommon events.[24-27] Supplementary sources of evidence such as non-randomised studies or phase IV post marketing surveillance data may provide additional supportive evidence to inform on safety considerations.[28] The MS (p8) states that the European Medicines Agency (EMA) raised concerns on the potential increase in bleeding when rivaroxaban is added to platelet function inhibitors for secondary CV prophylaxis in patients with ACS. As a result a Post Authorisation Safety Study for ACS was considered conditional to the marketing authorisation.[2] The manufacturer's response to clarification question A3 suggests that discussions on the Post Authorisation Safety Study with the EMA are still ongoing, thus no results are currently available. In addition, as noted in the previous section, limiting a systematic review to English language only studies can lead to publication bias.

Table 3: Inclusion/exclusion criteria used to select studies of rivaroxaban in the MS (p30-32)

	Inclusion criteria	Exclusion criteria
Population	• Adults initially hospitalised with ACS (unstable angina, STEMI, or NSTEMI) who are managed for secondary prevention of their ACS event	• Patients with stable angina, or other CV disease that is not ACS • Primary prevention of ACS (mainly relevant for studies with aspirin) • Children • Mixed populations of stable and unstable angina, which do not present data for unstable angina separately
Intervention	• Rivaroxaban	• Interventions other than rivaroxaban e.g. aspirin, clopidogrel, prasugrel, ticagrelor, warfarin, ticlopidine, vitamin K antagonist, phenprocoumon, acute and subacute therapy for ACS (i.e., study intervention period < 30 days after discharge and/or with outcomes measured only at < 30 days after discharge), therapies used in the acute phase of ACS management such as (this is not an exhaustive list): bivalirudin, fondaparinux, enoxaparin, otamixaban, streptokinase, alteplase, and other “ase” products that are used for acute management
Comparator	• Any	• None specified

Outcomes	• Studies reporting clinical (efficacy and safety) and patient-reported outcomes o death from any cause o non-fatal cardiovascular events o incidence of revascularisation procedures o adverse effects of treatment (including bleeding events) o health-related quality of life • Other outcomes included, as specified on p27 of the MS o Cardiovascular mortality o Stent thrombosis	• Biochemical or immunological endpoints
Study design	• Randomised controlled prospective clinical trials • Long-term follow-up studies of RCTs (e.g. open-label follow-up of randomised clinical trials)	• Preclinical studies • Phase 1 studies • Non-comparative phase 2 trials • Prognostic studies • Retrospective studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Single arm studies • Genetic studies • Non-human studies • Non-randomised controlled clinical trials • Prospective observational studies (e.g. phase 4 studies)
Other	• English language	• Non-English language

ACS, acute coronary syndrome; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction

4.1.3 Critique of data extraction

The data extracted and presented in the MS clinical section appear appropriate and comprehensive. As noted in the manufacturer's response to clarification question A8, data extraction was performed by one researcher and checked by a second. Any disagreements were resolved by consensus and if necessary, a third reviewer was consulted.

4.1.4 Quality assessment

The validity assessment tool used to appraise the included studies in the MS (p B363) was based on the minimum criteria for assessment of risk of bias in RCTs, as suggested by the Centre for Reviews and Dissemination.[21] As noted in the manufacturer's response to clarification question A8, methodological quality assessment of included studies was performed by one researcher and checked by a second. The ERG acknowledges that the validity assessment tool used in the manufacturer's submission was appropriate.

4.1.5 Evidence synthesis

The manufacturer did not undertake a formal meta-analysis as only one rivaroxaban RCT study was considered relevant to the submission. As a result, the manufacturer undertook a narrative synthesis of the evidence; however, no explicit details were provided on how this approach was undertaken. Ideally, a narrative synthesis approach should be pre-specified, justified, rigorous (i.e. describe results without being selective or emphasising some finding over others) and transparent to reduce potential bias.[21,22] Despite the lack of transparency, the ERG acknowledges that the narrative synthesis approach undertaken by the manufacturer was acceptable.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The manufacturer's PRISMA (formerly QUORUM) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/statement.htm). Despite this, the flow diagram (p35; MS) appears to be an adequate record of the literature searching and screening process for rivaroxaban studies. Moreover, although the MS initially failed to provide a full and explicit breakdown of the reasons why each citation was rejected (especially after full text papers were retrieved for detailed evaluation), further details were provided by the manufacturer in their response to clarification question A9.

Of the 562 citations identified, two RCTs (representing 21citations) met the inclusion criteria (the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with

Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46 [ATLAS ACS-TIMI 46] study[29] and the ATLAS ACS 2-TIMI 51 trial).[30,31]

As noted in the MS (p36-38) the ATLAS ACS-TIMI 46 study (NCT00402597)[29] was a phase II, randomised, double blind, placebo controlled, multicentre (297 sites in 27 countries including the UK) study designed to select the most favourable dose and dosing regimen of rivaroxaban in patients receiving aspirin with or without a thienopyridine for further assessment in a phase III trial. The study enrolled 3491 patients who had been stabilised (within seven days) after hospital admission for an ACS index event. All of the patients were given standard background therapy of either aspirin (n=761) or aspirin plus a thienopyridine (n=2730). Then, in each of these two groups, patients were randomised in a 1:1:1 ratio to receive either placebo or rivaroxaban (at doses 5 to 20 mg daily) given once daily or the same total daily dose given twice daily. The primary safety endpoint was clinically significant bleeding. The primary efficacy endpoint was death, MI, stroke, or severe recurrent ischaemia (inadequate blood flow) to the heart requiring intervention within 6 months.

Compared with placebo, the risk of clinically significant bleeding increased in a dose-dependent manner in all patients receiving rivaroxaban (n=2309): the hazard ratios (HR) were 2.21, 3.35, 3.60, and 5.06 for the 5 mg, 10 mg, 15 mg, and 20 mg for total daily doses, respectively ($p<0.0001$). The rate of the primary efficacy endpoint of death, MI, stroke, or severe recurrent ischemia requiring revascularization during 6 months was lower in the rivaroxaban group than in the placebo group (5.6% [126/2331] versus 7.0% [79/1160]), but this difference did not reach statistical significance ($p=0.10$). In contrast to the dose-dependent rate of bleeding, there was little evidence of a dose-related effect on the primary efficacy endpoint. In a FDA briefing document[32] it is reported that 'the hazard ratio for rivaroxaban 5 mg, 10 mg, 15 mg and 20 mg total daily dose groups, as compared with the pooled placebo group, were 1.07, 0.82, 1.43, and 1.10, respectively.' It is further stated that 'no relationship between dose and outcomes is apparent in the TIMI 46 analysis'.

On the basis of the bleeding data and the observed efficacy data, (for detailed safety and efficacy results by dose and group see p39-41 of the MS) 2.5 mg and 5 mg of rivaroxaban administered twice daily were selected for further assessment in a large, phase III clinical trial (ATLAS ACS 2-TIMI 51). Despite providing a brief overview (p38-41, MS), the manufacturer excluded the ATLAS ACS-TIMI 46 study from further detailed discussion as it was primarily considered as a dose finding study for the larger phase III study. In addition, this study had only a small number of subjects on rivaroxaban 2.5 mg twice daily (n=153; the licensed dose) or 5 mg twice daily (n=527).[29]

- Main evidence (pivotal study: ATLAS ACS 2-TIMI 51)

The MS (p42-70) included one randomised, double blind, placebo controlled, event driven, multicentre (766 sites in 44 countries including the UK) study that was designed to evaluate the efficacy and safety of rivaroxaban in 15,526 adults (75% male) aged 18 years or over (mean age 61.7 years) who presented with symptoms suggestive of ACS and in whom a STEMI (50.3%), NSTEMI (25.6%) and UA (24.0%) had been diagnosed. Patients who were under 55 years of age had either diabetes mellitus or previous MI in addition to the index event. A summary of the study design and population characteristics is provided in Table 4. The key exclusion criteria included a platelet count less than 90,000/mm^3, a haemoglobin level less than 10g/100ml, or a creatinine clearance of less than 30ml/min; clinically significant gastrointestinal bleeding in the 12 months before randomisation; previous intracranial haemorrhage; and previous ischaemic stroke (IS) or TIA in patients who were taking both aspirin and a thienopyridine.

Table 4: Characteristics of included study

Study	Country (sites)	Design	Population	Interventions	Comparator	Primary outcome measures	Duration
ATLAS ACS 2- TIMI 51 (NCT 00809965)[30,31]	44 countries (766 sites) from North America (n=874, 6%), South America (n=1669, 11%), Western Europe (n=2241, 14%), Eastern Europe (n=6074, 39%), Asia (n=3195, 21%) and other (n=1473, 9%)	Phase III randomised, double-blind, placebo-controlled, trial (n=15,526)	Patients aged ≥18 years with symptoms of ACS (ST-segment MI, non-ST-segment MI, or unstable angina) in past 7 days receiving standard medical therapy with either aspirin or aspirin plus any thienopyridine. Patients aged 18–54 years also had to have diabetes mellitus or previous MI.	All strata: Rivaroxaban plus standard care (n= 10,350; 2.5 mg bd, n=5174 or 5 mg bd, n=5176) Stratum 1: Rivaroxaban 2.5 mg bd plus aspirin (n=349) Rivaroxaban 5 mg bd plus aspirin (n= 349) Stratum 2: Rivaroxaban 2.5mg bd plus aspirin and a thienopyridine (n=4825) Rivaroxaban 5 mg bd plus aspirin and a thienopyridine (n= 4827)	All strata: Placebo plus standard care (n=5176) Stratum 1: Placebo plus aspirin (n=355) Stratum 2: Placebo plus aspirin and a thienopyridine (n=4821)	Efficacy: Composite of CV death, MI, and stroke (ischaemic, haemorrhagic or stroke of uncertain cause) Safety: Non-CABG-related TIMI major bleeding	Event driven study with a target of 983 primary efficacy endpoint events (mean treatment duration 13.1 months with maximum 31 months follow-up)

ACS, acute coronary syndrome; bd, bis die (twice daily); CABG, coronary artery bypass grafting; CV, cardiovascular; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction

The ATLAS ACS 2-TIMI 51 trial[30,31] consisted of three phases, including a 6-day screening phase, a double blind treatment phase and follow-up phase. The study began with participants being enrolled into the study within 7 days of being admitted to hospital for an ACS. After stabilisation of the index ACS event (and with completion of any initial management strategies such as revascularisation), participants were randomised to rivaroxaban 2.5 mg (n=5174), rivaroxaban 5 mg (n=5176) or placebo (n=5176) taken twice daily with a maximum follow-up of 31 months (patients were not randomised in the 24 hours immediately following hospitalisation). In addition, 99% of participants received low dose aspirin (75 to 100 mg/day) and 93% also received a thienopyridine according to national or local prescribing guidelines (p46, 132, 135, MS). The summary of product characteristics[17] states that 'among patients receiving dual anti-platelet therapy 98.8% received clopidogrel, 0.9% received ticlopidine and 0.3% received prasugrel' (the primary published paper[31] and the MS [p45-48] suggest that thienopyridine use was limited to clopidogrel or ticlopidine) with a mean treatment duration of 13.3 months.[31] The MS (p132) notes that prasugrel and ticagrelor were not approved or part of standard care protocols at the time the ATLAS ACS 2-TIMI 51 trial was initiated.

Randomisation was stratified according to planned use of a thienopyridine (Stratum 1: aspirin only; Stratum 2: aspirin plus thienopyridine). The length of treatment was not fixed because the trial was event-driven. Participants continued to receive treatment for at least 30 days and until the required number of primary efficacy end points occurred. A total of 983 primary efficacy endpoint events were estimated to have approximately 96% power to detect a 22.5% relative risk reduction between the pooled doses of rivaroxaban and placebo arms pooled across Stratum 1 and Stratum 2, with a two-sided type I error rate of 0.05. The total of 983 events was estimated based on the sum of the events required at approximately 90% power in each stratum to detect a 35% relative reduction in Stratum 1 (255 primary efficacy endpoints required) and 22.5% relative reduction in Stratum 2 (728 primary efficacy endpoints required) between the combined rivaroxaban group (2.5 mg twice daily and 5 mg twice daily) and placebo group. The mean duration of treatment with the study drug was 13.1 months. Participants were followed up at 4 weeks, 12 weeks and every 12 weeks thereafter.

The primary and secondary endpoints were all composite endpoints and subject to a strict hierarchical testing strategy. If statistical superiority of the combined rivaroxaban doses compared with placebo for the primary efficacy endpoint was declared significant across all strata (initially) and for stratum 2 only, then each of the doses was tested separately. If the superiority of a dose group was declared for the primary efficacy endpoint, the secondary efficacy endpoints were tested for that dose group in a sequential order (p64-65, 74, MS). The primary efficacy endpoint (p54-56, MS) was a composite of CV death, MI or stroke (ischaemic, haemorrhagic, or stroke of uncertain cause). The first secondary

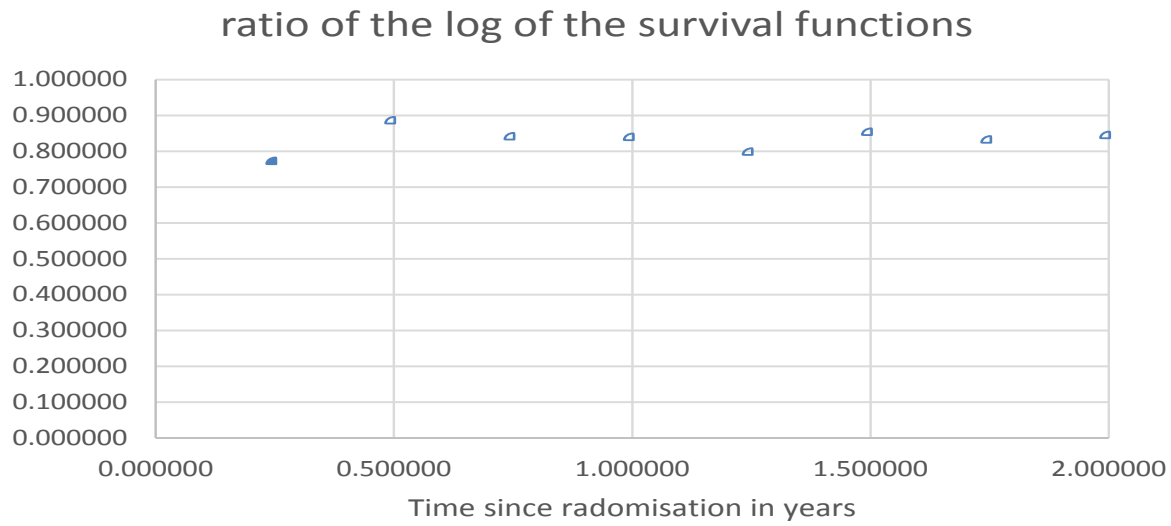
efficacy endpoint was a composite of death from any cause, MI or stroke. The second was a pre-specified net clinical outcome defined as the composite of CV death, MI, IS or TIMI major bleeding event not associated with coronary artery by-pass graft (CABG) surgery. The third was a composite of CV death, MI, stroke or severe recurrent ischaemia requiring revascularisation. The fourth was composite of CV death, MI, stroke or severe recurrent ischaemia leading to hospitalisation (p56, MS). Although not a formal study endpoint (as noted in the study protocol),[33] the incidence of stent thrombosis was a pre-defined, stand-alone efficacy endpoint that was independently adjudicated based upon the Academic Research Consortium designations of definite, probable or possible (p57, MS). The primary safety endpoint was TIMI major bleeding not related to CABG.

Efficacy data (provided in the MS [p61-64] and the manufacturer's response to clarification question A11) were analysed using three different approaches (the modified intention-to-treat analysis (mITT), intention-to-treat analysis (ITT) and intention-to-treat total (ITT-total) analysis) that differed from each other in censoring rules for determining evaluable events. The mITT analysis set was the pre-specified primary analysis and consisted of all randomised subjects and the endpoint events occurring at or after randomisation and up to the earliest of the Global Treatment End Date, or 30 days after last dose of study drug (for participants who discontinued study drug prematurely), or 30 days after randomisation (for those subjects who were randomised but not treated). The ERG note that the FDA briefing documents for the Cardiovascular and Renal Drugs Advisory Committee[32,34] considered the manufacturer's mITT analysis as an 'on-treatment plus 30 day' analysis. The ITT analysis set, which included all randomised subjects and endpoint events occurring at or after randomisation until the global treatment end date and the ITT-total analysis set, which included all events from randomisation up to last contact for each subject were conducted as sensitivity efficacy analyses. The primary safety analyses set included all participants who underwent randomisation and received at least 1 dose of study drug, with evaluation carried out from the time the first dose of the study drug was administered until 2 days after discontinuation. The pre-planned analysis was to compare the combined rivaroxaban group with placebo, and if this statistically significantly favoured rivaroxaban then each of the 2 doses of rivaroxaban would be compared with placebo simultaneously.[31]

Finally, the manufacturer's clarification response to question A10 provided analyses to test the validity of the proportional hazards assumption used when reporting clinical data. These data suggest that this assumption does not seem unreasonable based on the relatively constant ratio of the log hazards, as seen in replicated Figure 3 (note, it is not clear to the ERG if the data in Figure 3 are for the 'all strata' or 'stratum 2 group only'). However, it is noted that this may not be the case in the early period, where the the FDA briefing document for the Cardiovascular and Renal Drugs Advisory Committee[32] states, albeit for a population broader than that considered in the decision problem that

'Not only does the effect of rivaroxaban not appear to be greater earlier, but an effect in the first 90 days or so is not apparent at all.'

Figure 3: The ratio of the log of the survival functions for rivaroxaban provided by the manufacturer (reproduced: manufacturer's clarification response to question A10)



- *Ongoing studies of rivaroxaban for ACS*

No ongoing studies were noted in the MS (p9) or identified by the ERG.

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that all relevant studies were included in the MS and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported.

4.2.3 Summary and critique of manufacturer's analysis of validity assessment

The manufacturer provided a formal appraisal of the validity of the included rivaroxaban RCT using standard and appropriate criteria. The completed validity assessment tool for the ATLAS ACS 2-TIMI 51 trial, as reported in the MS, is reproduced (with minor changes) in Table 5.

Table 5: Manufacturer's quality assessment results for included RCT (p72, B363-4, MS)

Quality assessment criteria	Trial
	ATLAS ACS 2-TIMI 51
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes [See text for ERG comment on this]

The MS (p45-46, B361-362) states that in the ATLAS ACS 2-TIMI 51 trial, randomisation was performed according to a computer generated randomisation list, allocation concealment was done centrally using an interactive voice response system or interactive web response system and participants and investigators (including outcome assessors) were blinded to treatment allocation (double-blind). The ERG acknowledges that adequate methods of randomisation, allocation concealment and blinding were used in the conduct of the included trial.

The primary published paper[31] and the MS suggest (p50-53) that no clinically relevant differences in baseline demographic or clinical characteristics (p-values were not provided) were observed between the treatment groups (rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily and placebo) in the ATLAS ACS 2-TIMI 51 trial (total population). In 2013, rivaroxaban (2.5 mg twice daily) co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine received EMA marketing authorisation for the prevention of atherothrombotic events restricted to adult patients after an ACS with elevated cardiac biomarkers (i.e. patients with STEMI and NSTEMI). However, rivaroxaban is contraindicated for the treatment of ACS in patients with a prior stroke or TIA (licensed population).

[redacted]

[redacted]

Whilst all study withdrawals were adequately described and all patients were accounted for (p70, MS), 15.5% (n=2402) of the total randomised population (n=15,526) prematurely discontinued from the study (2.5 mg twice daily, 15.0% [redacted] 5 mg twice daily, 16.3% [redacted] placebo, 15.1% [redacted]). Corresponding data for the licensed population were not provided by the manufacturer, despite an ERG request (manufacturer's response to clarification question A21). As noted by Krantz & Kaul,[35] rates of premature withdrawal in the ATLAS ACS 2-TIMI 51 trial were considerably higher than other similar randomised ACS trials: APPRAISE-2 (apixaban), 1.8% [131/7392][36]; TRACER (vorapaxar), 5.9% [761/12,944][37]; PLATO (ticagrelor), 3.0% [562/18,624][38] and TRITON (prasugrel), 5.9% [804/13,619].[39] Due to high discontinuation rates, the ERG consider the validity of the ATLAS ACS 2-TIMI 51 trial to be questionable.[40]

The main reason for premature discontinuation in the ATLAS ACS 2-TIMI 51 trial was 'consent withdrawn' (1294/15,526 [8.3%]; p70, MS). Of the subjects who withdrew consent, most were in the rivaroxaban treatment groups compared with the placebo group. At the end of the trial, vital status was unknown in 1117 patients of the 1294 patients who withdrew consent.[35] Following extensive efforts by the manufacturer to obtain vital status information on consent withdrawn patients (p102-103, MS and manufacturer's clarification response to question A21) the proportion of patients with unknown vital status was reduced to 495/15,526 patients (3.2%). [redacted] As noted by Krantz & Kaul,[35] missing vital status data in the ATLAS ACS 2-TIMI 51 trial was higher than other recent randomised ACS trials: TRACER, 1.9% [249/12,944][37]; PLATO, 0.01% [2/18,624][38] and TRITON, 0.12% [16/13,619][39]).

Due to the missing data, there is a potential risk that it may lead to informative censoring (i.e. patients who drop out [and are therefore censored] are more or less likely to experience the primary outcome of interest compared to those remaining in the study in a non-random manner), which may be compounded if the reasons for, or frequency of, dropout differs between treatment groups.[35] This issue was discussed in detail by the FDA,[32] albeit in the total population of the ATLAS ACS 2-TIMI 51 trial, rather than the licensed subgroup population being appraised here. In contrast, no detailed discussions were provided in the EMA assessment report.[2] Nevertheless, the ERG note that the FDA briefing document[32] states that 'informative censoring should be expected in the ATLAS ACS 2-TIMI

51 trial as rivaroxaban causes more bleeding, bleeding leads to dropouts, and ACS patients with bleeding suffer more CV events as documented by many publications.[41-43] Further analysis of the missing follow-up data showed (as expected) that bleeding rates were higher with incomplete follow-up (as indicated in Figure 3 of the FDA briefing document)[32] as is mortality and CV death, MI and stroke with bleeding severity (as indicated in Figure 4 of the FDA briefing document).[32] The FDA briefing document[32] also noted that the possibility of bias due to incomplete follow-up is minimised if the primary analysis is of observations that occur while subjects are taking the study drug (i.e. on-treatment) and for 30 days after premature discontinuation (i.e. on-treatment plus 30 days). As a result, the amount of time for which follow-up is incomplete in the on-treatment plus 30 days analysis as a proportion of the total follow-up time in the ATLAS ACS 2-TIMI 51 trial is small, thus only a small impact on the resulting analysis is expected. As noted in section 4.2.1 of the ERG report, the FDA briefing document considers the manufacturer's mITT analysis in the MS as an 'on-treatment plus 30 day' analysis. [redacted]

Nevertheless, the ERG believes that both the ITT-total and the mITT are at risk of bias due to informative censoring as prognoses may differ in those patients who discontinue. The likely magnitude of any bias introduced by informative censoring in the HR for clinical outcomes and in cost-effectiveness analyses are unknown. Given individual patient data there may be techniques, such as inverse probability of censoring weights, that may have been beneficial to use to attempt to overcome informative censoring as these would apply differential weightings to account for those thought to have been informatively censored.

Ideally in an ITT analysis participants should be analysed in the groups to which they were randomised regardless of which (or how much) treatment they actually received, and regardless of other protocol irregularities such as noncompliance, protocol deviations and withdrawals. In the ATLAS ACS 2-TIMI 51 trial, the primary analysis was based on a mITT analysis, which included all randomised patients (except those from three excluded sites which had issues with potential trial misconduct) and endpoint events that occurred from randomisation up to the earlier date of the global treatment end date, or 30 days after last dose of study drug (for patients who discontinued study drug prematurely), or 30 days after randomisation (for patients who were randomised but never treated). As noted in section 4.2.1, the FDA briefing documents for the Cardiovascular and Renal Drugs Advisory Committee[32,34] considered the manufacturer's mITT analysis as an 'on-treatment plus 30 day' analysis. However, the manufacturer undertook a efficacy sensitivity analysis (p61-64, MS and manufacturer's response to clarification question A11) using the ITT analysis set (which included all randomised subjects and endpoint events occurring at or after randomisation until the global treatment

end date) and the ITT-total analysis set (which included all events from randomisation up to last contact for each subject were conducted as sensitivity efficacy analyses). [redacted]

4.2.4 Summary and critique of results

This section presents the results, as reported by the manufacturer, for the licensed population i.e. adult patients after an ACS with elevated cardiac biomarkers without prior stroke or TIA (all strata, n=12,353; 80% of total population) of the ATLAS ACS 2-TIMI 51 trial. As noted in the MS (p74), this population was identified as the group of patients who derived the most favourable benefit from the addition of rivaroxaban to existing antiplatelet therapy, at the lowest risk. All primary and secondary efficacy endpoint analyses were subject to a hierarchical testing strategy and were conducted according to the mITT principle (the primary evaluation strategy) with sensitivity analyses using the ITT and ITT-total analysis sets (further details and definitions are provided in section 4.2.1). In addition, 184 (1.2%) participants from three sites were excluded from the efficacy population (equally distributed between treatment groups) due to potential trial misconduct (p61, MS). The exclusion of these data was considered to be acceptable by the EMA.[2] Additional information, not reported in the MS, was provided by the manufacturer in their response to the clarification questions raised by the ERG. Where applicable, data have been re-tabulated in a consistent and more transparent format by the ERG. For completeness, results based on the total population of the ATLAS ACS 2-TIMI 51 trial are provided in Appendix 1 and Appendix 2, respectively.

Moreover, although all event rates were reported as Kaplan-Meier estimates through 24 months in the primary published paper,[31] the MS presents data as crude rates. As noted in the manufacturer's clarification response to question A17, this method shows the proportion of patients that have experienced the respective endpoint in the study, is easy to understand and no assumptions have to be made. However, the limitation of this method is that the timing of an event as well as the length of the observation is ignored. For completeness the manufacturer presented Kaplan-Meier estimates over time in steps of 30 days and as Kaplan-Meir plots for the total (primary and secondary endpoints) and licenced populations (primary endpoints only) by dose, strata and analysis type (mITT and ITT). Unfortunately, secondary endpoint data for the licensed population were not available but the manufacturer states that it is currently working in collaboration with Janssen to provide the full dataset. For further details see manufacturer's clarification response to question A17.

4.2.4.1 Efficacy (licensed population)

- Primary endpoint

A summary of the main results for the post-hoc subgroup analysis of patients after an ACS with elevated cardiac biomarkers without prior stroke or TIA is provided in Table 6. In all strata, treatment with rivaroxaban significantly reduced the primary composite efficacy endpoint of CV death, MI or stroke for the combined rivaroxaban group (2.5 mg and 5 mg twice daily) compared with the placebo group, with rates of 6.2% and 7.9%, respectively (HR 0.79, 95% confidence interval [CI]: 0.69 to 0.91, p<0.001). As a result, hierarchical testing of each of the two doses was undertaken. The reduction in the primary efficacy endpoint was statistically significant for both the 2.5 mg and 5 mg twice daily doses compared with placebo (6.2% compared with 7.9%, HR 0.80, 95% CI: 0.68 to 0.94, p=0.007; and 6.1% compared with 7.9%, HR 0.79, 95% CI: 0.67 to 0.93, p=0.004, respectively). The results for both doses were driven by stratum 2 (aspirin and thienopyridine) as the proportion of patients in stratum 1 (only aspirin) was small ([redacted])

When the components of the primary efficacy endpoint were analysed individually, rivaroxaban 2.5 mg twice daily significantly reduced the risk of death from CV causes compared with placebo (HR 0.55, 95% CI: 0.41 to 0.74, p<0.001), but did not reduce the risk of MI (HR 0.88, 95% CI: 0.72 to 1.08, p=0.215) or stroke (HR 1.23, 95% CI: 0.75 to 2.02, p=0.403). In contrast, rivaroxaban 5 mg twice daily significantly reduced the risk of MI (HR 0.75, 95% CI: 0.61 to 0.92, p=0.007), but did not reduce the risk of CV death (HR 0.89, 95% CI: 0.69 to 1.15, p=0.360) or stroke (HR 1.38, 95% CI: 0.85 to 2.24, p=0.190). A similar pattern was also observed for the total population of the ATLAS ACS 2-TIMI 51 trial (Appendix 1) [redacted]

The described numerical inconsistencies between the two dose groups for the components of the composite efficacy endpoint have been extensively discussed in a FDA briefing document (albeit in the total population of the ATLAS ACS 2-TIMI 51 trial, rather than the licensed subgroup population being discussed here) which states that 'The proposition that a lower dose of an antithrombotic drug is significantly more effective than a higher dose lacks biological plausibility' and concludes with 'Hence analyses which suggest efficacy results are superior for the 2.5 mg bid dose should be viewed as likely spurious. They should not be used to support the notion that the demonstrated efficacy of rivaroxaban is any greater than that demonstrated in the analyses that pool the results of both doses.' Similarly, the EMA assessment report[2] concluded that these findings may partly have been due to chance. In addition, the manufacturer's response to clarification question A18 states that '…the 2 rivaroxaban doses tested in the ATLAS ACS 2-TIMI 51 study are "more similar than they are

different" at reducing important clinical events of an ischaemic nature in ACS patients.' As a result of these deliberations, the ERG considers the HR from the combined dose to be more plausible than those of the individual doses. Moreover, whilst the combined doses have substantial overlapping confidence intervals for the composite endpoint and for its components, the mid-points of the total population and licensed population are not highly dissimilar. Pooling data also confers the advantage of reducing the width of the confidence interval.

Table 6: Effect of rivaroxaban compared with placebo on the primary endpoint (mITT analysis excluding 3 sites): Licensed population (p79-80, MS)

Stratum	**Rivaroxaban**			**Placebo**	**2.5mg bd vs. placebo**		**5mg bd vs. placebo**		**Combined vs. placebo**	
	2.5mg bd	**5mg bd**	**Combined**							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All strata	*N=4104*	*N=4089*	*N=8193*	*N=4160*						
Primary Endpoint: Composite of CV death, MI, stroke	[redacted] (6.2)	[redacted] (6.1)	[redacted] (6.2)	[redacted] (7.9)	0.80 (0.68-0.94)	0.007	0.79 (0.67-0.93)	0.004	0.79 (0.69-0.91)	0.001
CV Death	[redacted] (1.7)	[redacted] (2.6)	[redacted] (2.1)	[redacted] (3.1)	0.55 (0.41-0.74)	<0.001	0.89 (0.69-1.15)	0.360	0.72 (0.57-0.90)	0.004
MI	[redacted] (4.3)	[redacted] (3.6)	[redacted] (3.9)	[redacted] (4.9)	0.88 (0.72-1.08)	0.215	0.75 (0.61-0.92)	0.007	0.81 (0.68-0.97)	0.021
Stroke	[redacted] (0.9)	[redacted] (0.9)	[redacted] (0.9)	[redacted] (0.7)	1.23 (0.75-2.02)	0.403	1.38 (0.85-2.24)	0.190	1.30 (0.85-2.01)	0.225
Stratum 1: Aspirin	[redacted]									
Primary Endpoint: Composite of CV death, MI, stroke	[redacted]									
CV Death	[redacted]									
MI	[redacted]									
Stroke	[redacted]									
Stratum 2: Aspirin plus thienopyridine	[redacted]									
Primary Endpoint: Composite of CV death, MI, stroke	[redacted]									
CV Death	[redacted]									
MI	[redacted]									

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bd, bis die (twice daily); CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; mITT, modified intention-to-treat

- Secondary efficacy endpoints

A summary of the secondary outcome results is presented in Table 7. In all strata, secondary endpoint 1, a composite efficacy endpoint of all-cause death, MI or stroke was significantly reduced by the combined rivaroxaban group compared with the placebo group, with rates of 6.3% and 8.1%, respectively (HR 0.79, 95% CI: 0.69 to 0.91, p<0.001). These findings were very similar to the primary efficacy endpoint (composite of CV death, MI or stroke) [redacted]. In the analysis of the two individual doses of rivaroxaban, each significantly reduced the composite of all-cause death, MI or stroke compared with placebo (2.5 mg twice daily: HR 0.80, 95% CI: 0.68 to 0.94, p=0.007; and 5 mg twice daily: HR 0.79, 95% CI: 0.67 to 0.93, p=0.004, respectively). [redacted] When the survival component of the secondary efficacy endpoint was analysed individually, rivaroxaban 2.5 mg twice daily significantly reduced the risk of death from all causes compared with placebo ([redacted]). In contrast, rivaroxaban 5 mg twice daily did not reduce the risk of death from all causes ([redacted]). A similar pattern was also observed for the total population (Appendix 2).

For secondary endpoint 2, the net clinical outcome (a composite of CV death, MI, IS or TIMI major bleeding not associated with CABG), neither the combined rivaroxaban group (p=0.110) nor the individual 2.5 mg twice daily (p=0.166) or the 5 mg twice daily group (p=0.184) significantly decreased the net clinical endpoint compared with the placebo group. As a result, the hierarchical testing for secondary endpoints 3 and 4 was stopped in all strata. [redacted]. Although results of the remaining composite secondary efficacy endpoints are presented in Table 7 significance cannot be claimed (p64, 86, MS).

- Other analyses

Stent thrombosis was evaluated as a pre-specified standalone efficacy endpoint (p57, MS) and the results are summarised in Table 7. [redacted]. The ERG note that the EMA assessment report[2] states that 'Regarding the analyses of the occurrence of stent thrombosis the comparisons between rivaroxaban and placebo were post-hoc… These analyses were no part of the hierarchical testing procedure and hence, nor the initially planned confirmatory strategy. Formally

this may be a false positive finding, and, strictly, no claims should be made as a part of the indication'.

Table 7: Effect of rivaroxaban compared with placebo on secondary endpoints (mITT analysis excluding 3 sites): Licensed population (p85-97, MS)

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All strata	*N=4104*	*N=4089*	*N=8193*	*N=4160*						
Secondary endpoint 1: Composite of all cause death, MI, stroke	[redacted] (6.4)	[redacted] (6.2)	[redacted] (6.3)	[redacted] (8.1)	0.80 (0.68-0.94)	0.007	0.79 (0.67-0.93)	0.004	0.79 (0.69-0.91)	<0.001
Secondary endpoint 2: Net clinical outcome (composite of CV death, MI, ischaemic stroke or non-CABG TIMI major bleeding)	[redacted] (7.2)	[redacted] (7.2)	[redacted] (7.2)	[redacted] (8.1)	0.90 (0.77-1.05)	0.166	0.90 (0.77-1.05)	0.184	0.90 (0.78-1.03)	0.110
Secondary endpoint 3: Composite of CV death, MI, stroke, SRIR	[redacted] (8.5)	[redacted] (7.9)	[redacted] (8.2)	[redacted] (9.8)	0.87 (0.76-1.01)	0.059	0.81 (0.70-0.94)	0.006	0.84 (0.75-0.95)	0.006
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH	[redacted] (7.1)	[redacted] (7.4)	[redacted] (7.2)	[redacted] (8.9)	0.80 (0.68-0.93)	0.004	0.84 (0.72-0.98)	0.026	0.82 (0.72-0.93)	0.002
Individual outcomes										
Death (all-cause)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CABG TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
SRIH										
Stent thrombosis [a]										
Stratum 1: Aspirin										
Secondary endpoint 1: Composite of all cause death , MI, stroke										
Secondary endpoint 2: Net clinical outcome (composite of CV death, MI, ischaemic stroke or non-CABG TIMI major bleeding)										
Secondary Endpoint 3: Composite of CV death, MI, stroke, SRIR										
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH										
Individual outcomes										
Death (all-cause)										
Ischaemic stroke					-					
Non-CABG TIMI					-	-	-		-	

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
major bleeding										
SRIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stent thrombosis [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 2: Aspirin plus thienopyridine	[redacted]	[redacted]	[redacted]	[redacted]						
Secondary endpoint 1: Composite of all cause death, MI, stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoint 2: Net clinical outcome (composite of CV death, MI, ischaemic stroke or non-CABG TIMI major bleeding)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary Endpoint 3: Composite of CV death, MI, stroke, SRIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual outcomes										
Death (all-cause)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Ischaemic stroke										
Non-CABG TIMI major bleeding										
SRIR										
SRIH										
Stent thrombosis [a]										

bd, bis die (twice daily); CABG, coronary artery bypass grafting; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IS, Ischaemic stroke; MI, myocardial infarction; mITT, modified intention-to-treat; SRIR, Severe recurrent ischaemia requiring revascularisation; SRIH; Severe recurrent ischaemia requiring hospitalisation; TIMI, Thrombolysis in Myocardial Infarction

[a] Defined as definite, probable or possible by Academic Research Consortium definitions; method of analysis using ITT approach (p95-96, MS)

In the MS (p98-100) a range of subgroup analyses were presented for the total population; however, no subgroup analyses based on the licensed population were undertaken by the manufacturer. The MS (p100) states that 'such analyses are not statistically sound as the trial was not powered to draw conclusions about (non-specified) subgroups of subgroups.' The ERG notes that whether the trial was powered for the licensed population was not stated. Nevertheless, following an ERG request (manufacturer's clarification response to question A20), the manufacturer provided subgroup analysis data for the following groups (as per the final scope issued by NICE)[8]: people with NSTEMI, people with STEMI, people with diabetes mellitus, people who received prior primary PCI; and people who did not receive prior primary PCI in the acute phase of management. Whilst caution is urged in interpreting these data, rivaroxaban treatment (combined and individual doses) was generally associated with improved outcomes on the primary efficacy endpoint for type of index event (STEMI, NSTEMI, UA or NSTEMI plus UA), PCI for index event and for people with diabetes. The manufacturer states that 'In general, the rivaroxaban treatment was consistently associated with improved outcomes on the primary efficacy endpoint across all major subgroups. A favourable HR for rivaroxaban compared with placebo was observed across the majority of subgroups, both for the combined rivaroxaban groups, as well as for the 2.5 mg b.i.d. and 5 mg b.i.d. doses individually compared with placebo. For the majority of analyses, interaction p values were >0.05.' For detailed results, see the manufacturer's clarification response to question A20. [redacted]

4.2.4.2 Safety and tolerability

This section presents the main safety evidence, as reported by the manufacturer, of the licensed population from all participants who received at least one dose of study drug within the ATLAS ACS 2-TIMI 51 trial (i.e. primary safety analysis population). Where applicable, data have been re-tabulated in a consistent and more transparent format by the ERG.

The MS (including the manufacturer's clarification response to question A21 and A23, which suggest that data are not currently available) did not report any data in relation to treatment compliance or premature discontinuation of study treatments for the licenced population. Available data from the published ATLAS ACS 2-TIMI 51 trial[31] (including data from the MS [p102] and the manufacturer's clarification response to question A23) suggest that compliance with study treatment was high for the total population. During treatment, the proportion of patients who were at least 85% compliant with the study drug was 93.9%, 94.0% and 94.6% for the rivaroxaban 2.5 mg dose, 5 mg dose and placebo respectively. However, compliance with aspirin and thienopyridines was not reported. As a result, it

is not known if patients stopped using these drugs or were poorly compliant with them. Among patients who received at least one dose of a study drug, premature discontinuation of treatment occurred in 26.9% (1376/5115) of patients receiving the 2.5 mg dose of rivaroxaban, 29.4% (1504/5110) receiving the 5 mg dose of rivaroxaban and 26.4% (1351/5125) receiving placebo (p102, MS). No statistical comparisons were reported for these differences. The most common reasons for discontinuation of study treatment were adverse events (rivaroxaban 2.5 mg twice daily, 8.8%; rivaroxaban 5.0 mg twice daily, 10.9%; placebo, 7.3%), consent withdrawal (rivaroxaban 2.5 mg twice daily, 4.7%; rivaroxaban 5.0 mg twice daily, 4.3%; placebo, 4.3%) and 'other' (rivaroxaban 2.5 mg twice daily, 11.5%; rivaroxaban 5.0 mg twice daily, 11.3%; placebo, 11.8%). Further details are provided in the manufacturer's clarification response to question A21.

A summary of the main safety results for the licensed population is provided in Table 8. For completeness, results based on the total population of the ATLAS ACS 2-TIMI 51 trial are provided in Appendix 3. The primary safety endpoint was non-CABG TIMI major bleeding in the treatment-emergent safety analysis set, which comprised events that occurred from the first dose of the study drug up to the date of last dose of study drug plus 2 days (no reason was provided in the MS for the 2 day post dosing window). In all strata, treatment with rivaroxaban significantly increased the numbers of primary safety endpoint events in both the 2.5 mg twice daily (licensed dose) group (HR 3.44, 95% CI: 1.97 to 6.01, $p<0.001$) and the 5 mg twice daily group (HR 4.40, 95% CI: 2.55 to 7.60, $p<0.001$) compared with placebo in a dose-dependent manner. Similar significant results were observed in [redacted] and the total population (Appendix 3).

Table 8: Effect of rivaroxaban compared with placebo on safety endpoints (treatment-emergent safety analysis set)[a]: Licensed population (p108-109, MS)

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All strata	*N=4096*	*N=4072*	*N=8168*	*N=4157*						
Primary safety endpoint:[b] Non-CABG TIMI major bleeding	[redacted] (1.3)	[redacted] (1.6)	[redacted] (1.5)	[redacted] (0.4)	3.44 (1.97-6.01)	<0.001	4.40 (2.55-7.60)	<0.001	3.91 (2.32-6.59)	<0.001
Secondary safety endpoint: Clinically significant bleeding (composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual outcomes										
Fatal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI minor bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI bleeding requiring medical attention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intracranial haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bd, bis die (twice daily); CI, confidence interval; HR, hazard ratio; TIMI, Thrombolysis in Myocardial Infarction

[a] Treatment-emergent safety analysis set included all events from first dose up to the date of last dose of study drug plus 2 days

[b] Stratum 1: [redacted]

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Stratum 2										
[redacted]										

[redacted]

In the MS (p116-122), the reporting of treatment-emergent adverse events data was not well reported or transparent for the licensed (post-hoc analysis) and total population of the ATLAS ACS 2-TIMI 51 trial. A summary of the treatment-emergent adverse events (defined as those events starting on or after the first dose of study drug up to 2 days after the last dose of study medication) occurring in at least 1% of patients in any treatment group, as reported by the manufacturer, is reproduced (with minor changes) in Table 9.

[redacted]

Table 9: Treatment-emergent adverse events in at least 1% of patients (safety analysis set): Licensed population (reproduced with minor changes; p117-118, MS)

Adverse events	Rivaroxaban			Placebo n (%)
	2.5mg bd n (%)	5mg bd n (%)	Combined n (%)	
All strata	*N=4096*	*N=4072*	*N=8168*	*N=4157*
Total number of patients with treatment-emergent adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-emergent adverse events excluding bleeding adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Angina Pectoris	[redacted]	[redacted]	[redacted]	[redacted]
Angina Unstable	[redacted]	[redacted]	[redacted]	[redacted]
Acute Myocardial Infarction	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial Infarction	[redacted]	[redacted]	[redacted]	[redacted]
Atrial Fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac Failure	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gingival bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, Thoracic, Mediastinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and Medical Procedures	[redacted]	[redacted]	[redacted]	[redacted]
Percutaneous Coronary Intervention	[redacted]	[redacted]	[redacted]	[redacted]
Coronary Artery Bypass	[redacted]	[redacted]	[redacted]	[redacted]
Coronary Revascularisation	[redacted]	[redacted]	[redacted]	[redacted]
General Disorders & Administration Site Conditions	[redacted]	[redacted]	[redacted]	[redacted]
Chest Pain	[redacted]	[redacted]	[redacted]	[redacted]
Non-Cardiac Chest Pain	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and Procedural Complications	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Haematoma	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Infections & Infestations	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ecchymosis	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Arteriogram Coronary	[redacted]	[redacted]	[redacted]	[redacted]
Alanine Aminotransferase Increased	[redacted]	[redacted]	[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Renal and Urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]

bd, bis die (twice daily); NR, not reported

[redacted]

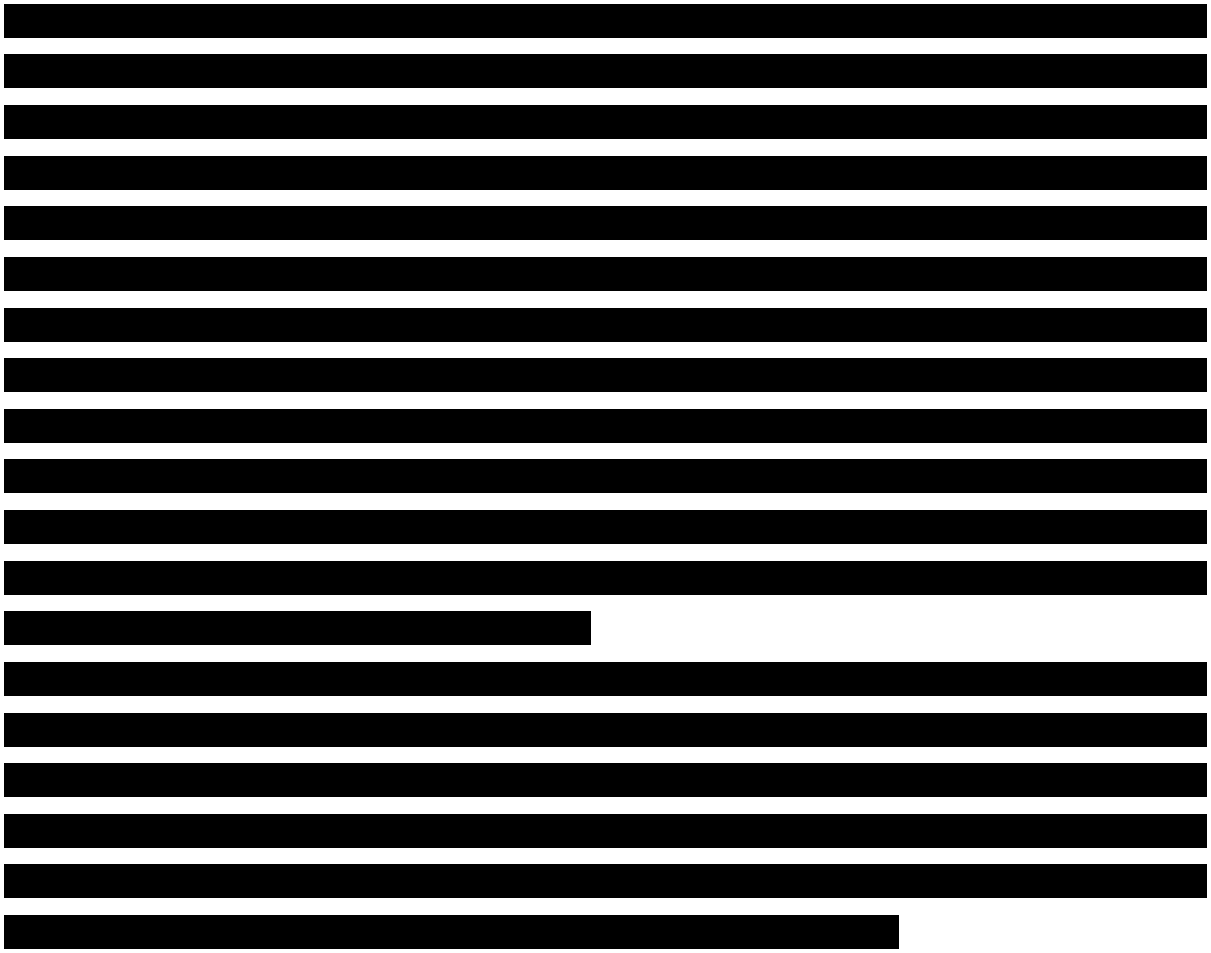


Figure 4: Confidential therefore removed

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the manufacturer to supplement the direct evidence as there is only one trial that has evaluated the use of rivaroxaban (in combination with aspirin or with aspirin as a thienopyridine [clopidogrel]) compared with aspirin alone or with aspirin and a thienopyridine (clopidogrel) in patients with ACS with elevated cardiac biomarkers (manufacturer's clarification response to question A24). The ERG agreed with this position, which is in line with the final scope issued by NICE.[8]

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the manufacturer (see section 4.3).

4.5 Additional work on clinical effectiveness undertaken by the ERG

As the manufacturer undertook a comprehensive systematic review (no major limitations were noted) of rivaroxaban for the prevention of adverse outcomes in patients after the acute management of ACS, no additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the MS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence in the MS is based on a systematic review of rivaroxaban for the prevention of adverse outcomes in patients after the acute management of ACS. The ERG is reasonably confident that all relevant studies (published and unpublished) of rivaroxaban (in combination with aspirin or with aspirin and a thienopyridine [clopidogrel]) were included in the MS, including data from ongoing/planned studies.

4.6.2 Interpretation of treatment effects reported in the MS in relation to relevant population, interventions, comparator and outcomes

A key issue that may limit the robustness of the efficacy and safety data reported in the MS relates to the post-hoc subgroup analyses of participants from the ATLAS ACS 2-TIMI 51 trial that had a recent ACS with elevated cardiac biomarkers but without prior stroke or TIA (the licensed population). As the study was not powered for this post-hoc subgroup analysis, the effect of initial randomisation may have been lost. In addition to the known limitations of post-hoc subgroup analyses,[44] Sun *et al*.[45] also suggest that the credibility of subgroup effects, even when claims are strong, is usually low. However, the EMA assessment report[2] states that '…the overall results appear sufficiently convincing in the targeted subgroup of patients after an acute coronary syndrome (ACS)

with elevated cardiac biomarkers (post-hoc analysis)'. As discussed in section 4.2.3 the ERG believes that there is still the scope for informative censoring to be present which may have biased the results in a manner favourable for rivaroxaban.

Another issue that may limit the robustness of the evidence relates to the high dropout rates and missing vital status data in the ATLAS ACS 2-TIMI 51 trial. Despite the lack of corresponding data for the licensed population, 15.5% (2402/15,526) of the total randomised population prematurely discontinued from the study (rivaroxaban 2.5 mg twice daily, 15.0%; rivaroxaban 5 mg twice daily, 16.3%; placebo, 15.1%). In general, the validity of a study may still be compromised for losses between 5% and 20%.[46]

[redacted]

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The key uncertainties in the clinical evidence in addition to that of informative censoring primarily relate to optimal dosing, duration of treatment and generalisability to the UK population. Further details are provided below.

Optimal dosing

Although the ATLAS ACS-TIMI 46 study[29] was designed to select the most favourable dose and dosing regimen of rivaroxaban in patients receiving aspirin with or without a thienopyridine for further assessment in a phase III trial (ATLAS ACS 2-TIMI 51 study), the 2.5 mg twice daily dose (or 5 mg once daily) was the lowest effective dose tested. It remains unclear whether alternative, lower dosage regimens, such as 2 mg twice daily or 1.5 mg twice daily may have been clinically effective with fewer adverse events.

Duration of treatment

The mean treatment duration with the study drug in the ATLAS ACS 2-TIMI 51 study was 13.1 months. As a result, efficacy and safety of rivaroxaban 2.5 mg twice daily beyond this time is limited. This is reflected in the summary of product characteristics,[17] which recommends that extension of treatment beyond 12 months should be done on an individual patient basis because experience up to 24 months is limited. Despite an ERG request for further clarification (manufacturer's clarification response to A1) on a more precise continuation rule, this was not explicitly provided by the manufacturer. In addition, the terminology 'elevated cardiac biomarkers' is less sensitive than if a

patient exhibits a rise and/ or fall in their cardiac biomarkers (preferably troponins) as many patients have persistently raised biomarkers outside the context of ACS[18] and in contemporary practice, the diagnosis of NSTEMI requires evidence of myocardial ischaemia combined with a rise and/or fall in the blood level of a cardiac biomarker (troponin). Also, the sensitivity of biomarker assays has increased since the study was conducted and 'biomarker negative' at the time of the trial might be 'biomarker positive' using current more sensitive assays. Hence, the use of more sensitive assays in the ATLAS ACS 2-TIMI 51 trial might have led to the reclassification of patients with UA and inclusion of these patients in the subgroup considered in the licensed population.

Generalisability to the population of England and Wales

The ATLAS ACS 2-TIMI 51 study was a large, well designed, multicentre RCT. Of all randomised patients 74.7% were men, and the mean age of participants was 61.8 years [redacted] However, ACS patients in England and Wales are usually older, with a mean age of 65 years and 72 years for patients with STEMI and NSTEMI, respectively.[6] Moreover, as noted in the EMA assessment report[2] and the NICE evidence summary,[47] study participants in the overall ATLAS ACS 2-TIMI 51 study were considered to be at low risk. The ACS population in the trial had little co-morbidity, lower than usual use of PCI and included a relatively small proportion of people who were aged over 75 years (n=1405, 9.0%) or had impaired renal function with creatinine clearance <50 ml/min (n=1086, 7.1%). As a result, the findings from the ATLAS ACS 2-TIMI 51 trial may not be applicable to an older population or those with a greater incidence of renal impairment and a higher baseline bleeding risk.

5 COST-EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 State objective of cost-effectiveness review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

The manufacturer performed a literature search to identify published cost-effectiveness analyses of interventions for the secondary prevention of ACS events. The search was performed in March 2014 in several electronic bibliographic databases: MEDLINE, MEDLINE in Process, EMBASE and the Cochrane Library. Additional sources included UK HTA websites (NICE and the Scottish Medicines Consortium) and conference proceedings of the American Heart Association scientific sessions (2012-13), European Society of Cardiology (2013), American College of Cardiology (2013) and the International Society for Pharmacoeconomics and Outcomes Research (2013). Appropriate filters were used to retrieve cost-effectiveness studies and details of searches for conference proceedings and of UK HTA websites were clearly reported.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

The inclusion/exclusion criteria used in the manufacturer's study selection are provided in Table 10. The search strategy was broad and covered many relevant interventions for ACS. Cost-effectiveness studies of ticagrelor and prasugrel were included in the systematic review even though they were not included in the final scope issued by NICE.[8] This was because cost-effectiveness models for these interventions could provide useful information on costs and utilities of the health states in a *de novo* model, if developing one was required.

The ERG had some concerns about the country specific inclusion/exclusion criteria, as no rationale was provided for only identifying studies from the USA, Canada, United Kingdom, Germany, France, Italy and Spain. However, given the values used in the model it is unlikely that the country specific exclusion criteria lead to the exclusion of studies which contained parameters of greater relevance to the decision problem.

Table 10: Inclusion/exclusion criteria used to select studies of the cost-effectiveness of rivaroxaban in the MS (p139-143, Table 24, MS)

	Inclusion criteria	Exclusion criteria	Rationale/comments
Population	• Adults initially hospitalised with ACS (unstable angina, STEMI, or NSTEMI) who are managed for secondary prevention of their ACS event	• Patients with stable angina, or other CV disease that is not ACS • Primary prevention of ACS (mainly relevant for studies with aspirin) • Children • Mixed populations of stable and unstable angina, which do not present data for unstable angina separately	
Interventions	*Cost/resource use studies:* • All studies reporting cost and resource use data will be included in the review regardless of the treatment type *Economic evaluations:* • Rivaroxaban • Ticagrelor • Prasugrel • Aspirin alone (≤150mg once daily) • Clopidogrel • Aspirin (≤150mg once daily) + clopidogrel	*Cost/resource use studies*: None *Economic evaluations:* • High-dose aspirin (if dose is > 150 mg/day) • Warfarin • Ticlopidine • Vitamin K antagonist • Phenprocoumon • Therapies used in the acute phase of ACS management, e.g. (this is not an exhaustive list): o Bivalirudin o Fondaparinux o Enoxaparin o Otamixaban o Streptokinase, alteplase, and other “ase” products that are used for acute management	Although ticagrelor and prasugrel are not included as comparators in the scope, these interventions were included in the economic review as studies evaluating these interventions would report cost and utility values relevant to the patient population of the current review.

Outcomes	• Direct medical costs of managing secondary prevention in ACS (including management of adverse events), resource utilisation associated with managing secondary prevention in ACS (including management of adverse events), hospitalisations, short-term disability costs of secondary prevention in ACS, indirect costs such as absence from work • Cost-effectiveness and budget-impact analysis results for the relevant therapies in secondary prevention in ACS	• Measures of clinical effectiveness or quality of life measures	
Study design	• Any studies (e.g., clinical trials or other prospective or cross-sectional studies) reporting resource utilisation and costs • Economic evaluation studies, e.g., studies based on models, cost analyses performed alongside clinical trials, and budget-impact analyses	*Study designs other than cost/resource use studies and economic evaluations including the following:* • Reviews • Letters • Comment articles • Studies focused on short-term in-hospital treatment of ACS • Models with a time horizon of < 30 days Any non-primary source of cost or resource use data • Studies not reporting cost/resource use data	These study designs will provide data on the economic burden of ACS, cost of illness and resource use These studies report economic evaluations and will provide cost or resource use data adapted from other studies for use as model inputs

Other	• English language • Countries: USA, Canada, Germany, France, Italy, Spain, United Kingdom • Publication timeframe restrictions: 2000-2014	• Non-English language • Articles not concerned with any of the countries of interest (the US, Canada, France, Germany, Italy, Spain, the UK) • Publication timeframe restrictions: Studies published prior to 2000	• The searches were conducted from 2000 to present in all the literature databases to identify relevant articles with recent cost data. Older articles contain older costs, which would need to be inflated to current costs to be useful; however, inflating costs in this way over many years can introduce errors. Further, the standard of care in management of ACS has changed dramatically since 2000, because of the introduction of clopidogrel into clinical practice; therefore, much of the information published before 2000 is not relevant.

ACS, acute coronary syndrome; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction

5.1.3 What studies were included in the cost-effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the most important cost-effectiveness studies

The systematic review identified a total of 59 records, 46 of which were unique mathematical models. Of the 46 identified mathematical models, 8 were presented in conference abstract form. The manufacturer identified no studies which had evaluated the cost-effectiveness of rivaroxaban plus aspirin with or without clopidogrel compared to aspirin with or without clopidogrel for the secondary prevention of ACS.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost-effectiveness review? If not, provide details

As no cost-effectiveness studies comparing rivaroxaban plus aspirin with or without clopidogrel to aspirin with or without clopidogrel in the secondary prevention of ACS were identified by the manufacturer, a *de novo* model was constructed.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 Objective of the model, intervention and comparator

Several errors were identified with the initial model; some of these errors were fixed through the manufacturer's response to clarification questions. The errors which were fixed include:

- An option to age adjust the general population utilities (manufacturer's clarification response to question B22)
- An option to alter the treatment duration of rivaroxaban (manufacturer's clarification response to question B28)
- An option to estimate the transition probabilities using the ATLAS ACS 2-TIMI 51 trial data (manufacturer's clarification response to question B26)

Several errors which were not fixed include:

- Ignoring the published uncertainty in the PSA (manufacturer's clarification response to question B1)
- Inappropriately ignoring the correlation between model parameters (manufacturer's clarification response to question B3)

Further to these errors the manufacturer partially fixed time cycle in the first 96 weeks of the model in clarification question B4. In the manufacturer's response, the health state costs were appropriately adjusted; however, the life years gained matrix and the times used for discounting costs and QALYs was not.

The ERG will consider the model sent following the clarification process for most of this critique. The ERG did ask the manufacturer to change their approach to the probabilistic sensitivity analyses (PSA) in clarification questions B1, B2 and B3. In the manufacturer's response to these clarification questions, some additional PSAs were conducted. However, a full set of PSA results was not presented in the manufacturer's response to these questions. Therefore the ERG will focus on critiquing the original PSA.

The objective of the model was to estimate the costs incurred and QALYs accrued by two competing strategies: providing aspirin with or without clopidogrel (the comparator); or providing rivaroxaban plus aspirin with or without clopidogrel. For patients who could not take clopidogrel the model compared rivaroxaban with aspirin to aspirin alone.

It was assumed that patients aspirin treatment would continue indefinitely, their clopidogrel treatment would continue for one year and their rivaroxaban treatment would continue for between one and two years. The summary of product characteristics[17] states that 'among patients receiving dual anti-platelet therapy 98.8% received clopidogrel, 0.9% received ticlopidine and 0.3% received prasugrel' (the primary published paper[31] and the MS [p45-48] suggest that thienopyridine use was limited to clopidogrel or ticlopidine) with a mean treatment duration of 13.3 months.[31] The MS (p132) notes that prasugrel and ticagrelor were not approved or part of standard care protocols at the time the ATLAS ACS 2-TIMI 51 trial was initiated; however, the ERGs clinical advisors believe that ticlopidine is not standard practice in the UK and is excluded from the scope of this appraisal.

5.2.2 The population modelled

The population modelled was the patient subgroups who were biomarker positive and had not experienced a prior TIA in the ATLAS ACS 2-TIMI 51 trial. The data in the rivaroxaban model arm was not pooled from both rivaroxaban trial arms. As such, the population for rivaroxaban is limited to those patients who received 2.5 mg rivaroxaban twice daily. Therefore all issues with the generalisability of the population identified in section 4.6.3 apply to the mathematical model results.

5.2.3 The model structure

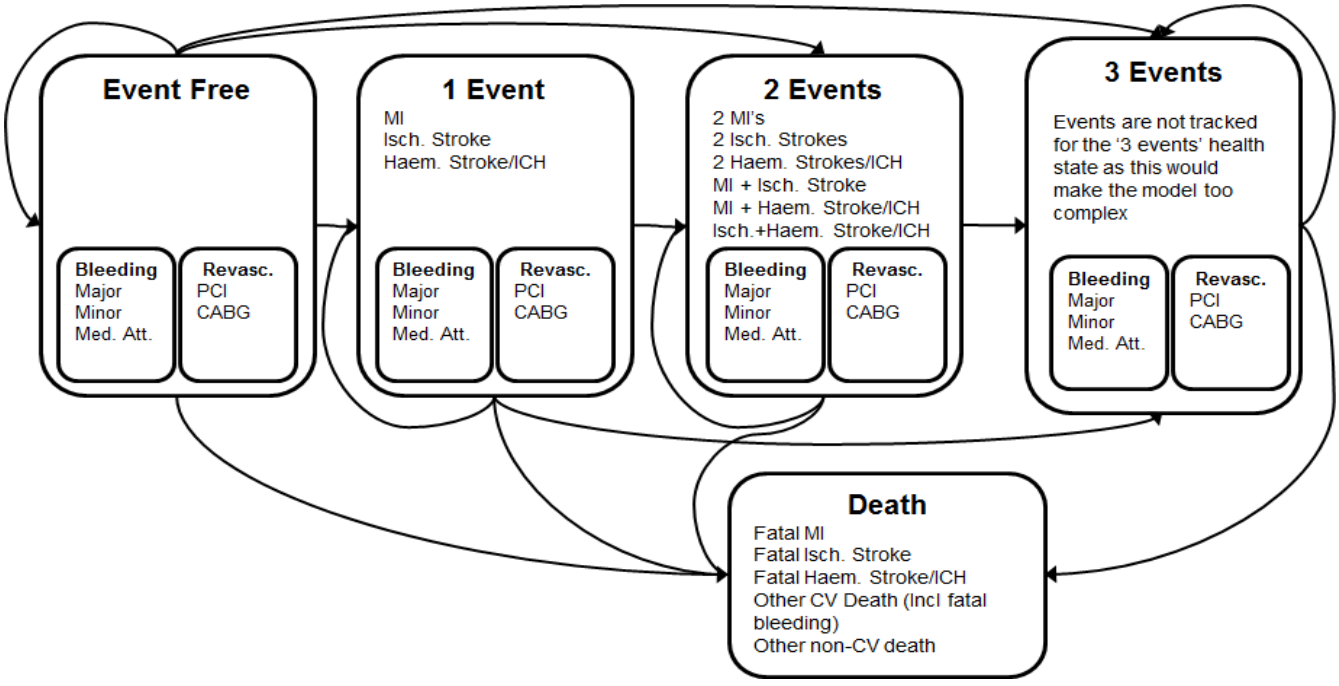
The manufacturer submitted a state transition cohort model written in Microsoft Excel (Microsoft Corporation, Redmond, Washington). The model used a time horizon of 40-years that was divided into two periods: an observation period which was intended to replicate the duration of the trial data and an extrapolation period. The extrapolation period started after 96 weeks and had a cycle length of 6 months. In the observation period the initial two cycles had a cycle length of 4 and 8 weeks

respectively and the remaining cycles used a cycle length of 12 weeks. In the manufacturer's initial submission 96 weeks was assumed to last two years instead of 104 weeks. This discrepancy was introduced by assuming that cycle lengths of 12 weeks represented a quarter of a year (13 weeks).

In the manufacturer's response to clarification question B4, it was established that these time cycles were chosen so that the model cycles matched the data collection points in the trial. It is unclear to the ERG why this was done, as in the manufacturer's base case Weibull curves were used to interpolate the data (see section 5.2.5.1). Therefore the manufacturer could obtain transition probabilities between any two time points that they chose, not just the data collection points in the trial data.

In the base case, costs and QALYs are both discounted at a rate of 3.5% as recommended by NICE.[20] Half cycle correction was performed on the markov trace. The model structure is presented in Figure 5, in the manufacturer's response to clarification question B21 it was established that it was not possible for patients to transition from the no event health state to the multiple ACS event health states in the extrapolation period of the model.

Figure 5: The model structure (p174, Figure 19, MS)



MI, myocardial infarction; Isch. Stroke, ischaemic stroke; Haem.Stroke/ICH, haemorrhagic stroke/ intracranial haemorrhage; Med. Att., requiring medical attention; CV, cardiovascular

5.2.4 The health states within the model

The model consisted of a number of health states corresponding to whether no further ACS event occurred or whether the patient suffered an ACS event. The ACS events considered in the model were: MI, IS, haemorrhagic stroke or intracranial haemorrhage (HS/ICH); a bleeding event measured on the TIMI scale; and revascularisation. These ACS events fell into two broad categories: those with longer term implications for the relative risks of developing further conditions, utility and costs; and those deemed to be transient events where the impacts were limited to one model cycle.

Patients could die at any time in the model and there were multiple causes of death simulated in the model. Patients could die from an MI, IS or HS/ICH or other CV death, which included deaths relating to bleeding. Patients could also die from non-CV causes, at any time point in the model.

The long term ACS events included the MI, IS and HS/ICH conditions. The long term ACS events had two subsequent tunnel states to allow for the patients utility to improve over time, and for the cost of treatment and the relative risk of suffering from a subsequent event to fall over time. Patients could suffer from up to three ACS events; the specific types of ACS event were recorded when patients suffered from two or fewer events. When three events occur, it is assumed that one event of each type (i.e. an MI, an IS and a HS/ICH) has occurred to the patients in this health state.

The submitted model structure leads to the potential for systematic errors to occur, as the time between multiple events is not tracked. This causes the potential for systematic errors in three ways; firstly, the patients who suffer from two events in one time cycle are not distinguished from those patients who suffer multiple events in separate time cycles. Secondly, for the patients who suffer from multiple events in separate time cycles any improvement over time that they may have experienced is ignored. Finally, for those patients who transition into the multiple event states from the single event states, the first event is not tracked. The exact errors relating to the structure will be addressed in sections 5.2.6.2 and 5.2.7.1. There are two solutions to this problem; firstly, a more complicated state transition cohort model could be developed so that cost and utilities for each multiple event state can vary by the preceding health state and the time between the events. Secondly, a patient level simulation approach could be taken.

The health states corresponding to the bleeding and revascularisations were assumed to be transient health states, when a patient enters these states a one off cost and utility decrement was applied. These transient health states were applied to only the patients in the observation period of the model, implicitly assuming that the bleeding and revascularisation rates for the two interventions are

comparable after rivaroxaban treatment was discontinued for all patients at the end of the second year. The clinical advisors to the ERG agree that the time horizon of the transient events was appropriate but that this approach ignored the possibility that multiple bleeding events could occur in one time cycle.

In accordance with the ATLAS ACS 2-TIMI 51 trial, it was assumed that in the base case 93% of patients received clopidogrel plus aspirin and 7% of patients received aspirin alone. A scenario analysis was presented considering only those patients who received clopidogrel and aspirin.

5.2.5 Transition probabilities

5.2.5.1 Transition probabilities in the observation period.

In the base case the transition probabilities for future ACS-related events were determined by fitting a Weibull distribution to the trial data. This was undertaken independently for both the rivaroxaban 2.5 mg data and for the placebo data and thus there was no assumption of proportional hazards. This curve fitting was conducted as the manufacturer states that the Kaplan-Meier curves did not make clinical sense, (MS, p191), a statement that is concerning given that these were the direct results from the trial. The clinical advisors to the ERG did not agree with this explanation but did note that there were too few patients after approximately 15 months to estimate the transition probabilities from the Kaplan-Meier curves reliably. A problem with using the Weibull curves suggested by the manufacturer to inform the transition probabilities within the model is illustrated in Table 11, which clearly shows that when the interpolated results are used, the numbers of ACS events in both the intervention and the comparator arms are over predicted.

Table 11: Summary of model results compared with clinical data for the observation period (p325, Table 70, MS)

	Clinical trial result (licensed population)[a]	Model result (from interpolation)
Rivaroxaban		
MI	4.24%	5.92%
IS	0.58%	0.80%
HS/ICH	0.19%	0.27%
OCD	1.54%	3.41%
NCD	0.39%	0.90%
Comparator	**Clinical trial result**	**Model result (from interpolation)**
MI	4.83%	6.42%
IS	0.50%	0.72%
HS/ICH	0.10%	0.17%
OCD	2.60%	4.57%
NCD	0.46%	0.96%

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non-cardiovascular death

[a] It is unclear to the ERG if the population refers to the licensed population in all strata or for just one strata, or if the patient population is those patients included in the ITT or mITT analysis

In the manufacturer's clarification response to question B7, the manufacturer stated that there were three reasons for this. Firstly, in the model, clopidogrel may only be administered for one year. In the ATLAS ACS 2-TIMI 51 trial not all patients who received dual anti-platelet therapy received clopidogrel and those patients who received clopidogrel could continue treatment for more than one year. Secondly, the Weibull parameters mean that the transition probabilities do not match the event rates suggested by the trial data. The manufacturer did fit an exponential curve to the event rates (p192–194), these functions were rejected in favour of the Weibull distribution. Other parametric models to fit the Kaplan curves were rejected as being inappropriate by the manufacturer (p191-192, Table 33, MS). Finally, the manufacturer used a different discontinuation rate for rivaroxaban than that used in the ATLAS ACS 2-TIMI 51 trial. The rationale for this was that the license for rivaroxaban did not allow for its use as in the ATLAS ACS 2-TIMI 51 trial.

5.2.5.2 Transition probabilities for the transient health states

The transition probabilities for the transient event states were informed by the event rates in the ATLAS ACS 2-TIMI 51trial. For each transient event, the total number of events in the trial period was added together. The event rate was then calculated by dividing through by the total number of patients in the trial. The ERG believes that this approach is inappropriate as cost and QALYs of the events which occur in the second year were not appropriately discounted. Also, there is no clear adjustment for the number of additional patients who are assumed to discontinue rivaroxaban in year

2 (see section 5.2.5.5) or for those patients who are assumed to discontinue their clopidogrel or rivaroxaban treatment after an ACS event (see section 5.2.5.4). The number of events used to populate the mathematical model is given in Table 12. It should be noted that fatal bleeding events were included in the model in the other cardiovascular death health state. As such, fatal bleeding events are not presented in Table 12.

Table 12: 12 weekly bleeding and revascularisation events reported in the ATLAS ACS 2-TIMI 51 trial (biomarker positive, no prior stroke / TIA patients) (p196, Table 34, MS)

	Comparator: CLOP + ASA + placebo / ASA monotherapy + placebo								**Intervention: Rivaroxaban 2.5mg + CLOP + ASA / Rivaroxaban 2.5mg + ASA monotherapy**							
	1st 12 weeks	2nd 12 weeks	3rd 12 weeks	4th 12 weeks	5th 12 weeks	6th 12 weeks	7th 12 weeks	8th 12 weeks	1st 12 weeks	2nd 12 weeks	3rd 12 weeks	4th 12 weeks	5th 12 weeks	6th 12 weeks	7th 12 weeks	8th 12 weeks
Bleeding Events																
TIMI major	12	2	4	2	2	0	1	0	21	12	9	5	8	1	2	1
TIMI minor	13	5	3	1	1	0	1	0	9	6	4	3	4	1	1	0
TIMI req med attention	130	54	40	24	24	14	10	6	227	104	65	49	40	18	8	5
Revascularisation Events																
PCI/PTCA	338	99	69	45	39	18	15	9	327	130	80	43	24	22	2	9
CABG	63	20	17	6	6	3	1	0	49	23	11	9	3	3	1	0

PTCA/PCI, Percutaneous transluminal coronary angioplasty/ Percutaneous coronary intervention; CABG, coronary artery bypass graft; CLOP, clopidogrel; ASA, aspirin
The number of patients who were been followed up at each trial time point was not presented by the manufacturer in this table

The transient event states were only applied in the observation period. This is equivalent to assuming that any differences in bleeding risks between the two populations are equivalent after rivaroxaban has been discontinued.

5.2.5.3 Transition probabilities in the extrapolation period

The transition probabilities in the extrapolation period were estimated from the trial data assuming that the underlying rates in the last cycle were maintained but then subjected to changes due to patients ageing. In the manufacturer's response to clarification question B18, it was established that the manufacturer did not extrapolate the Weibull curves as they felt that the hazard function should

start increasing over time after the observation period. It would be expected that the hazard function should decline for some period of time due to treatment effects, but would start to increase after some period of time due to ageing effects. The manufacturer has assumed that the hazard function for all transition probabilities is decreasing prior to the 96th week and is increasing after the 96th week. It is of concern to the ERG that the manufacturer has provided no evidence to support the assumption that the hazard function will start to increase for all event rates after the 96th week.

In the manufacturer's response to clarification question B19, it was established that the manufacturer used visual checks to assess if the last transition probability from the observation period was an outlier when trial data was used. The manufacturer believes that by using interpolation methods the effects of any outliers are minimised. The ERG notes that unless the outliers were removed when the Weibull curves were fitted, then these would influence the fitted curves. It is of concern to the ERG that there was no formal check for outliers in the last cycle of the observation period in the manufacturer's base case as this was extrapolated for the remainder of the model.

The manufacturer calculated the initial case fatality values from a variety of sources. The methods of calculation have been summarised in Table 13.

Table 13: The initial case fatalities used in the manufacturer's model

Parameter	Initial case fatality	Source
Fatal MI	13.4%	ATLAS ACS 2- TIMI 51 trial Proportion of fatal MIs out of all MIs in the last cycle of the observation period
Fatal Stroke (IS and HS/ICH)	11.7%	Hippisley-Cox *et al.*[48] Multiplication of the percentage of stroke fatalities and the percentage of stroke fatalities within the first 30 days of the study.
Non-cardiovascular mortality	Depends on the age used in the model	UK life tables ONS[49a] Calculated the non-cardiovascular mortality was a weighted average of the male and female non-cardiovascular mortality. The proportion of males and females in the ATLAS ACS 2- TIMI 51 trial was used to conduct the weighted average.

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke / intracranial haemorrhage
[a] Full bibliographic details were not provided by the manufacturer

In the manufacturer's response to clarification question B9, it was established that the growth rates of event probabilities over time were calibrated using the SOLVER add in for Microsoft Excel (Microsoft Corporation, Redmond, Washington). It was also established in the manufacturer's response to clarification question B9 that the following parameters were calibrated:

- The age specific increase in the probability to have an MI

- The age specific increase in the probability to have an IS
- The age specific increase in the probability to have a haemorrhagic stroke
- The age specific increase in the probability to die of other vascular death
- The age specific increase in the probability to die of a non-vascular death
- The age specific increase in the probability to die of a MI, given an MI
- The age specific increase in the probability to die of a stroke, given a stroke

Table 14: Annual age specific increased risk estimates derived by means of calibration and applied to each model cycle within the extrapolation period (p210, Table 47, MS)

Event	% Increase with age from calibration	Source
MI	8.70%	Calibration
IS	10.65%	Calibration
HS/ICH	10.73%	Calibration
OCD	10.03%	Calibration
NCD	10.28%	Calibration
Case fatality MI	-13.90%	Calibration
Case fatality IS	-9.00%	Calibration
Case fatality HS/ICH	-9.00%	Calibration

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non-cardiovascular death

The clinical advisors to the ERG believe that the negative growth rates over time for the case fatalities of MI, IS and HS/ICH lack face validity. In the manufacturer's response to clarification question B9 the manufacturer clarified that the parameters given in Table 15 and a life expectancy of 13.55 years[50] were used to calibrate the model parameters in Table 14. The manufacturer felt that the calibrated values were acceptable as the competing risks of the other CV death and the non CV death led to the fatality rate increasing over time. The ERG believes that the negative growth rate of the case fatality of MI, IS and HS/ICH is not acceptable as each type of death has a cost associated with it (see section 5.2.6.2).

Table 15: Annual age specific increased risk estimated for ACS events obtained from literature and predicted by the model (p210, Table 46, MS)

Event	% Increase with age from literature	% Increase with age predicted by the model	Literature source
MI	1.075	1.074	Smolina et al 2012[50]
IS	1.093	1.093	Hippisley-Cox et al 2004[48]
HS/ICH	1.093	1.094	Assumption based on Hippisley-Cox et al 2004[48]
OCD	1.103	1.087	Smolina et al 2012[50]
NCD	1.097	1.089	ONS 2012[49]
Case fatality MI	1.045	1.046	Smolina et al 2012[50]
Case fatality IS	1.056	1.048	Factor of 1.67 based on relative difference in fatal and non-fatal MI presented in Smolina et al 2012[50]
Case fatality HS/ICH	1.056	1.048	Assumption based on case fatality IS

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non-cardiovascular death

The ERG is uncertain as to how the '% increase with age' predicted by the model in Table 15 is calculated, as these figures appear to contradict the growth rates used in the model which are presented in Table 14.

The conversion of the trial event rates from 12 weeks to 26 weeks was conducted appropriately.

The formulae used to extrapolate the transition probabilities over time are given in Appendix 14 of the MS (p449 – 451). An error was identified in the growth rate of surviving and dying from an ACS event given that one occurred in the manufacturer's response to clarification question B26 it was established that the correct formulae should apply $(1+r_{change})^t$ instead of $1/(1+r_{change})^t$. In the model these formulae were correctly applied.

For example the probability that a MI is fatal should read:

And the probability that a MI is non-fatal should read:

The ERG could not verify all of the 19,968 transition probabilities were correctly specified due to time constraints. However these formulae were generally appropriate.

5.2.5.4 Continuation rates due to ACS events

In the model it was assumed that patients could discontinue treatment in the observation period after they had suffered an ACS event. The probability of discontinuation following an ACS event was derived from the ATLAS ACS 2-TIMI 51 trial. This was calculated by using the whole trial population, not the subgroup under consideration.

Table 16: Permanent continuation rates in the rivaroxaban arm – following a MI, IS or HS/ICH event (base case) (p197, Table 35, MS)

	Rivaroxaban
Following a MI	94.69%
Following an IS	54.29%
Following a HS/ICH	0.00%

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage

As the ATLAS ACS 2-TIMI 51 trial was an international, multicentre study, clopidogrel or ticlopidine could be used in combination with aspirin to prevent a second ACS event. The clinical advisors to ERG note that ticlopidine is not used in current clinical practice in the UK. The discontinuation rate in Table 17 is calculated from proportion of patients who continued their clopidogrel or ticlopidine treatment after an ACS event. To make this clear the term thienopyridine had been used, this is the class of drugs which clopidogrel and ticlopidine belong to.

Table 17: Permanent continuation of thienopyridine in both the rivaroxaban and comparator arms following a MI, IS or HS/ICH event (base case) (p198, Table 36, MS)

	Rivaroxaban	Comparator
Following a MI	69.27%	70.74%
Following an IS	66.67%	50.00%
Following a HS/ICH	0.00%	0.00%

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage

5.2.5.5 Continuation rates of rivaroxaban beyond the first 48 weeks

The UK marketing authorisation for rivaroxaban states that “Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited” (p 10, Table A1, MS). To reflect this, the manufacturer adjusted the efficacy and the costs of rivaroxaban after 48 weeks as in Table 18. The change in efficacy and costs were calculated by selecting numbers which ensured that 19% of patients continued on rivaroxaban after 48 weeks. It is of concern to the ERG as to how the continuation rates were calculated. There is no clear indication in the MS as to

how the patients who continue rivaroxaban treatment after one year are selected from the rest of the patient population. It is unknown whether the data presented in Table 18 would be applicable to the UK population if rivaroxaban were to be recommended by NICE.

Table 18: Base case parameters for the change in efficacy and costs to represent patient discontinuation in the second year of treatment. Table adapted from that on p199, Table 38, MS

	ATLAS 2 treatment continuation (2.5 mg bd, combined strata) [1-discontinuation rate]	Assumed proportion of patients who continue in the trial that would continue treatment in a real-world setting	Model treatment continuation rate
0-4 weeks	1-6.90%=93.10%	100 %	93.10%
4-12 weeks	1-10.46%=89.54%	100 %	89.54%
12-24 weeks	1-13.06%=86.94%	100 %	86.94%
24-36 weeks	1-17.77%= 82.23%	100 %	82.23%
36-48 weeks	1-21.55%=78.45%	100 %	78.45%
48-60 weeks	1-23.94%= 76.06%	25 %	19.02%
60-72 weeks	1-26.51%= 73.49%	18 %	13.23%
72-84 weeks	1-27.94%= 72.06%	12 %	8.65%
84-96 weeks	1-29.73%= 71.27%	6%	4.28%

bd, bis die (twice daily)

The change in efficacy and costs reflect the proportion of the costs and efficacy that are assumed to remain in the rivaroxaban arm, for those patients who have continued rivaroxaban treatment. No treatment effect or cost was applied to those patients who discontinued rivaroxaban treatment.

For example, in the 48-60 week of the ATLAS ACS 2-TIMI 51, 23.94% of patients had discontinued rivaroxaban treatment. For these patients the efficacy of rivaroxaban is zero and no costs are applied. The remaining 76.06% of patients continued rivaroxaban treatment in the 48-60 week period. However, the manufacturer does not believe that this many patients will continue rivaroxaban outside of a trial setting. It was assumed that the proportion continuing rivaroxaban would be only 25% of the trial value in a real-world setting. In the manufacturer's response to clarification question B9 they stated that the adjustment to the proportion of patients continuing on rivaroxaban was made on the basis of discussion with key opinion leaders. No further details were provided.

5.2.5.6 The relative risk of suffering a further ACS event after a model ACS event in the extrapolation period

Table 19 shows the relative risk of suffering further events given that an event has already occurred.

Table 19: Relative risk of suffering subsequent events (p207, Table 44, MS)

Relative risks for subsequent events	**After MI**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	4.9	2.1	1.5
IS	3.2	1.8	1.5
HS/ICH	1.0	1.0	1.5
Fatal MI	4.9	2.1	1.5
Fatal IS	3.2	1.8	1.5
Fatal HS/ICH	1.0	1.0	1.5
OCD	3.0	1.6	1.5
Relative risks for subsequent events	**After IS**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	4.9	2.1	1.5
IS	3.2	1.8	1.5
HS/ICH	1.0	1.0	1.5
Fatal MI	4.9	2.1	1.5
Fatal IS	3.2	1.8	1.5
Fatal HS/ICH	1.0	1.0	1.5
OCD	3.0	1.6	1.5
Relative risks for subsequent events	**After HS**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	1.0	1.0	1.5
IS	1.0	1.0	1.5
HS/ICH	4.9	2.1	1.5
Fatal MI	1.0	1.0	1.5
Fatal IS	1.0	1.0	1.5
Fatal HS/ICH	4.9	2.1	1.5
OCD	1.0	1.0	1.5
Relative risks for subsequent events	**3 events**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI			
IS	1.5	1.5	1.5
HS/ICH			
Fatal MI	1.5	1.5	1.5
Fatal IS	1.5	1.5	1.5
Fatal HS/ICH	1.5	1.5	1.5
OCD	1.5	1.5	1.5

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non-cardiovascular death

In the manufacturer's response to clarification question B10, it was established that the post 12 months relative risk was calculated from the data reported by Smolina *et al.*[50] which states that 'the risk of death from any cause in survivors of first or recurrent AMI was, respectively, 2 and 3 times higher than that in the English general population of equivalent age.' The long term relative risk of subsequent ACS events, after the initial ACS event was assumed to be 1.5 (3/2). The relative risks of

fatal and non-fatal CV events were then backward calculated from the long term relative risk of 1.5 using the data in Table 20.

Table 20: The event rates reported in the ATLAS ACS 2-TIMI 51 trial data in comparison to the first 6 months of the trial (p204, Table 43, MS)

Event	1st 6 months	2nd 6 months	Later
MI	100.00%	41.72%	30.45%
IS	100.00%	55.87%	47.36%
OCD	100.00%	33.00%	33.00%

MI, myocardial infarction; IS, ischaemic stroke; OCD, other cardiovascular death
Source: Tables for crude rates at 12 weekly intervals of the absolute (n) number of events by dose and stratum (intent to treat) – the manufacturer has the data on file.

The adjustment was conducted using the following formula:

$$\frac{\qquad}{\qquad}$$

Were D(t) is the event rate for a future ACS event of interest in Table 20.

It is of concern to the ERG that no apparent adjustment has been made for censoring in the calculation of the event rates in Table 20.

For example, the relative risk of an IS occurring in the 2nd 6 months, after an MI is:

$$(55.87/47.36)* 1.5 = 1.8$$

The ERG is unclear if this approach is appropriate to model the relative risk of further ACS events in the first 12 months following an ACS event. As such the ERG will conduct sensitivity analyses on the parameters in Table 19 to determine the impact of this assumption (see section 5.3.2.1)

In the manufacturer's response to clarification question B11 it was established that the relative risk of a HS/ICH event was assumed to be one in the 12 months following a IS or MI due to the small number of HS/ICH events. For the same reasons it is assumed that the relative risk of a MI or IS event is one when a prior HS/ICH has occurred. The ERG believes that this lacks face validity as the relative risk of suffering these events increases over time from one in the second 6 months after a MI or an IS to 1.5 in all subsequent model cycles.

5.2.6 Costs

5.2.6.1 Costs of the intervention and comparator

In the model patients receive clopidogrel (75 mg) once per day, aspirin (75 mg) once per day and rivaroxaban (2.5 mg) twice daily where appropriate. As rivaroxaban enters the treatment pathway after the stabilisation of ACS any further difference in costs between the intervention and comparator are due to ACS events and discontinuations related to an ACS event occurring.

Table 21: The purchasing cost of the drugs included in the decision problem in the UK. Adapted from Table 63, p303, MS

Drug	Loading Dose	Daily Dose (Maintenance)	Pack Size	Pack Price	Cost of loading dose	Cost per day
Rivaroxaban	None	2 x 2.5mg	56-tabs	£58.80	None	£2.10
Clopidogrel	300mg	75mg	28-tabs	£1.74	£0.25	£0.06
Aspirin	300mg	75mg	28-tabs	£0.82	£0.12	£0.03

The ERG identified that the cost per day of rivaroxaban was potentially incorrectly calculated as £2.10 corresponded to the use of one tablet and not two tablets in Table 63 of the MS. In the manufacturer's response to the ERGs additional clarification question it was established that the representative pack of 2.5 mg rivaroxaban would cost £58.80 and would have 56 tablets. The cost per day of rivaroxaban was correctly calculated.

5.2.6.2 Costs of ACS events

The ACS event costs were determined by the NHS reference costs 2012-13[51] of treating the ACS event and the cost of follow up for the patient.

An assumption was made that if a patient suffered from multiple long term ACS events then the cost of hospitalisation and the follow up of both events were applied. This was the case irrespective of the time between the ACS events. It is possible that patients will transition into the multiple event states from the single event states, with the cost of the first event being double-counted for those patients.

The PSA method used by the manufacturer is of concern to the ERG and is addressed in section 5.2.8. The ERG has further concerns about the PSA of these parameters as the upper and lower bounds available for each reference cost code was not used to create the standard errors for each reference cost. In the manufacturer's response to clarification question B1, the manufacturer stated that standard errors were not calculated from the reference costs as they believed this introduced a false sense of certainty around the cost. The ERG disagrees with this statement.

It was assumed by the manufacturer, that on average, patients experience 5, 14 and 28 days rehabilitation following a MI, IS and HS/ICH respectively. These rehabilitation costs occurred in the first 3 months after an ACS event. The reference cost code for the rehabilitation of a patient who experienced a MI was VC38Z and the reference cost code for a patient who experienced an IS or HS/ICH was VO4Z. In the multiple event states the assumption surrounding how the rehabilitation cost applied depended on whether the events where similar or dissimilar. Where multiple dissimilar events occurred, for example MI+IS, the rehabilitation costs of both events were applied. This can lead to double-counting where a patient has already had an event and is transitioning from a single event health state. Where multiple similar events occurred, the rehabilitation costs are only applied once, even if the events occurred in different time cycles.

Table 22: Health state costs (p307-312, Table 66, MS)

Health states	Items	Value	Reference in submission
MI	Acute Care (3 months)	£3,585.55	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E) + (VC38Z*5)[51]
	Follow-on care (second 3 months)	£1,980.14	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£1,440.10	Heeg *et al.* (2007)[52]
	Follow-on care (later per 3 months)	£540.04	Heeg *et al.* (2007)[52]
IS	Acute Care (3 months)	£7,756.05	NHS reference costs 2012/2013 (Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G) + (VC04Z*14)[51]
	Follow-on care (second 3 months)	£3,060.21	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£4,200.29	Heeg *et al.* (2007)[52]
	Follow-on care (later 3 months)	£1,560.11	Heeg *et al.* (2007)[52]
HS/ICH	Acute Care (3 months)	£12,778.22	NHS reference costs 2012/2013 (Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) +(VC04Z*28)[51]
	Follow-on care (second 3 months)	£3,060.21	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£4,200.29	Heeg *et al.* (2007)[52]
	Follow-on care	£1,560.11	Heeg *et al.* (2007)[52]

Health states	Items	Value	Reference in submission
	(later 3 months)		
Fatal MI		£1,500.10	Heeg *et al.* (2007)[52]
Fatal IS		£4,500.31	Heeg *et al.* (2007)[52]
Fatal HS/ICH		£4,500.31	Heeg *et al.* (2007)[52]
OCD		£3,000.21	Heeg *et al.* (2007)[52]
NCD		£300.02	Heeg *et al.* (2007)[52]
MI + MI	Acute Care (3 months)	£7,171.10	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E) + (VC38Z*5)[51]
	Follow-on care (second 3 months)	£1,980.14	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£1,440.10	Heeg *et al.* (2007)[52]
	Follow-on care (later 3 months)	£540.04	Heeg *et al.* (2007)[52]
IS + IS	Acute Care (3 months)	£15,512.10	NHS reference costs 2012/2013 (Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G) + (VC04Z*14)[51]
	Follow-on care (second 3 months)	£3,060.21	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£4,200.29	Heeg *et al.* (2007)[52]
	Follow-on care (later 3 months)	£1,560.11	Heeg *et al.* (2007)[52]
HS/ICH + HS/ICH	Acute Care (3 months)	£25,556.44	NHS reference costs 2012/2013 (Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) + (VC04Z*28)[51]
	Follow-on care (second 3 months)	£3,060.21	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£4,200.29	Heeg *et al.* (2007)[52]
	Follow-on care (later 3 months)	£1,560.11	Heeg *et al.* (2007)[52]
MI + IS	Acute Care (3 months)	£11,341.60	NHS reference costs 2012/2013(Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E plus Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G) + (VC04Z*14) + (VC38Z*5)[51]
	Follow-on care (second 3 months)	£5,040.35	Heeg *et al.* (2007)[52]
	Follow-on care	£5,640.39	Heeg *et al.* (2007)[52]

Health states	Items	Value	Reference in submission
	(third and fourth 3 months)		
	Follow-on care (later 3 months)	£2,100.15	Heeg *et al.* (2007)[52]
MI + HS/ICH	Acute Care (3 months)	£16,363.77	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E plus Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) + (VC04Z*14) + (VC38Z*5)[51]
	Follow-on care (second 3 months)	£5,040.35	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£5,640.39	Heeg *et al.* (2007)[52]
	Follow-on care (later 3 months)	£2,100.15	Heeg *et al.* (2007)[52]
IS + HS/ICH	Acute Care (3 months)	£20,534.27	NHS reference costs 2012/2013 (Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G plus Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) + (VC04Z*14)+ (VC04Z*28)[51]
	Follow-on care (second 3 months)	£6,120.42	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£8,400.58	Heeg *et al.* (2007)[52]
	Follow-on care (later 3 months)	£3,120.22	Heeg *et al.* (2007)[52]
3 Events	Acute Care (3 months)	£24,119.82	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E plus Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G plus Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) + (VC38Z*5) + (VC04Z*14)+ (VC04Z*28)[51]
	Follow-on care (second 3 months)	£8,100.56	Heeg *et al.* (2007)[52]
	Follow-on care (third and fourth 3 months)	£9,840.68	Heeg *et al.* (2007)[52]
	Follow-on care (later 3 months)	£3,660.25	Heeg *et al.* (2007)[52]

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non-cardiovascular death

5.2.6.3 Transient event costs

The transient events all have a cost associated with them, the values used in the model and the assumptions used to generate them are presented in Table 23 and 24.

Table 23: List of adverse events and summary of costs included in the mathematical model (p314, Table 67, MS)

Adverse events	Value	Reference in submission
TIMI major bleed	£669.83	NHS reference costs 2012/2013 (Weighted average of FZ24G, FZ24H, FZ24J, FZ27E, FZ27F, FZ27G, FZ38G, FZ38H, FZ38J, FZ28K, FZ38M, FZ38N, FZ38L, FZ38P, FZ59Z, FZ60Z, FZ70Z, FZ83G, FZ83H, FZ83J, FZ83K)[51]
TIMI minor bleed	£67.79	NHS reference costs 2012/2013 (VB11Z)[51]
Bleed requiring medical attention	£130.26	NHS reference costs 2012/2013 (Weighted average of VB01Z, VB02Z, VB03Z, VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z)[51]

TIMI, Thrombolysis in Myocardial Infarction

Table 24: Revascularisation costs included in the mathematical model (p314, Table 68, MS)

Revascularisation	Value	Reference in submission
PTCA / PCI	£2,081.77	NHS reference costs 2012/2013 (Weighted average of EA31A, EA31B, EA31C, EA31D, EA49A, EA49B, EA49C, EA49D)[51]
CABG	£9,618.84	NHS reference costs 2012/2013 (Weighted average of EA14A, EA14B, EA14C, EA14D, EA16A, EA16B, EA16C, EA16D)[51]

PTCA/PCI, Percutaneous transluminal coronary angioplasty/ Percutaneous coronary intervention; CABG, coronary artery bypass graft

5.2.7 Utilities

5.2.7.1 Utilities associated with long-term health states

The utilities were largely taken from the study by Greenhalgh *et al*.[53] In the MS (p267) an unorthodox method, was used to calculate the improvement in utility that the patients would

experience in the stroke health states. A study by Ara and Brazier[54] was used to obtain the utility of stroke patients in the UK at baseline and 12 months after the stroke occurred. Based on the utility values from the two time points a 33% improvement in stroke patients utility over 12 months was calculated. This improvement was then applied to the stroke state values from Greenhalgh *et al.* to produce the utility of stroke patients one year after their stroke. To calculate the utility of stroke patients 6 months after a stroke, the average of the stroke 1st 6 months and the stroke (post 12 months) health states was taken. The ERG has concerns with this methodology, as it is unclear why the values from Ara and Brazier are appropriate to calculate the improvement in utility of patients who experience a stroke but are not appropriate to be used as the utility of stroke patients in the model.

Table 25: The health state utilities used in the model (p269–273, Table 57, MS)

State	Utility value	Confidence interval in the MS	Reference
No event	0.842	Beta, min=0.632, max= 1.000	Greenhalgh *et al.* 2011[53]
MI 1st 6 months	0.779	Beta, min=0.584, max= 0.974	Greenhalgh *et al.* 2011[53]
MI 2nd 6 months	0.821	Beta, min=0.616, max= 1.000	Greenhalgh *et al.* 2011[53]
MI later (post 12 months)	0.821	Beta, min=0.616, max= 1.000	Greenhalgh *et al.* 2011[53]
IS 1st 6 months	0.703	Beta, min=0.527, max= 0.879	Greenhalgh *et al.* 2011[53]
IS 2nd 6 months	0.748	Beta, min=0.561, max= 0.935	Greenhalgh *et al.* 2011[53] plus adjustment based on Ara and Brazier 2010[54]
IS later (post 12 months)	0.792	Beta, min=0.594, max= 0.990	Greenhalgh *et al.* 2011[53] plus adjustment based on Ara and Brazier 2010[54]
HS/ICH 1st 6 months	0.703	Beta, min=0.527, max= 0.879	Greenhalgh *et al.* 2011 [53] plus assumption that utility after a HS/ICH is the same as utility after an IS
HS/ICH 2nd 6 months	0.748	Beta, min=0.561, max= 0.935	Greenhalgh *et al.* 2011[53] plus adjustment based on Ara and Brazier 2010[54] (plus assumption that utility after an HS/ICH is the same as after an IS)
HS/ICH later (post 12 months)	0.792	Beta, min=0.594, max= 0.990	Greenhalgh *et al.* 2011[53] plus adjustment based on Ara and Brazier 2010[54] (plus assumption that utility after an HS/ICH is the same as after an IS)
MI + MI 1st 6 months	0.607	Beta, min=0.455, max= 0.759	Greenhalgh *et al.* 2011[53] plus assumption that utility values should be multiplied in the case of multiple events
MI + MI 2nd 6 months	0.674	Beta, min=0.506, max= 0.843	Greenhalgh *et al.* 2011[53] plus assumption that utility values should be multiplied in the case of multiple events
MI + MI later (post 12 months)	0.674	Beta, min=0.506, max= 0.843	Greenhalgh *et al.* 2011[53] plus assumption that utility values should be multiplied in the case of multiple events
IS+ IS 1st 6 months	0.494	Beta, min=0.371, max= 0.618	Greenhalgh *et al.* 2011[53] plus assumption that utility values should be multiplied in the case of

			multiple events
IS +IS 2nd 6 months	0.559	Beta, min=0.419, max= 0.0.699	Greenhalgh *et al.* 2011[53] and adjustment based on Ara and Brazier 2010[54] plus assumption that utility values should be multiplied in the case of multiple events
IS + IS later (post 12 months)	0.627	Beta, min=0.471, max= 0.784	Greenhalgh *et al.* 2011[53] and adjustment based on Ara and Brazier 2010[54] plus assumption that utility values should be multiplied in the case of multiple events
HS/ICH + HS/ICH 1st 6 months	0.494	Beta, min=0.371, max= 0.618	Greenhalgh *et al.* 2011[53] plus assumption that utility values should be multiplied in the case of multiple events
HS/ICH + HS/ICH 2nd 6 months	0.559	Beta, min=0.419, max= 0.699	Greenhalgh *et al.* 2011[53] and adjustment based on Ara and Brazier 2010[54] plus assumption that utility values should be multiplied in the case of multiple events
HS/ICH +HS/ICH later (post 12 months)	0.627	Beta, min=0.471, max= 0.784	Greenhalgh *et al.* 2011[53] and adjustment based on Ara and Brazier 2010[54] plus assumption that utility values should be multiplied in the case of multiple events
MI + IS 1st 6 months	0.548	Beta, min=0.411, max=0.685	Greenhalgh *et al.* 2011[53] plus assumption that utility values should be multiplied in the case of multiple events
MI + IS 2nd 6 months	0.614	Beta, min=0.460, max= 0.767	Greenhalgh *et al.* 2011[53] and Ara and Brazier 2010[54] adjustment for IS plus assumption that utility values should be multiplied in the case of multiple events
MI + IS later (post 12 months)	0.650	Beta, min=0.488, max= 0.813	Greenhalgh *et al.* 2011[53] and Ara and Brazier 2010[54] adjustment for IS plus assumption that utility values should be multiplied in the case of multiple events
MI + HS/ICH 1st 6 months	0.548	Beta, min=0.411, max=0.685	Greenhalgh *et al.* 2011[53] plus assumption that utility values should be multiplied in the case of multiple events
MI +HS/ICH 2nd 6 months	0.614	Beta, min=0.460, max= 0.767	Greenhalgh *et al.* 2011[53] and Ara and Brazier 2010[54] adjustment for HS/ICH plus assumption that utility values should be multiplied in the case of multiple events
MI + HS/ICH later (post 12 months)	0.650	Beta, min=0.488, max= 0.813	Greenhalgh *et al.* 2011[53] and Ara and Brazier 2010[54] adjustment for HS/ICH plus assumption that utility values should be multiplied in the case of multiple events
IS + HS/ICH 1st 6 months	0.494	Beta, min= 0.371, max=0.618	Greenhalgh *et al.* 2011[53] plus assumption that utility values should be multiplied in the case of multiple events
IS + HS/ICH 2nd 6 months	0.559	Beta, min=0.419, max= 0.699	Greenhalgh *et al.* 2011[53] and Ara and Brazier 2010[54] adjustment plus assumption that utility values should be multiplied in the case of multiple events
IS +HS/ICH later (post 12 months)	0.627	Beta, min=0.471, max= 0.784	Greenhalgh *et al.* 2011[53] and Ara and Brazier 2010[54] adjustment plus assumption that utility values should be multiplied in the case of multiple events
3 events 1st 6	0.385	Beta, min=0.289,	Greenhalgh *et al.* 2011[53] plus assumption that

months		max= 0.481	utility values should be multiplied in the case of multiple events
3 events 2nd 6 months	0.459	Beta, min=0.344, max= 0.574	Greenhalgh *et al.* 2011[53] and adjustment based on Ara and Brazier 2010[54] plus assumption that utility values should be multiplied in the case of multiple events
3 events later (post 12 months)	0.515	Beta, min=0.386, max= 0.644	Greenhalgh *et al.* 2011[53] and adjustment based on Ara and Brazier 2010[54] plus assumption that utility values should be multiplied in the case of multiple events

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage

The ERG also has concerns with how the improvement in utility over time is modelled in the multiple event states. In the multiple event states, the utility of both events which have occurred are multiplied together. The utility used corresponds to the utilities at the same time as the multiple event tunnel state, for example:

U(MI+IS) initial six months = U(MI) initial six months x U(IS) initial six months

If the patient transitions into the multiple event states from a single event state their utility in the multiple event state could be understated as their improvement in utility after the first event has been ignored. This problem is again related to the model structure's inability to distinguish when events have occurred. The ERG notes that this is not the only assumption which the manufacturer could have made to calculate the utility in the multiple event states. It could have been assumed that the lowest utility of the two applied to the patients or if the model could track the chronicity of events it could be assumed that the utility of the most recent event applied.

Table 26 shows that the standard errors for the utilities used in the MS were available in Greenhalgh *et al.*[53] It is of concern to the ERG that this information was ignored in the MS. The method which was used for the PSA is discussed in section 5.2.8.

Table 26: Summary of quality of life values for cost-effectiveness analysis used in the manufacturer's base case (Greenhalgh *et al.*[53] and p56, Table 16, MS)

State	Utility Value	Standard Error	Reference in submission
No event	0.842	0.002	PLATO HECON sub-study (AstraZeneca STA submission[55], Section 6.4.3)
Non-fatal MI	0.779	0.10	As above
Post MI*	0.821	0.038	As above + Lacey[56]
Non-fatal stroke	0.703	0.010	As above
Post stroke**	0.703	0.038	As above + assumption
Dead	0.000	N/A	N/A

The meaning of the symbols * and ** was not provided in Greenhalgh *et al.*[53]

5.2.7.2 Utilities associated with the transient health states

The utilities associated with the transient states are given in Table 27. In the manufacturer's base case the utility values from the literature are used. To calculate the quality of life decrement associated with bleeding the utility value associated with the transient event state was subtracted from the no event health state and was then multiplied by the proportion of days in a 12 week period a patient would spend in the transient health state.

Table 27: The utilities of the transient states (p273–274, Table 57, MS)

Health State / Event	**Value from the trial**	**Values from the literature (which were used in the model).**	**Assumed length of utility decrement (days) (p275, Table 58, MS)**	**Literature reference**
Major bleed	0.77	0.75	30	Crespin *et al.* 2011[57]
Minor bleed	0.84	0.80	2	Kazi *et al.* 2014[58]
Bleeding requiring medical attention	0.87	0.80	2	Sullivan *et al.* 2006[59]
PTCA / PCI	N/A	0.792	30	Latour-Perez 2008[60]
CABG	N/A	0.742	84	Latour-Perez 2008[60]

PTCA/PCI, Percutaneous transluminal coronary angioplasty/ Percutaneous coronary intervention; CABG, coronary artery bypass graft

5.2.8 Implementation of PSA

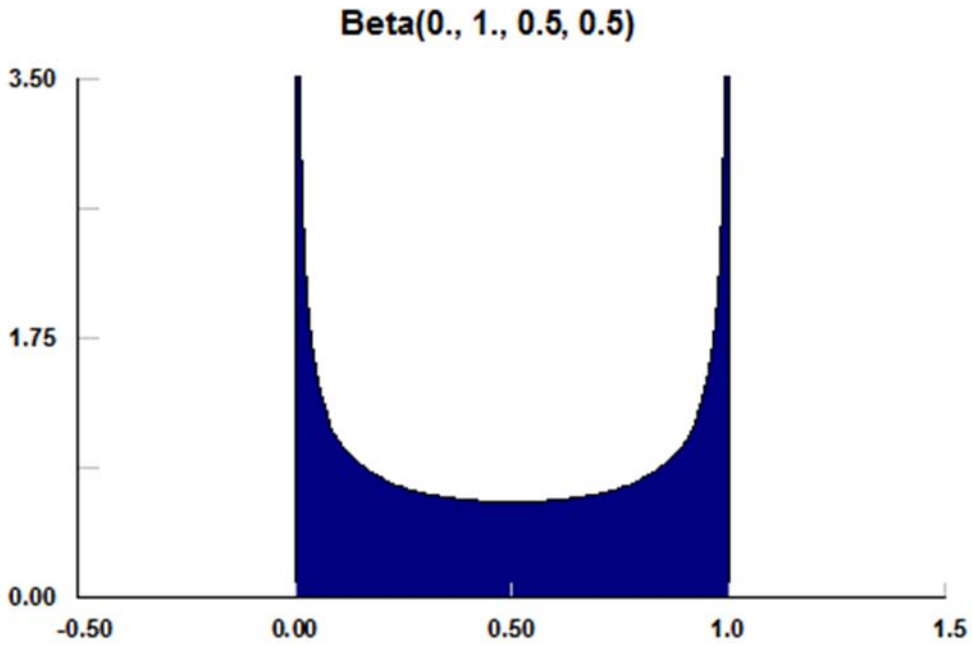
5.2.8.1 Incorrect sampling of the shape and scale parameters of the Weibull distributions

The ERG has concerns in how the uncertainty in the Weibull distributions used to interpolate the trial data in the manufacturer's base case was parameterised in the PSA. The standard errors of the shape and scale parameters were used to draw both parameters from independent distributions. This is inappropriate as the parameters should be correlated using the variance-covariance matrix to ensure that in the PSA the fitted curve has a good fit to the data. In the manufacturer's response to clarification question B3, it was established that the manufacturer adopted this approach as they believed that correlating the shape and scale parameters in the Weibull distributions would lead to a false sense of certainty around the Weibull curve. The ERG disagrees with this statement.

5.2.8.2 Non-standard sampling distribution

The MS states that a beta distribution with an alpha of 0.5 and a beta of 0.5 was used as it 'provided a good fit to the trial data' (MS, p 308). It is unclear to the ERG for which piece of trial data this beta distribution provided a good fit. This distribution was then used to create a probabilistic draw of all parameters except the shape and scale of the Weibull parameters. The beta distribution was used to draw parameters values of ±25% of the mean value of most the remaining parameters. The only exception to this was the relative risk of subsequent events after an ACS event where the beta distribution was used to draw parameter values of ±50% of the mean value.

Figure 6: The probability density function of the beta distribution with alpha equal to 0.5 and the beta equal to 0.5



As shown in Figure 6 the distribution used for the PSA in the MS tends to draw extreme values for the parameters. It is unclear to the ERG why this distribution was used for parameters with reported standard errors of the mean, see sections 5.2.6.2 and 5.2.7.1. Furthermore, it is unclear to the ERG why this distribution was used for the parameters for which standard errors were not available. Of further concern to the ERG is that the unit cost of the drugs were treated as uncertain parameters in the PSA, even though the drug cost to the NHS is known with certainty through the British National Formulary.[19] In the manufacturer's response to clarification question B2 this distribution was fixed; however, only the probability that rivaroxaban was cost-effective at the £20,000 per QALY cost-effectiveness threshold was presented. As the manufacturer's corrected PSA results are incomplete, the original PSA results are presented.

5.2.9 Results

5.2.9.1 Results from the manufacturer's base case analysis

The manufacturer's base case included the following key assumptions, which were relaxed in scenario analyses

- The data from all trial strata is used to inform the model data
- Weibull curves are used to calculate the event rates
- Clopidogrel has a relative risk reduction (RRR) applied when a patient discontinues clopidogrel treatment
- Utility values from the literature are used
- Utility values associated with MI, IS and HS/ICH ACS events

The base case deterministic costs and QALYs are presented in Table 27.

Table 28: The manufacturer's base case deterministic ICER within the licensed population (p332, Table 75, MS)

Interventions	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) incremental
Rivaroxaban + CLOP+ ASA or Rivaroxaban + ASA (all strata)	£14,767.63	11.48	9.56	£763.58	0.12	£6,202.84
CLOP+ASA or ASA (all strata)	£14,004.05	11.34	9.44	-	-	

CLOP, clopidogrel; ASA, aspirin

PSA was undertaken using 1000 random draws from each distribution. There was a problem in how the manufacturer conducted the PSA using the Beta distribution with an alpha and beta equal to 0.5. In the original analysis, the cost of rivaroxaban, clopidogrel and aspirin were included in the PSA. In the manufacturer's response to clarification question B2, the manufacturer undertook two additional analyses with a beta distribution with an alpha and beta equal to one and another with a beta

distribution with an alpha and beta equal to two. When conducting these analyses the manufacturer did not present a full set of PSA results, as such the original results will be presented below. In both of these scenarios the drug costs were removed from the PSA. More importantly, none of the ERGs other issues with the PSA raised in the clarification questions B1 and B3 (e.g. no published uncertainty was used, PSA draws for the shape and scale parameters of the Weibull curves were not correlated using the variance-covariance matrix) were addressed in the manufacturer's response to those questions. In neither analysis did altering the PSA have an effect on the presented results.

Table 29: The manufacturer's base case probabilistic ICER within the licensed population (p332, Table 76, MS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) incremental
Rivaroxaban + CLOP+ ASA or Rivaroxaban + ASA (all strata)	£14,802.17	9.53	£702.98	0.13	£5407.54
CLOP+ASA or ASA (all strata)	£14,099.20	9.40	-	-	-

CLOP, clopidogrel; ASA, aspirin

Table 29 presents the mean cost and QALYs across all of the PSA runs. It is clear that the ICER in the PSA is not substantially different from the deterministic ICER. However, the PSA results were generally more favourable to rivaroxaban producing more incremental QALYs at a lower incremental cost. The original ICER presented by the manufacturer was higher than that of the deterministic ICER. As such, the ERG has recalculated the ICER from the incremental costs and QALYs presented in Table 29. For completeness the cost-effectiveness plane and the cost-effectiveness acceptability curve (CEAC) provided by the manufacturer are presented in Figures 7 and 8.

Figure 7: **The cost-effectiveness plane of rivaroxaban and aspirin with or without clopidogrel compared to aspirin with or without clopidogrel presented by the manufacturer**

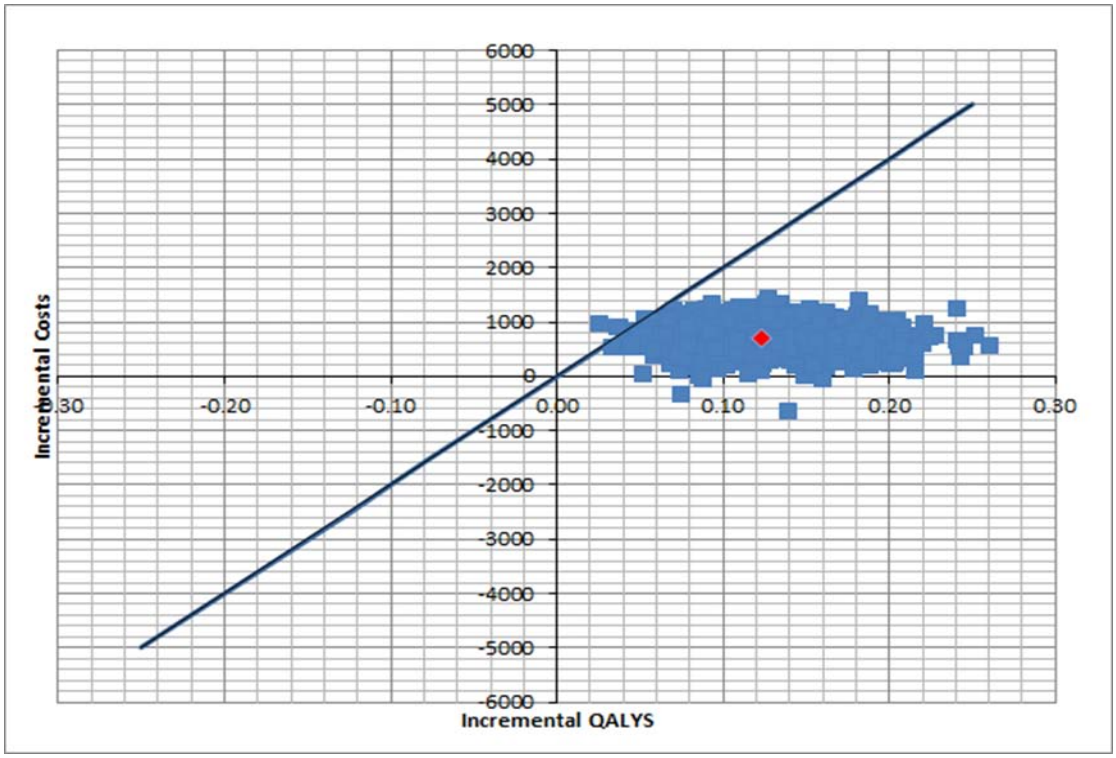
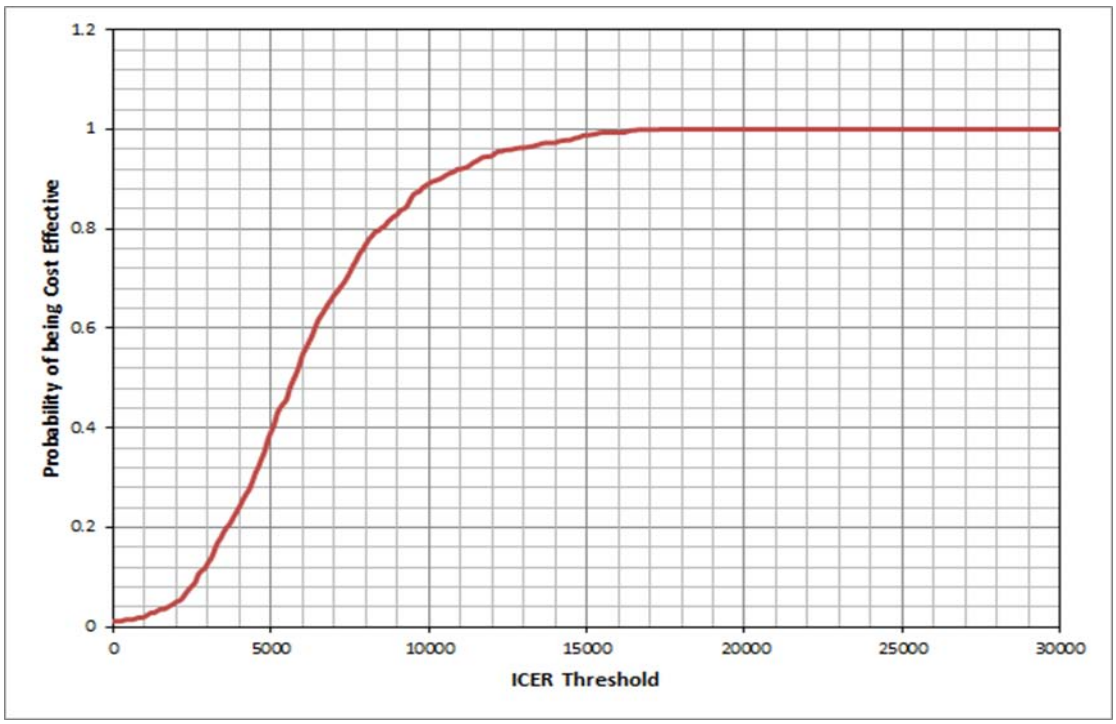


Figure 8: **The CEAC of rivaroxaban and aspirin with or without clopidogrel compared to aspirin with or without clopidogrel presented by the manufacturer**



In both of the corrected PSA analyses (conducted by the manufacturer in response to clarification question B2), only the probability that rivaroxaban was cost-effective using a cost-effectiveness threshold of £20,000 per QALY was reported. In both PSAs the probability that rivaroxaban was cost-effective was greater than 99.9%.

5.2.9.2 One way sensitivity analyses

The manufacturer conducted extensive one way sensitivity analyses on the deterministic results. An error was identified by the manufacturer in the tornado plot presented in the MS (p333, MS); the corrected results are presented in the manufacturer's response to clarification question B13. Table 30 presents the values used for each one way sensitivity analysis. Figure 9 reproduces the tornado diagram provided by the manufacturer.

Table 30: The value of the parameters used in the one way sensitivity analyses (manufacturer's clarification response to clarification question B13, p151)

Parameters changed in each sensitivity analysis	Base case value	Minimum Value	Maximum Value
Utility no event			
Utility - no event	0.84	0.63	1.00
Cost of rivaroxaban			
Daily cost rivaroxaban	£2.10	£1.58	£2.63
Discount Rates			
Discount rates	3.50%	0.00%	5.83%
RR-later events			
AFTER MI			
1st 6 months			
MI	4.93	2.46	7.39
IS	3.17	1.58	4.75
HS	1.00	0.50	1.50
death MI	4.93	2.46	7.39
death IS	3.17	1.58	4.75
death HS	1.00	0.50	1.50
other vascular death	3.03	1.52	4.55
2nd 6 months			
MI	2.06	1.03	3.08
IS	1.77	0.88	2.65
HS	1.00	0.50	1.50
death MI	2.06	1.03	3.08
death IS	1.77	0.88	2.65
death HS	1.00	0.50	1.50
other vascular death	1.61	0.80	2.41
Later			
MI	1.50	0.75	2.25
IS	1.50	0.75	2.25
HS	1.50	0.75	2.25

Parameters changed in each sensitivity analysis	Base case value	Minimum Value	Maximum Value
death MI	1.50	0.75	2.25
death IS	1.50	0.75	2.25
death HS	1.50	0.75	2.25
other vascular death	1.50	0.75	2.25
AFTER IS			
1st 6 months			
MI	4.93	2.46	7.39
IS	3.17	1.58	4.75
HS	1.00	0.50	1.50
death MI	4.93	2.46	7.39
death IS	3.17	1.58	4.75
death HS	1.00	0.50	1.50
other vascular death	3.03	1.52	4.55
2nd 6 months			
MI	2.06	1.03	3.08
IS	1.77	0.88	2.65
HS	1.00	0.50	1.50
death MI	2.06	1.03	3.08
death IS	1.77	0.88	2.65
death HS	1.00	0.50	1.50
other vascular death	1.61	0.80	2.41
Later			
MI	1.50	0.75	2.25
IS	1.50	0.75	2.25
HS	1.50	0.75	2.25
death MI	1.50	0.75	2.25
death IS	1.50	0.75	2.25
death HS	1.50	0.75	2.25
other vascular death	1.50	0.75	2.25
AFTER HS			
1st 6 months			
MI	1.00	0.50	1.50
IS	1.00	0.50	1.50
HS	4.93	2.46	7.39
death MI	1.00	0.50	1.50
death IS	1.00	0.50	1.50
death HS	4.93	2.46	7.39
other vascular death	1.00	0.50	1.50
2nd 6 months			
MI	1.00	0.50	1.50
IS	1.00	0.50	1.50
HS	2.06	1.03	3.08
death MI	1.00	0.50	1.50
death IS	1.00	0.50	1.50
death HS	2.06	1.03	3.08
other vascular death	1.00	0.50	1.50
Later			
MI	1.50	0.75	2.25
IS	1.50	0.75	2.25

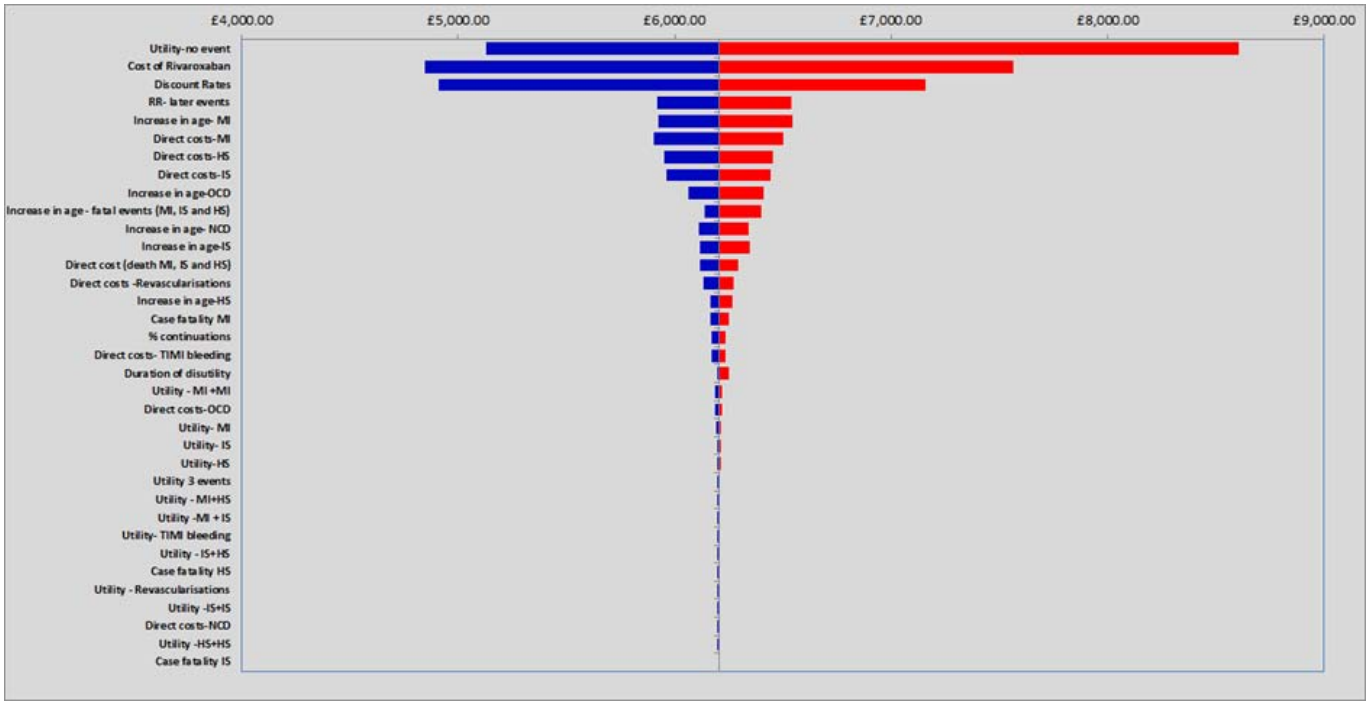
Parameters changed in each sensitivity analysis	Base case value	Minimum Value	Maximum Value
HS	1.50	0.75	2.25
death MI	1.50	0.75	2.25
death IS	1.50	0.75	2.25
death HS	1.50	0.75	2.25
other vascular death	1.50	0.75	2.25
> 2 Events			
Any Event	1.50	0.75	2.25
Increase in age MI			
% increase due to age MI	8.70%	4.35%	13.05%
Direct costs MI			
MI - first three months (acute phase)	£3,585.55	£2,689.16	£4,481.94
MI- second three months	£1,980.14	£1,485.11	£2,475.18
MI second 6 months	£1,440.10	£1,080.08	£1,800.13
MI post 12 months	£1,080.08	£810.06	£1,350.10
Direct costs HS			
HS first three months (acute phase)	£12,778.22	£9,583.67	£15,972.78
HS second three months	£3,060.21	£2,295.16	£3,825.26
HS second 6 months	£4,200.29	£3,150.22	£5,250.36
HS post 12 months	£3,120.22	£2,340.17	£3,900.28
Direct costs - IS			
IS- first three months (acute phase)	£7,756.05	£5,817.04	£9,695.06
IS -second three months	£3,060.21	£2,295.16	£3,825.26
IS second 6 months	£4,200.29	£3,150.22	£5,250.36
IS post 12 months	£3,120.22	£2,340.17	£3,900.28
Increase in age - OCD			
% increase due to age - other vascular death	10.03%	5.01%	15.04%
Increase in age – fatal events (MI,IS and HS/ICH)			
% increase due to age - case fatality MI	-13.90%	-6.95%	-20.84%
% increase due to age - case fatality IS	-9.00%	-4.50%	-13.50%
% increase due to age – case fatality HS	-9.00%	-4.50%	-13.50%
Increase in age - NCD			
% increase due to age - non cardiovascular death	10.28%	5.14%	15.42%
Increase in age - IS			
% increase due to age - IS	10.65%	5.32%	15.97%
Direct cost (death MI, IS and HS/ICH)			
Direct cost - death MI	£1,500.10	£1,125.08	£1,875.13
Direct cost - death IS	£4,500.31	£3,375.23	£5,625.39
Direct cost – death HS	£4,500.31	£3,375.23	£5,625.39
Direct cost – Revascularisations			
PCI/PTCA	£2,081.77	£1,561.33	£2,602.21
CABG	£9,618.84	£7,214.13	£12,023.55
Increase in age - HS			
HS	10.73%	5.36%	16.09%
Case fatality - MI			
Starting Case fatality - MI	13.37%	6.69%	20.06%
% continuations			
% continuing treatment - after MI			

Parameters changed in each sensitivity analysis	Base case value	Minimum Value	Maximum Value
Rivaroxaban	92.58%	74.06%	111.09%
Clopidogrel	60.00%	48.00%	72.00%
% continuing treatment – after IS			
Rivaroxaban	94.69%	75.75%	113.63%
Clopidogrel	54.29%	43.43%	65.14%
Direct costs – TIMI bleeding			
Direct cost - TIMI major bleeding	£669.83	£502.37	£837.29
Direct cost - TIMI minor bleeding	£67.79	£50.84	£84.74
Direct cost - TIMI requiring medical attention	£130.26	£97.70	£162.83
Duration of disutility			
Disutility durations (years)-duration of bleed	0.08	0.04	0.23
Disutility durations (years)-duration of PTCA/PCI	0.08	0.04	0.23
Disutility durations (years)-duration of CABG	0.23	0.04	0.23
Utility MI+MI			
Utility - MI + MI 1st 6 months	0.61	0.46	0.76
Utility - MI + MI 2nd 6 months	0.67	0.51	0.84
Utility – MI + MI later (post 12 months)	0.67	0.51	0.84
Direct costs - OCD			
other cardiovascular death	£3,000.21	£2,250.16	£3,750.26
Utility MI			
Utility - MI 1st 6 months	0.78	0.58	0.97
Utility - MI 2nd 6 months	0.82	0.62	1.00
Utility - MI later (post 12 months)	0.82	0.62	1.00
Utility IS			
Utility -IS 1st 6 months	0.70	0.53	0.88
Utility -IS 2nd 6 months	0.75	0.56	0.93
Utility -IS later (post 12 months)	0.79	0.59	0.99
Utility - HS			
Utility -HS 1st 6 months	0.70	0.53	0.88
Utility -HS 2nd 6 months	0.75	0.56	0.93
Utility -HS later (post 12 months)	0.79	0.59	0.99
Utility – 3 events			
Utility -3 events 1st 6 months	0.38	0.29	0.48
Utility -3 events 2nd 6 months	0.46	0.34	0.57
Utility -3 events later (post 12 months)	0.52	0.39	0.64
Utility – MI+HS			
Utility -MI + HS 1st 6 months	0.55	0.41	0.68
Utility -MI +HS 2nd 6 months	0.61	0.46	0.77
Utility -MI + HS later (post 12 months)	0.65	0.49	0.81
Utility – MI+IS			
Utility -MI + IS 1st 6 months	0.55	0.41	0.68
Utility -MI + IS 2nd 6 months	0.61	0.46	0.77
Utility -MI + IS later (post 12 months)	0.65	0.49	0.81
Utility – TIMI bleeding			
Utility -TIMI Major bleeding	0.75	0.56	0.94

Parameters changed in each sensitivity analysis	Base case value	Minimum Value	Maximum Value
Utility -TIMI Minor bleeding	0.80	0.60	1.00
Utility -TIMI requiring medical attention	0.80	0.60	1.00
Utility – IS+HS			
Utility -IS + HS 1st 6 months	0.49	0.37	0.62
Utility -IS + HS 2nd 6 months	0.56	0.42	0.70
Utility –IS +HS later (post 12 months)	0.63	0.47	0.78
Case fatality HS			
Starting case fatality – HS	11.65%	5.83%	17.48%
Utility – revascularisations			
Utility – PCI/PTCA	0.79	0.59	0.99
Utility - CABG	0.74	0.56	0.93
Utility – IS+IS			
Utility – IS+ IS 1st 6 months	0.49	0.37	0.62
Utility – IS +IS 2nd 6 months	0.56	0.42	0.70
Utility – IS + IS later (post 12 months)	0.63	0.47	0.78
Direct costs - NCD			
Direct cost - non cardiovascular death	£300.02	£225.02	£375.03
Utility HS+HS			
Utility - HS + HS 1st 6 months	0.49	0.37	0.62
Utility - HS + HS 2nd 6 months	0.56	0.42	0.70
Utility - HS +HS later (post 12 months)	0.63	0.47	0.78
Case fatality - IS			
Starting Case fatality - IS	11.65%	5.83%	17.48%

PTCA/PCI , Percutaneous transluminal coronary angioplasty/ Percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; TIMI, Thrombolysis in Myocardial Infarction

Figure 9: The tornado plot of the one way sensitivity analyses (manufacturer's clarification response to clarification question B13, p151)



As Figure 9 shows the model is relatively robust to the univariate sensitivity analyses run by the manufacturer. None of ICERs were greater than £10,000 per QALY, which is under the £20,000 - £30,000 per QALY cost-effectiveness threshold used by NICE.[20] However, there are a number of key parameters that could not be adjusted within the model that may influence the ICER to a larger extent such as: amending the HR for fatal bleeds; using pooled efficacy data rather than the 2.5 mg dose alone; and adjusting for the possibility of informative bias.

5.2.9.3 Sensitivity analysis on the efficacy related parameters

The manufacturer explored the uncertainty surrounding the efficacy of rivaroxaban using regression equations. In the manufacturer's response to clarification question B14 it was established that the following method was used to conduct a sensitivity analysis around the efficacy of rivaroxaban.

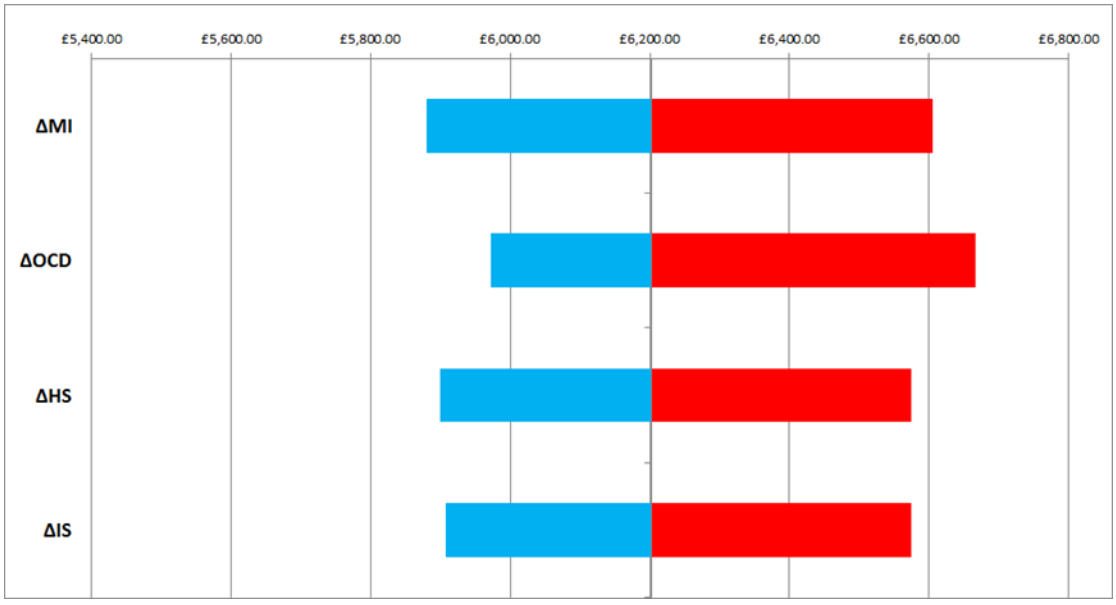
The first step that the manufacturer undertook was to sample the shape and scale parameters from independent normal distributions of the Weibull curves associated with MI, IS, HS/ICH and other cardiovascular death. The sampled shape and scale parameters were then used to calculate the transition probabilities for each of these health states. This methodology was applied to both model arms and 1000 random samples were taken. The ERG believes that the manufacturer's approach for sampling the shape and scale parameters of the Weibull curves was not appropriate, as the correlation between the parameters was ignored in the manufacturer's random sampling.

Incremental costs and QALYs were recorded for each model run. The net monetary benefit (NMB) was calculated for each model run using the following formula:

The differences in the incidence of MIs, strokes and other cardiovascular death between the rivaroxaban plus aspirin with or without clopidogrel arm and the aspirin with or without clopidogrel arm were calculated. The regression analysis uses NMB as the dependent variable although it is unclear to the ERG how the regression equation was estimated and therefore of the appropriateness of this sensitivity analysis.

The results from the manufacturer's analysis are presented in Figure 10. This presents ICERs, although it is unclear to the ERG how these were transformed from the NMB values, as NMB is not associated with a unique ICER. For example, assuming a threshold of £20,000 per QALY a NMB of 1000 could be associated with the intervention dominating (equal QALYs and £1000 cost savings), an ICER of £16,000 (additional costs of £4000 and 0.25 additional QALYs) or an ICER of £10,000 (additional costs of £1000 and 0.10 additional QALYs). However, the midpoint values presented in Figure 10 appear to have face validity.

Figure 10: Tornado plot of the one-way sensitivity analysis for the efficacy related parameters (reproduced from p334, Figure 35, MS)



The ERGs preferred approach to conducting one way sensitivity analyses of the uncertainty surrounding the efficacy parameters would be to use HRs. This approach is not possible within the current structure of the mathematical model.

5.2.9.4 Scenario analyses

The manufacturer presented a substantial array of scenario analyses in the MS (Table 79, p338); further scenario analyses at the request of the ERG were presented in the manufacturer's response to clarification questions B4, B22, B25 and B28.

Table 31: Scenario analyses presented by the manufacturer (p340, Table 79, MS)

Parameters tested	Scenarios
Strata and transition probabilities (proportional hazards)	
Stratum 2 (rivaroxaban + thienopyridine+ aspirin vs. aspirin + thienopyridine)	Stratum 2 from the trial to test the impact on the ICER of adding rivaroxaban to ASA+clopidogrel vs. ASA+clopidogrel
Transition probabilities	
Non-parametric	Using the ATLAS 2 trial data as it was reported without any adjustments (hence no interpolation)
Clopidogrel efficacy	
Clopidogrel RRR = 1	Adjustments are no longer made for the standard of care treatment duration of 1 year. The scenario will present the efficacy data as it was reported in the ATLAS 2 trial data and comparing rivaroxaban in addition to the standard of care (ASA + clopidogrel) versus clopidogrel for the observation period.
Utilities	
Utility values from trial	Utilities obtained from the trial where there is no distinction between the tunnel states considered in the model.
Utility values return to the baseline utility value in the post event cycles	Utilities for MI, IS, HS are applied to the first 6 months only. After this, utility values are assumed to revert back to the baseline "no event" utility.
Utility applied to fatal events	A utility of 0.22 (Greenhalgh *et al*.[53]) is applied to all the fatal events in the model in both the observation period and the full 40 year time horizon.
Cost of events	
Cost of death = £0.00	Costs of mortality is not captured by the ICER.
Increased risk of events due to age and subsequent events	
RR = 1, for all subsequent events following a MI, IS or HS	Patients are not at an increased risk of suffering a subsequent event following a MI, IS or HS/ICH. Patients suffering from non-fatal and fatal events will be driven by the efficacy data and increased risk of ageing in the extrapolation period.
Increased risk due to age = 0	The dynamic transition probabilities will remain unchanged over time as patient will not be at an increased risk of suffering an event in the extrapolation period.
RR = 1 and increased risk due to age = 0	Patients have no increased risk of suffering an event due to ageing or from having a prior event.

RR, relative risk; RRR, relative risk reduction

Table 32: The results of the scenario analyses presented in the MS (p341, Table 80, MS)

Parameters tested	Rivaroxaban		"standard of care"		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
Manufacturer's base case							
None	£14,802.17	9.56	£14,004.05	9.44	£763.58	0.12	£6,202.84
Strata and transition probabilities (proportional hazards)							
Stratum 2	£15,362.74	9.52	£14,479.67	9.40	£883.07	0.12	£7,404.53
Transition probabilities							
Non-parametric	£16,290.40	9.75	£15,431.41	9.62	£858.99	0.13	£6,468.00
Clopidogrel efficacy							
Clopidogrel RRR=1	£13,794.17	10.09	£13,044.73	9.96	£749.44	0.13	£5,824.01
Utilities							
Utility values from trial	£14,767.63	9.83	£14,004.06	9.71	£763.58	0.13	£5,935.11
Utility values return to the baseline utility value in the post event cycles	£14,767.63	9.61	£14,004.05	9.49	£763.58	0.12	£6,195.36
Utility values applied to fatal events	£14,767.63	13.39	£14,004.05	13.28	£763.58	0.10	£7,147.39
Cost of events							
Cost of death = £0.00	£13,522.08	9.56	£12,707.38	9.44	£814.70	0.12	£6,618.13
Increased risk of events due to age and subsequent events							
RR = 1 for all subsequent events following a MI, IS or HS	£15,960.00	9.81	£15,169.14	9.68	£790.86	0.12	£6,439.04
Increased risk due to age = 0	£31,093.77	14.09	£30,194.98	13.91	£898.79	0.18	£4,927.81
RR = 1 and increased risk due to age = 0	£29,633.17	14.34	£28,704.75	14.16	£928.42	0.18	£6,745.04

The additional scenario analyses presented in Table 33 were conducted in the manufacturer's response to the clarification questions B4, B22, B25 and B28. The first set of additional scenario analyses involved adapting the model to have age adjusted utilities.

To age adjust all utilities in the model, the manufacturer used the formulae presented in Table 33 to age adjust the event free utility. To age adjust the ACS event health states, the manufacturer calculated the relative difference between the utility of each ACS event and the event free health state

from the base case. These relative differences were then used to calculate the utility for each ACS event from the event free utility in that time period.

The other additional scenario analysis considered the effects of: assuming that the cost of a multiple ACS event state was the maximum of the single events costs and discontinuing rivaroxaban treatment after one year.

Table 33: The scenario analyses presented by the manufacturer in the clarification process

Parameters tested	Scenarios	Clarification question in which the manufacturer's response included the additional analysis
Age adjusted utilities		
Kind *et al.* age adjustment[a]	The utilities were adjusted by the following formula : Utility = 1.060 – 0.004*age	B22
Ara[54] [1] age adjustment	The utilities were age adjusted using the following formula from Ara and Brazier [54]: Utility = 0.9508566 + 0.0212126*gender - 0.0002587*age – 0.0000332*age^2 This formula was calculated from the general population in their dataset	B22
Ara[54] [2] age adjustment	The utilities were age adjusted using the following formula from Ara and Brazier [54]: Utility = 0.9454933 + 0.0256466*gender - 0.0002213*age – 0.0000294*age^2 This formula was calculated from the population without cardiovascular disease in their dataset	B22
Cost of the multiple ACS event states		
One follow-up cost for multiple ACS events	Instead of summing the cost of the individual ACS events for the multiple ACS event states, the most costly event was applied instead.	B25
Costs in the observation period		
Costs were adjusted to reflect the cycle length of the observation period	All costs in the observation period were altered using the following formula: _____	B4
Treatment duration of rivaroxaban		
Limited duration of rivaroxaban treatment	All patients were assumed to discontinue rivaroxaban treatment after one year.	B28

[a] The manufacturer did not supply a full reference for this source.

Table 34: The ICER of the base case and the scenario analyses presented by the manufacturer in the clarification process (manufacturer's clarification response to question B4, B22, B25 and B28 [p142, 154, 158])

	Incremental Cost	Incremental QALY	ICER
Base case	£763.58	0.12	£6,202.84
Kind *et al*.	£763.58	0.11	£6,747.92
Ara[54] [1] age adjustment	£763.58	0.12	£6,536.26
Ara[54] [2] age adjustment	£763.58	0.12	£6,358.40
One follow-up cost for multiple ACS events	£818.82	0.12	£6,651.58
Costs were adjusted to reflect the cycle length of the observation period	£862.45	0.12	£7,005.97
Limited duration of rivaroxaban treatment	£624.76	0.12	£5,322.56

As shown in Table 34, none of the ICER's lie above £10,000 per QALY in the manufacturer's scenario analyses. However, there are a number of key parameters that could not be adjusted within the model that may influence the ICER to a larger extent such as: amending the HR for fatal bleeds; using pooled efficacy data rather than the 2.5 mg dose alone; and adjusting for the possibility of informative bias.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 PSA with published values for the uncertainty

The ERG conducted an exploratory analysis where published levels of uncertainty were taken into account rather than an arbitrary range. The PSA was conducted using the manufacturer's base case, so that the ERG's probabilistic ICER could be compared with the manufacturer's deterministic ICER. This comparison was undertaken to inform the ERG as to whether the model appeared linear (that is the mean PSA answer and the deterministic answer are similar) or not using published values for the uncertainty. Depending on model linearity, the ERG undertook relevant exploratory analyses.

5.3.1.1 Parameterising the uncertainty in the utilities

To parameterise the uncertainty in the utilities, the ERG took the uncertainty in the standard errors available from Greenhalgh *et al.*[53] and Ara and Brazier.[54] The utility of the bleeding events was calculated using the same methods reported in the MS (p 268).

Table 35: The mean values and standard errors used in the PSA

Parameter	Mean	Standard error	Assumed distribution	Source
No Event	0.842	0.002	Normal	Greenhalgh *et al.*[53]
Non-fatal MI	0.779	0.010	Normal	Greenhalgh *et al.*[53]
Post MI	0.821	0.038	Normal	Greenhalgh *et al.*[53]
Non-fatal stroke	0.703	0.010	Normal	Greenhalgh *et al.*[53]
Post stroke	0.703	0.038	Normal	Greenhalgh *et al.*[53]
Stroke <12 months, history of stroke + other CV condition	0.479	0.087	Normal	Ara and Brazier[54]
No event <12 months, history of stroke and other CV condition	0.641	0.037	Normal	Ara and Brazier[54]

MI , myocardial infarction; CV, cardiovascular

All utilities were constrained to be equal to or less than one so that the PSA did not produce results that lacked face validity. The ERG chose to keep the improvement in stroke utility using the manufacturer's method in this model, so that the ERG's PSA ICER could be compared to the manufacturer's deterministic ICER. The uncertainty in the post stroke state from Greenhalgh *et al.*[53] was used in the ERG's PSA to calculate the final utility of patients who had experienced a stroke. The utility value of 12 months after a stroke health state was constrained so that the utility of patients who had not experienced an ACS event.

5.3.1.2 Parameterising the uncertainty in the costs

The ERG considered the uncertainty in the reference costs. To do this, standard errors for each reference cost were calculated. This was done using the following formulae:

[redacted]b

Each reference cost was assumed to be normally distributed. The standard error could not be calculated for all reference costs, for example if there was only one data submission. If using the normal distribution produced an error result, the mean unit cost was used. An activity weighted

b ±0.6745 is the z-score that gives the point on a normal distribution in which the top or bottom 25% of the distribution falls. On a normal distribution mean± (0.6745*standard deviation) will return the upper and lower quartile values.

average using the number of cases was used to produce the probabilistic acute phase cost as in the manufacturer's base case. All other assumptions regarding the cost of an event in the manufacturer's base case remained the same.

5.3.1.3 The uncertainty in all remaining parameters

The ERG used a beta distribution with an alpha and beta of one, this is equivalent to a uniform [0, 1] distribution. The uncertainty margins for the remaining parameters were the same as in the manufacturer's base case. As the cost per day of rehabilitation were now calculated using standard errors from the reference costs, the number of days spent in hospital rehabilitation were added to the PSA. The beta distribution with an alpha and beta of one was used to draw parameter values of ±25% of the mean.

As the manufacturer did not provide a variance-covariance matrix in their response to clarification question B3, the ERG could not assume that the shape and scale parameters of the Weibull distributions were correlated using a multivariate normal distribution. If this information was available, it would be included in this exploratory analysis.

5.3.1.4 The ERGs PSA results

The ERG's PSA results are summarised in Table 36. This shows that the probabilistic ICER is close in value to the manufacturer's deterministic ICER (£6203, see Table 27). Therefore, it was assumed that the model was linear. As such all further analyses were deterministic analyses.

Table 36: The ERG's probabilistic ICER

Technologies	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£) incremental**
Rivaroxaban+ CLOP+ASA or Rivaroxaban + ASA (all strata)	£14,806.22	9.54	£760.88	0.12	£6150
CLOP+ASA or ASA (all strata)	£14,045.35	9.42	-	-	-

CLOP, clopidogrel; ASA, aspirin

For completeness the ERG's cost-effectiveness plane and CEAC are presented in Figures 11 and 12.

Figure 11: **The cost-effectiveness plane of rivaroxaban and aspirin with or without clopidogrel compared to aspirin with or without clopidogrel presented by the ERG**

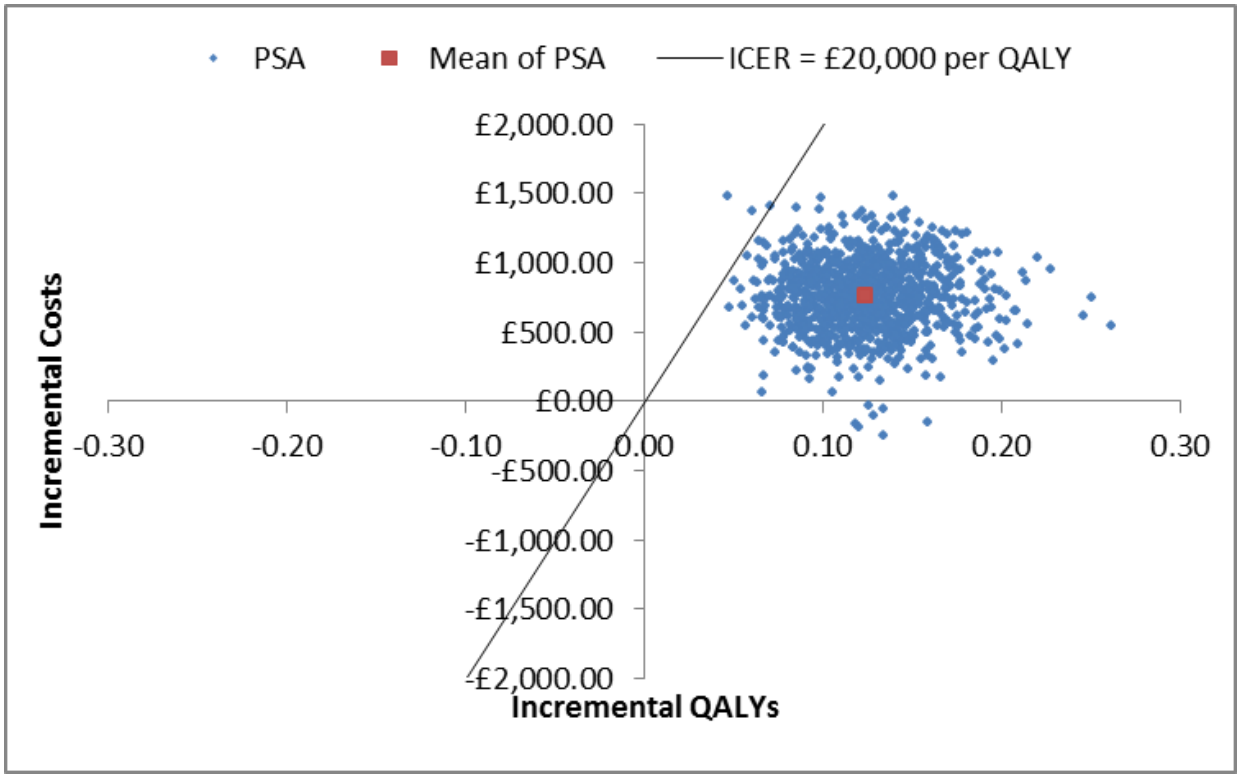
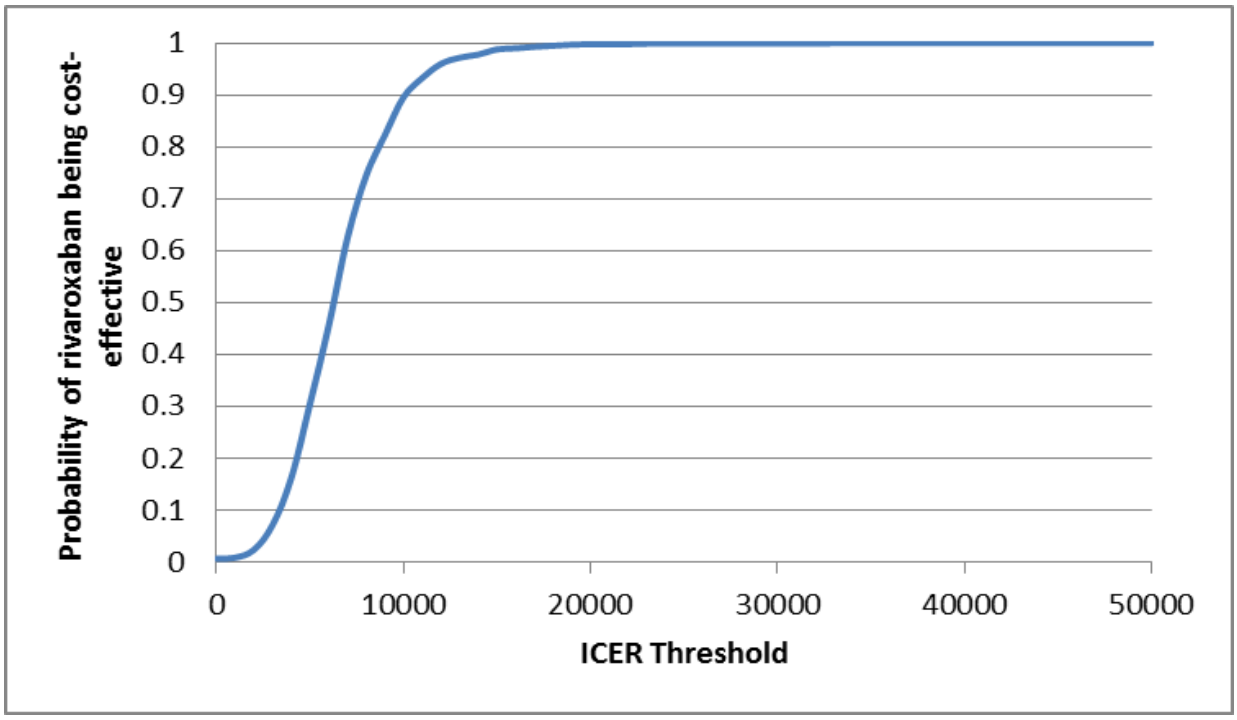


Figure 12: **The CEAC of rivaroxaban and aspirin with or without clopidogrel compared to aspirin with or without clopidogrel presented by the manufacturer**



5.3.1.5 The ERG's crude sensitivity analysis on the number of patients experience fatal bleeding events

The ERG could not alter the model to assess the sensitivity of the manufacturer's base case ICER to the HR for fatal bleeding. The ERG believed that this could be a key parameter particularly as the ERG has concerns regarding the plausibility of the midpoint of the HR for rivaroxaban 2.5 mg twice daily compared with placebo (see section 4.2.4.2). As such, the ERG conducted a crude sensitivity analysis to explore the effects on the ICER of increasing the number of patients who experienced a fatal bleeding event whilst receiving rivaroxaban, assuming that the event occurred immediately upon taking rivaroxaban. To conduct this sensitivity analysis, the ERG adjusted the total discounted cost and QALYs for those patients who received rivaroxaban. No adjustment was made to the total discounted cost or total discounted QALYs of those patients who did not receive rivaroxaban.

To adjust the total discounted QALYs, the following formula was used:

—

Where:

N denotes the total number of patients who received rivaroxaban

A denotes the additional number of patients assumed to have a fatal bleeding event

MQALYs denote the total discounted QALYs, for those patients who received rivaroxaban in the manufacturer's base case.

A similar methodology was used to adjust the total discounted costs. However, there was additionally a cost of death associated with other cardiovascular death in the model. As a fatal bleeding event was categorised as other cardiovascular death in the model, this was incorporated into the ERG's adjustment of the cost of rivaroxaban.

—

Where:

N are the total number of patients who received rivaroxaban

A are the number of patients who are assumed to have an additional fatal bleeding event

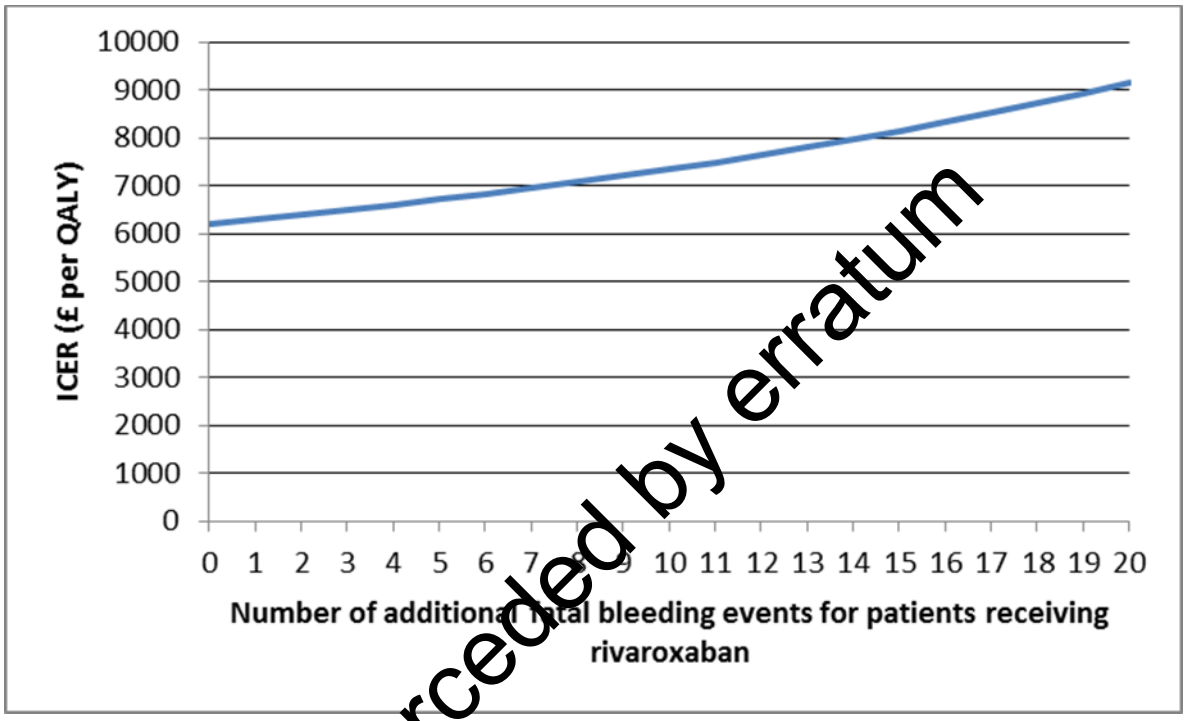
Most is the total discounted cost, for those patients who received rivaroxaban, in the manufacturer's base case.

Cost of a fatal bleeding event is the cost of other CV death (see section 5.2.6.2)

The ERG considered a range of additional fatal bleeding events ranging from no additional fatal bleeding events (manufacturer's base case) to 20 additional bleeding events. As there were 21 fatal bleeding events in the combined rivaroxaban arms of the total population in the ATLAS ACS 2-TIMI

51 trial (see Appendix 3) the ERG believes that 20 additional fatal bleeding events is an unfavourable scenario for rivaroxaban 2.5 mg twice a day dose. The result of the ERG's crude exploratory analysis is presented in Figure 13, it is seen that even if rivaroxaban 2.5 mg twice a day caused an additional 20 fatal bleeding events compared with the event rate observed in the trial the ICER was not estimated to be greater than £10,000 per QALY.

Figure 13: The impact of additional fatal bleeding events for patients on rivaroxaban on the ICER



5.3.1.6 The ERG's preferred base case

The differences in the ERG's exploratory analysis compared with the manufacturer's base case are listed below:

1. The trial data, not the Weibull curves are used to inform the transition probabilities. (see section 5.2.5.3)
2. The treatment duration of rivaroxaban is one year (see section 5.2.5.5)
3. Age adjusted utilities for the whole population from Ara and Brazier[54] are used to adjust the no event health state
4. The cost applied to the multiple event states is the maximum cost of both events (see sections 5.2.6.2 and 5.2.9.4)
5. Greenhalgh et al [53] utilities are applied to all stroke event states. (see section 5.2.7.1)
6. The relative risk of further events, as in Table 37 is applied. (see section 5.2.5.6)

7. In the observation period the cycle length was shortened to 12 weeks, to match reality, rather than the incorrect 13 weeks. To do this in the observation period the costs and the life years gained matrix were altered. (see section 5.2.5.6)
8. The number of non-fatal bleeding events was five times higher in both model arms than the manufacturer's base case (see section5.2.5.2)
9. There is no increased risk of a further ACS event, after an ACS event in the model extrapolation period, at all-time points (see section 5.2.5.6)
10. There is a five times greater risk of a further ACS event, after an ACS event in the model extrapolation period, at all-time points (see section 5.2.5.6)

Table 37: The relative risk of a subsequent event applied by the ERG in the exploratory analysis

Relative risks for subsequent events	**After MI**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	4.9	2.1	1.5
IS	3.2	1.8	1.5
HS/ICH	1.0	1.0	1.0
Fatal MI	4.9	2.1	1.5
Fatal IS	3.2	1.8	1.5
Fatal HS/ICH	1.0	1.0	1.0
OCD	3.0	1.6	1.5
Relative risks for subsequent events	**After IS**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	4.9	2.1	1.5
IS	3.2	1.8	1.5
HS/ICH	1.0	1.0	1.0
Fatal MI	4.9	2.1	1.5
Fatal IS	3.2	1.8	1.5
Fatal HS/ICH	1.0	1.0	1.0
OCD	3.0	1.6	1.5
Relative risks for subsequent events	**After HS**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	1.0	1.0	1.0
IS	1.0	1.0	1.5
HS/ICH	4.9	2.1	1.5
Fatal MI	1.0	1.0	1.0
Fatal IS	1.0	1.0	1.0
Fatal HS/ICH	4.9	2.1	1.5
OCD	1.0	1.0	1.0
Relative risks for subsequent events	**3 events**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI			
IS	1.5	1.5	1.5
HS/ICH			
Fatal MI	1.5	1.5	1.5
Fatal IS	1.5	1.5	1.5
Fatal HS/ICH	1.5	1.5	1.5
OCD	1.5	1.5	1.5

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non cardiovascular death

These analyses will be conducted individually, and then an analysis will be conducted with all of the changes made simultaneously. Table 38 presents the ERGs results for scenarios 5 - 10 individually and for when scenarios 1 to 7 are applied simultaneously. The manufacturer had already conducted scenarios 1 to 4, for clarity the results for these scenarios will also be presented in Table 38 even though they are presented elsewhere in the report.

Table 38: The ERGs exploratory analyses

Code	Change from MS base case	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
		Rivaroxaban plus ASA with or without CLOP	ASA with or without CLOP	Rivaroxaban plus ASA with or without CLOP	ASA with or without CLOP			
MS base case	-	£14,767.63	£14,004.05	9.56	9.44	£763.58	0.12	£6,203
1	The transition probabilities are estimated from the trial data	£16,290.40	£15,431.41	9.75	9.62	£858.99	0.13	£6,468
2	The treatment duration of rivaroxaban is limited to one year	£14,628.81	£14,004.05	9.56	9.44	£624.73	0.12	£5,323
3	The utilities are age adjusted, using Ara and Brazier's formula for the whole population[54]	£14,767.63	£14,004.05	9.07	8.95	£763.58	0.12	£6,536
4	Only one cost is applied to the multiple event states. Where there are two different costs added together in the manufacturer's base case , the maximum of the two costs is applied	£13,592.041	£12,818.43	9.56	9.44	£768.15	0.12	£6,240
5	No improvement over time in the stroke utility is modelled	£14,767.63	£14,004.05	9.53	9.41	£763.58	0.12	£6,289
6	The relative risk of suffering a subsequent event is given by Table 37	£15,007.30	£14,234.54	9.59	9.47	£772.76	0.12	£6,250
7	The life years gained matrix and the costs are adjusted for the 12 week cycle length in the observation period	£14,804.12	£14,026.06	9.49	9.37	£778.06	0.12	£6,357
8	There are 5 times as many bleeding events. (Excluding deaths due to bleeding)	£14,873.51	£14,049.43	9.56	9.44	£824.08	0.12	£6,714
9	The relative risk of a further ACS event following the first ACS event is one in the extrapolation period(i.e. all cells in Table 37 would be	£15,960.00	£15,169.14	9.80	9.68	£790.86	0.12	£6,439

	one)							
10	The relative risk of a further ACS event following the first ACS event is five in the extrapolation period(i.e. all cells in Table 37 would be five)	£12,292.55	£11,606.37	9.04	8.92	£686.19	0.13	£5,412
ERG base case 1+2+3+4+5+6+7		£14,650.11	£13,947.41	9.17	9.05	£702.70	0.12	£5,622

CLOP, clopidogrel; ASA, aspirin

5.4 Conclusions of the cost-effectiveness section

The mathematical model submitted by the manufacturer had many errors. Most of the errors were fixed, but errors introduced by the model structure's inability to track the timing of previous events could not be fixed within the timelines of an STA. The mathematical model was also highly inflexible, meaning the ERG could not characterise the effect of the uncertainty surrounding the side effects or clinical effectiveness of rivaroxaban. The efficacy of rivaroxaban was included in the PSA as Weibull curves where fitted to the event rates in the manufacturer's base case however, the shape and scale parameters were inappropriately sampled by the manufacturer.

The ERG's exploratory analysis had a lower ICER than the manufacturer's base case ICER. This effect was mainly driven by the fact that the ERG limited the treatment duration of rivaroxaban to one year. This was deemed to be appropriate as the manufacturer submitted limited evidence supporting a longer treatment duration (see section 5.2.5.5).

It has been noted by the clinical advisors to the ERG that prasugrel and ticagrelor are also in use for the secondary prevention of acute coronary syndrome in the UK. These treatments were outside of the scope and as such were not considered by the ERG in these analyses.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

None of the analyses undertaken by the ERG markedly changed the ICER calculated by the manufacturer. Whilst the ICERs estimated by the ERG are comfortably below £20,000 per QALY gained, there were some parameters that could not be meaningfully changed by the ERG. These relate to assumptions regarding: the HR for fatal bleeding; the HR for clinical efficacy; and that there was no informative censoring. A crude exploratory analysis undertaken by the ERG indicates that the impact of changes in assumptions regarding fatal bleeds did not substantially increase the ICER.

7 END OF LIFE CONSIDERATION

NICE end of life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
- The treatment is licensed or otherwise indicated, for small patient populations.

The manufacturer make no claim that rivaroxaban should be appraised under the supplementary 'end of life' advice. The ERG would concur with this view.

8 OVERALL CONCLUSIONS

Clinical effectiveness

Compared with standard care, the addition of rivaroxaban (2.5 mg twice daily) to existing antiplatelet therapy reduced the composite of CV mortality, MI or stroke MI but increased the risk of major bleeding and intracranial haemorrhage. There are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Due to the post-hoc mITT analyses, high dropout rates and missing vital status data, inference of treatment effects (including magnitude) may be confounded. The key uncertainties in the clinical evidence relate to optimal dosing, duration of treatment, generalisability to the UK population and the possibility of bias due to informative censoring.

Cost-effectiveness

The ERG identified several errors in the mathematical model. A substantial range of sensitivity analyses were presented, in all of which the ICER remained below £10,000 per QALY. However there were some parameters that could not be meaningfully changed by the ERG. These relate to assumptions regarding: the HR for fatal bleeding; the HR for clinical efficacy; and that there was no informative censoring. A crude exploratory analysis undertaken by the ERG indicates that the impact of changes in assumptions regarding fatal bleeds did not substantially increase the ICER. These results have been predicated on an assumed cost for rivaroxaban 2.5 mg of £58.80 per 56 tablets. Should this price differ from the confirmed cost then the ICERs would change. The scope for this STA did not include either prasugrel or ticagrelor, as such no comparison on the cost-effectiveness of rivaroxaban compared with these interventions has been provided.

8.1 Implications for research

Key research implications are bulleted below.

- A confirmatory trial to establish the benefits of rivaroxaban (in combination with aspirin or with aspirin and clopidogrel) in ACS patients without prior stroke or TIA, including optimal duration of treatment.
- Outside of the scope of this STA, a head-to-head trial comparing rivaroxaban (in combination with aspirin alone or with aspirin and clopidogrel) with ticagrelor (plus aspirin) or prasugrel (plus aspirin) would be beneficial.

9 APPENDICES

Appendix 1: Effect of rivaroxaban compared with placebo on the primary endpoint (mITT analysis excluding 3 sites): Total population (p79-80, MS)

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
All strata	*N=5114*	*N=5115*	*N=10229*	*N=5113*						
Primary Endpoint: Composite of CV death, MI, stroke	313 (6.1)	313 (6.1)	626 (6.1)	376 (7.4)	0.84 (0.72-0.97)	0.02	0.85 (0.73-0.98)	0.028	0.84 (0.74-0.96)	0.008
CV Death	94 (1.8)	132 (2.6)	226 (2.2)	143 (2.8)	0.66 (0.51-0.86)	0.002	0.94 (0.75-1.20)	0.633	0.80 (0.65-0.99)	0.038
MI	205 (4.0)	179 (3.5)	384 (3.8)	229 (4.5)	0.90 (0.75-1.09)	0.270	0.79 (0.65-0.97)	0.020	0.85 (0.72-1.00)	0.047
Stroke	46 (0.9)	54 (1.1)	100 (1.0)	41 (0.8)	1.13 (0.74-1.73)	0.562	1.34 (0.90-2.02)	0.151	1.24 (0.86-1.78)	0.246
Stratum 1: Aspirin	*N=349*	*N=348*	*N=697*	*N=353*						
Primary Endpoint: Composite of CV death, MI, stroke	27 (7.7)	24 (6.9)	51 (7.3)	36 (10.2)	0.74(0.45-1.22)	0.234	0.64 (0.38-1.07)	0.089	0.69 (0.45-1.05)	0.084
CV Death	12 (3.4)	9 (2.6)	21 (3.0)	10 (2.8)	1.20 (0.52-2.77)	0.673	0.89 (0.36-2.20)	0.805	1.04 (0.49-2.21)	0.913
MI	16 (4.6)	10 (2.9)	26 (3.7)	22 (6.2)	0.72 (0.38-1.37)	0.310	0.44 (0.21-0.93)	0.026	0.58 (0.33-1.02)	0.053
Stroke	2 (0.6)	8 (2.3)	10 (1.4)	7 (2.0)	0.28 (0.06-1.37)	0.095	1.13 (0.41-3.12)	0.812	0.71 (0.27-1.86)	0.483
Stratum 2: Aspirin plus thienopyridine	*N=4765*	*N=4767*	*N=9532*	*N=4760*						
Primary Endpoint: Composite of CV death, MI, stroke	286 (6.0)	289 (6.1)	575 (6.0)	340 (7.1)	0.85 (0.72-0.99)	0.039	0.87 (0.74-1.01)	0.075	0.86 (0.75-0.98)	0.024
CV Death	82 (1.7)	123 (2.6)	205 (2.2)	133 (2.8)	0.62 (0.47-0.82)	<0.001	0.95 (0.74-1.21)	0.669	0.78 (0.63-0.97)	0.028
MI	189 (4.0)	169 (3.5)	358 (3.8)	207 (4.3)	0.92 (0.75-1.12)	0.401	0.83 (0.68-1.02)	0.077	0.88 (0.74-1.04)	0.131
Stroke	44 (0.9)	46 (1.0)	90 (0.9)	34 (0.7)	1.31 (0.84-2.05)	0.238	1.39 (0.89-2.16)	0.144	1.35 (0.91-2.00)	0.135

bd, bis die (twice daily); CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; mITT, modified intention-to-treat

Appendix 2: Effect of rivaroxaban compared with placebo on secondary endpoints (mITT analysis excluding 3 sites): Total population (p85-97, MS)

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All Strata	*N=5114*	*N=5115*	*N=10229*	*N=5113*						
Secondary endpoint 1: Composite of all cause death, MI, stroke	320 (6.3)	321 (6.3)	641 (6.3)	386 (7.5)	0.83 (0.72-0.97)	0.016	0.84 (0.73-0.98)	0.025	0.84 (0.74-0.95)	0.006
Secondary endpoint 2: Net clinical outcome (composite of CV death, MI, ischaemic stroke or non-CABG TIMI major bleeding)	361 (7.1)	366 (7.2)	727 (7.1)	391 (7.6)	0.93 (0.81-1.07)	0.320	0.95 (0.83-1.10)	0.508	0.94 (0.83-1.06)	0.337
Secondary Endpoint 3: Composite of CV death, MI, stroke, SRIR	437 (8.5)	421 (8.2)	858 (8.4)	481 (9.4)	0.92 (0.8-1.04)	0.185	0.89 (0.78-1.01)	0.081	0.90 (0.81-1.01)	0.074
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH	372 (7.3)	388 (7.6)	760 (7.4)	447 (8.7)	0.84 (0.73-0.96)	0.011	0.88 (0.77-1.01)	0.070	0.86 (0.76-0.97)	0.011
Individual outcomes										
Death (all-cause)	103 (2.0)	142 (2.8)	245 (2.4)	153 (3.0)	0.68 (0.53-0.87)	0.002	0.95 (0.76-1.19)	0.662	0.81 (0.66-1.00)	0.044
Ischaemic stroke	30 (0.6)	35 (0.7)	65 (0.6)	34 (0.7)	0.89 (0.55-1.45)	0.643	1.05 (0.65-1.68)	0.844	0.97 (0.64-1.47)	0.886
Non-CABG TIMI major bleeding	68 (1.3)	85 (1.7)	153 (1.5)	23 (0.4)	2.99 (1.86-4.80)	<0.001	3.81 (2.40-6.04)	<0.001	3.40 (2.19-5.26)	<0.001
SRIR	132 (2.6)	122 (2.4)	254 (2.5)	121 (2.4)	1.10 (0.86-1.41)	0.445	1.03 (0.80-1.33)	0.798	1.07 (0.86-1.32)	0.557
SRIH	74 (1.4)	93 (1.8)	167 (1.6)	99 (1.9)	0.75 (0.56-1.02)	0.063	0.96 (0.73-1.28)	0.798	0.86 (0.67-1.10)	0.223
Stent thrombosis [a]	61 (1.2)	61 (1.2)	[redacted]	87 (1.7)	0.70 (0.51-0.97)	0.033	[redacted]	[redacted]	[redacted]	[redacted]

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
							[redacted]		[redacted]	
Stratum 1: Aspirin	*N=349*	*N=348*	*N=697*	*N=353*						
Secondary endpoint 1: Composite of all cause death, MI, stroke	28 (8.0)	24 (6.9)	52 (7.5)	36 (10.2)	0.77 (0.47-1.26)	0.291	0.64 (0.38-1.07)	0.089	0.70 (0.46-1.07)	0.101
Secondary endpoint 2: Net clinical outcome (composite of CV death, MI, ischaemic stroke or non-CABG TIMI major bleeding)	28 (8.0)	25 (7.2)	53 (7.6)	36 (10.2)	0.77 (0.47-1.26)	0.290	0.67 (0.4-1.11)	0.120	0.72 (0.47-1.09)	0.120
Secondary Endpoint 3: Composite of CV death, MI, stroke, SRIR	31 (8.9)	28 (8.0)	59 (8.5)	39 (11.0)	0.78 (0.49-1.26)	0.313	0.69 (0.43-1.13)	0.136	0.74 (0.49-1.10)	0.138
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH	32 (9.2)	30 (8.6)	62 (8.9)	42 (11.9)	0.75 (0.47-1.19)	0.219	0.69 (0.43-1.09)	0.112	0.72 (0.48-1.06)	0.093
Individual outcomes										
Death (all-cause)	13 (3.7)	9 (2.6)	22 (3.2)	10 (2.8)	1.30 (0.57-2.96)	0.533	0.89 (0.36-2.20)	0.805	1.09 (0.52-2.31)	0.814
Ischaemic stroke	1 (0.3)	5 (1.4)	6 (0.9)	6 (1.7)	0.17 (0.02-1.38)	0.059	0.82(0.25-2.70)	0.749	0.50 (0.16-1.54)	0.216
Non-CABG TIMI major bleeding	2 (0.6)	4 (1.1)	6 (0.9)	0 (0.0)	-	0.160	-	0.046	-	0.085
SRIR	4 (1.1)	4 (1.1)	8 (1.1)	4 (1.1)	1.00 (0.25-4.01)	0.995	1.00 (0.25-3.99)	0.997	1.00 (0.30-3.32)	0.999
SRIH	6 (1.7)	7 (2.0)	13 (1.9)	8 (2.3)	0.74 (0.26-2.13)	0.574	0.87 (0.31-2.39)	0.779	0.80 (0.33-1.94)	0.627
Stent thrombosis [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Stratum 2: Aspirin plus thienopyridine	*N=4765*	*N=4767*	*N=9532*	*N=4760*						
Secondary endpoint 1: Composite of all cause death, MI, stroke	292 (6.1)	297 (6.2)	589 (6.2)	350 (7.4)	0.84 (0.72-0.98)	0.028	0.87 (0.74-1.01)	0.068	0.85 (0.75-0.97)	0.019
Secondary endpoint 2: Net clinical outcome (composite of CV death, MI, ischaemic stroke or non-CABG TIMI major bleeding)	333 (7.0)	341 (7.2)	674 (7.1)	355 (7.5)	0.95 (0.82-1.10)	0.473	0.98 (0.85-1.14)	0.818	0.96 (0.85-1.10)	0.585
Secondary Endpoint 3: Composite of CV death, MI, stroke, SRIR	406 (8.5)	393 (8.2)	799 (8.4)	442 (9.3)	0.93 (0.81-1.06)	0.276	0.91 (0.79-1.04)	0.164	0.92 (0.82-1.03)	0.149
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH	340 (7.1)	358 (7.5)	698 (7.3)	405 (8.5)	0.85 (0.73-0.98)	0.022	0.90 (0.78-1.04)	0.159	0.87 (0.77-0.99)	0.031
Individual outcomes										
Death (all-cause)	90 (1.9)	133 (2.8)	223 (2.3)	143 (3.0)	0.64 (0.49-0.83)	<0.001	0.95 (0.75-1.21)	0.698	0.79 (0.64-0.98)	0.030
Ischaemic stroke	29 (0.6)	30 (0.6)	59 (0.6)	28 (0.6)	1.05 (0.62-1.76)	0.864	1.10 (0.66-1.84)	0.723	1.07 (0.68-1.68)	0.760
Non-CABG TIMI major bleeding	66 (1.4)	81 (1.7)	147 (1.5)	23 (0.5)	2.90 (1.81-4.67)	<0.001	3.64 (2.29-5.78)	<0.001	3.27 (2.10-5.07)	<0.001
SRIR	128 (2.7)	118 (2.5)	246 (2.6)	117 (2.5)	1.10 (0.86-1.42)	0.438	1.03 (0.80-1.34)	0.794	1.07 (0.86-1.33)	0.551
SRIH	68 (1.4)	86 (1.8)	154 (1.6)	91 (1.9)	0.75 (0.55-1.03)	0.077	0.97 (0.72-1.31)	0.853	0.86 (0.66-1.12)	0.259
Stent thrombosis [a]	58 (1.2)	60 (1.3)	[redacted]	85 (1.8)	0.68 (0.49-0.95)	[redacted]	0.71 (0.51-0.99)	[redacted]	[redacted]	[redacted]

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
									[redacted]	

bd, bis die (twice daily); CABG, coronary artery bypass grafting; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IS, Ischaemic stroke; MI, myocardial infarction; mITT, modified intention-to-treat; SRIR, Severe recurrent ischaemia requiring revascularisation; SRIH; Severe recurrent ischaemia requiring hospitalisation; TIMI, Thrombolysis in Myocardial Infarction

[a] Defined as definite, probable or possible by Academic Research Consortium definitions; method of analysis using ITT approach (p95-96, MS)

Appendix 3: Effect of rivaroxaban compared with placebo on safety endpoints (treatment-emergent safety analysis set)[a]: Total population (p108-109, MS)

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All strata	*N=5115*	*N=5110*	*N=10,225*	*N=5125*						
Primary safety endpoint:[b] Non-CABG TIMI major bleeding	65 (1.3)	82 (1.6)	147 (1.4)	19 (0.4)	3.46 (2.08-5.77)	<0.001	4.47 (2.71-7.36)	<0.001	3.96 (2.46-6.38)	<0.001
Secondary safety endpoint: Clinically significant bleeding (composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention)	586 (11.5)	748 (14.6)	1334 (13.0)	327 (6.4)	1.84 (1.61-2.11)	<0.001	2.43 (2.13-2.76)	<0.001	2.13 (1.89-2.40)	<0.001
Individual outcomes										
Fatal bleeding	6 [redacted]	15 [redacted]	21 [redacted]	9 [redacted]	0.67 (0.24-1.89)	0.45	1.72 (0.75-3.92)	0.195	1.19 (0.54-2.59)	0.664
TIMI major bleeding	68 (1.3)	85 (1.7)	153 (1.5)	27 (0.5)	2.55 (1.63-3.98)	<0.001	3.25 (2.11-5.02)	<0.001	2.90 (1.92-4.36)	<0.001
TIMI minor bleeding	32 (0.6)	49 (1.0)	81 (0.8)	20 (0.4)	1.62 (0.92-2.82)	0.09	2.52 (1.50-4.24)	<0.001	2.07 (1.27-3.37)	0.003
TIMI bleeding requiring medical attention	492 (9.6)	637 (12.5)	1129 (11.0)	282 (5.5)	1.79 (1.55-2.07)	<0.001	2.39 (2.08-2.75)	<0.001	2.09 (1.83-2.38)	<0.001
Intracranial haemorrhage	14 [redacted]	18 [redacted]	32 [redacted]	5 [redacted]	2.83 (1.02-7.86)	0.037	3.74 (1.39-10.07)	0.005	3.28 (1.28-8.42)	0.009

bd, bis die (twice daily); CI, confidence interval; HR, hazard ratio; TIMI, Thrombolysis in Myocardial Infarction

[a] Treatment-emergent safety analysis set included all events from first dose up to the date of last dose of study drug plus 2 days

[b] Stratum 1: rivaroxaban 2.5 mg bd (n=2 [0.6%]) compared with placebo (0%), p=0.154; rivaroxaban 5 mg bd (n=4 [1.2%]) compared with placebo (0%), p=0.083. Stratum 2 mirrored all strata results: rivaroxaban 2.5 mg bd (n=63 [1.3%]) compared with placebo (n=19 [0.4%]), HR 3.35, 95% CI: 2.01-5.60, p<0.001; rivaroxaban 5 mg bd (n=78 [1.6%]) compared with placebo (n=19 [0.4%]), HR 4.26, 95% CI: 2.58-7.03, p<0.001

Appendix 4: Treatment-emergent adverse events in at least 1% patients (safety analysis set): Total population (reproduced with minor changes; p117-118, MS)

Adverse events	**Rivaroxaban**			**Placebo n (%)**
	2.5mg bd n (%)	**5mg bd n (%)**	**Combined n (%)**	
All strata	*N=5115*	*N=5110*	*N=10225*	*N=5125*
Total number of patients with treatment-emergent adverse events	*2769 (54.1)*	*2898 (56.7)*	*5667 (55.4)*	*2694 (52.6)*
Treatment-emergent adverse events excluding bleeding adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	905 (17.7)	934 (18.3)	1839 (18.0)	973 (19.0)
Angina Pectoris	295 (5.8)	307 (6.0)	602 (5.9)	340 (6.6)
Angina Unstable	246 (4.8)	269 (5.3)	515 (5.0)	248 (4.8)
Acute Myocardial Infarction	94 (1.8)	91 (1.8)	185 (1.8)	114 (2.2)
Myocardial Infarction	66 (1.3)	59 (1.2)	125 (1.2)	68 (1.3)
Atrial Fibrillation	60 (1.2)	56 (1.1)	116 (1.1)	68 (1.3)
Cardiac Failure	75 (1.5)	47 (0.9)	122 (1.2)	56 (1.1)
Gastrointestinal disorders	543 (10.6)	685 (13.4)	1228 (12.0)	478 (9.3)
Gingival bleeding	104 (2.0)	192 (3.8)	296 (2.9)	63 (1.2)
Rectal haemorrhage	63 (1.2)	59 (1.2)	122 (1.2)	41 (0.8)
Respiratory, Thoracic, Mediastinal Disorders	496 (9.7)	582 (11.4)	1078 (10.5)	387 (7.6)
Epistaxis	268 (5.2)	350 (6.8)	618 (6.0)	141 (2.8)
Cough	63 (1.2)	58 (1.1)	121 (1.2)	74 (1.4)
Dyspnoea	56 (1.1)	65 (1.3)	121 (1.2)	79 (1.5)
Surgical and Medical Procedures	497 (9.7)	448 (8.8)	945 (9.2)	450 (8.8)
Percutaneous Coronary Intervention	249 (4.9)	247 (4.8)	496 (4.9)	240 (4.7)
Coronary Artery Bypass	82 (1.6)	76 (1.5)	158 (1.5)	77 (1.5)
Coronary Revascularisation	61 (1.2)	47 (0.9)	108 (1.1)	46 (0.9)
General Disorders & Administration Site Conditions	374 (7.3)	410 (8.0)	784 (7.7)	389 (7.6)
Chest Pain	113 (2.2)	99 (1.9)	212 (2.1)	90 (1.8)
Non-Cardiac Chest Pain	86 (1.7)	98 (1.9)	184 (1.8)	99 (1.9)
Injury, poisoning and Procedural Complications	290 (5.7)	356 (7.0)	646 (6.3)	225 (4.4)
Contusion	75 (1.5)	92 (1.8)	167 (1.6)	53 (1.0)
Vascular Disorders	297 (5.8)	318 (6.2)	615 (6.0)	291 (5.7)
Haematoma	103 (2.0)	125 (2.4)	228 (2.2)	79 (1.5)
Hypertension	86 (1.7)	59 (1.2)	145 (1.4)	75 (1.5)
Infections & Infestations	291 (5.7)	323 (6.3)	614 (6.0)	360 (7.0)
Nasopharyngitis	45 (0.9)	33 (0.6)	78 (0.8)	52 (1.0)
Skin and subcutaneous tissue disorders	262 (5.1)	275 (5.4)	537 (5.3)	228 (4.4)
Ecchymosis	82 (1.6)	89 (1.7)	171 (1.7)	53 (1.0)
Investigations	262 (5.1)	274 (5.4)	536 (5.2)	251 (4.9)
Arteriogram Coronary	59 (1.2)	72 (1.4)	131 (1.3)	73 (1.4)
Alanine Aminotransferase Increased	44 (0.9)	41 (0.8)	85 (0.8)	49 (1.0)
Nervous System Disorders	232 (4.5)	282 (5.5)	514 (5.0)	239 (4.7)
Dizziness	61 (1.2)	52 (1.0)	113 (1.1)	50 (1.0)
Renal and Urinary disorders	139 (2.7)	169 (3.3)	308 (3.0)	97 (1.9)
Haematuria	69 (1.3)	121 (2.4)	190 (1.9)	31 (0.6)

bd, bis die (twice daily); NR, not reported

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