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Rivaroxaban for preventing atherothrombotic events in people with acute coronary syndrome and elevated cardiac biomarkers: An Evidence Review Group perspective of a NICE Single Technology Appraisal

Short Title: Rivaroxaban for acute coronary syndromes

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Abstract

As part of its single technology appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited the company that manufactures rivaroxaban (Xarelto, Bayer) to submit evidence of the clinical and cost-effectiveness of rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome (ACS). The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a critical review of the evidence for the clinical and cost-effectiveness of the technology, based upon the company's submission to NICE. The evidence was derived mainly from a randomised, double-blind, phase III, placebo-controlled trial of rivaroxaban (either 2.5 mg or 5 mg twice daily) in patients with recent ACS (unstable angina, non-ST segment elevation myocardial infarction [NSTEMI] or ST segment elevation myocardial infarction [STEMI]). In addition, all patients received antiplatelet therapy (aspirin alone or aspirin and a thienopyridine either as clopidogrel [approx. 99%] or ticlopidine [approx. 1%] according to national or local guidelines). The higher dose of rivaroxaban (5 mg twice daily) did not form part of the marketing authorisation. A post-hoc sub group analysis of the licensed patients who had ACS with elevated cardiac biomarkers (that is, patients with STEMI and NSTEMI) without prior stroke or transient ischaemic stroke showed that compared with standard care, the addition of rivaroxaban (2.5 mg twice daily) to existing antiplatelet therapy reduced the composite endpoint of cardiovascular mortality, myocardial infraction or stroke but increased the risk of major bleeding and intracranial haemorrhage. However, there were a number of limitations in the evidence base which warrant caution in its interpretation. In particular, the evidence may be confounded due to the post-hoc subgroup analysis, modified intention to treat analyses, high dropout rates and missing vital status data. Results from the company's economic evaluation showed that the deterministic incremental cost-effectiveness ratio (ICER) for rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone compared with aspirin plus clopidogrel or aspirin alone was £6,203 per quality adjusted life year (QALY) gained. In contrast, the ERG's preferred base case estimate was £5,622 per QALY gained. The ICER did not rise above £10,000 per QALY gained in any of the sensitivity analyses undertaken by the ERG, although the inflexibility of the company's economic model precluded the ERG from formally undertaking all desired exploratory analyses. As such, only a crude exploration of the impact of additional bleeding events could be undertaken. The NICE Appraisal Committee concluded that the ICERs presented were all within the range that could be considered cost-effective and that the results of the ERG's exploratory sensitivity and scenario analyses suggested that the ICER was unlikely to increase to the extent that it would become unacceptable. The Appraisal Committee therefore concluded that rivaroxaban in combination with aspirin plus clopidogrel, or with aspirin alone, was a cost-effective use of NHS resources for preventing atherothrombotic events in people with ACS and elevated cardiac biomarkers.

Key points for decision makers

- Rivaroxaban, in combination with aspirin plus clopidogrel or aspirin alone resulted in clinically significant reductions in atherothrombotic events compared with standard care but increased the risk of major bleeding and intracranial haemorrhage in people who have had an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

- The population in the phase III trial of rivaroxaban may not be generalisable to adult patients with recent ACS in routine clinical practice, who are usually older or to those with a greater incidence of renal impairment and a higher baseline bleeding risk.

- Rivaroxaban, in combination with aspirin plus clopidogrel or aspirin alone appears to represent a cost-effective strategy in people with ACS and elevated cardiac biomarkers compared with standard care.

- Other dual antiplatelet regimens such as ticagrelor and prasugrel (which are recommended in current NICE guidelines for the acute and maintenance phases of ACS) were absent from the NICE scope and therefore the relative cost-effectiveness of rivaroxaban compared with these interventions rather than clopidogrel was not estimated.

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources in order for NICE to recommend their use within the NHS in England. The NICE Single Technology Appraisal (STA) process usually covers new single health technologies within a single indication, soon after the UK market authorisation [1]. Within the STA process, the company provides NICE with a written submission, alongside a mathematical model that summarises the company's estimates of the clinical and cost effectiveness of the technology. This submission is reviewed by an external organisation independent of NICE (the Evidence Review Group [ERG]), which consults with clinical specialists and produces a report. After consideration of the company's submission, the ERG report and testimony from experts and other stakeholders, the NICE Appraisal Committee formulates preliminary guidance, the Appraisal Consultation Document (ACD), which indicates the initial decision of the Appraisal Committee regarding the recommendation (or not) of the technology. Stakeholders are then invited to comment on the submitted evidence and the ACD, after which a further ACD may be produced or a Final Appraisal Determination (FAD) is issued, which is open to appeal. An ACD is not produced when the technology is recommended within its full marketing authorisation; in this case, a FAD is produced directly.

This paper presents a summary of the ERG report [2] for the STA of rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (ACS) and a summary of the subsequent development of the NICE guidance for the use of this drug in England. Full details of all relevant appraisal documents (including the appraisal scope, ERG report, company and consultee submissions, FAD and comments from consultees) can be found on the NICE website [3].

2. The Decision Problem

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 (an accumulation of fatty deposits within the arteries of the heart) [4]. The classification of ACS is largely based on the characteristics of the presenting electrocardiogram and levels of cardiac biomarkers. 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).

Although the incidence and prevalence of ACS are difficult to estimate, data from the Hospital Episode Statistics for England [5] and the Patient Episode Database for Wales [6] suggest that 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) in England and Wales. Similarly the Myocardial Ischaemia National Audit Project (MINAP) database [7] (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 between April 2012 and March 2013. 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. 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. A recent record linkage study [8] 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 with the cumulative risk increasing more gradually thereafter.

Dual antiplatelet regimens such as aspirin and an adenosine diphosphate (ADP) receptor antagonist are the mainstay of treatment in the pharmacological management of ACS. 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 may require less urgent intervention. The vast majority of patients with confirmed STEMI undergo (primary) percutaneous coronary intervention (PCI) to the occluded artery [7]. Immediately before primary 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 [4;9-12]. For patients with NSTEMI, treatment options in general, as recommended by NICE Clinical Guideline No. 94, [4] 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 [4;9;10;12].

In the UK, the 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 (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 (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 (ticagrelor is dosed twice a day compared with once a day clopidogrel and prasugrel), increased bleeding risk (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 (generic clopidogrel is markedly cheaper than either prasugrel or ticagrelor) [14]. Despite variation in practice among clinicians in the UK, aspirin in combination with ticagrelor or prasugrel are increasingly being used and recommended as first line treatments in the acute and maintenance phases of ACS [15;16].

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]. It was granted a new European marketing authorisation in May 2013 and was launched in the UK in October 2014. 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 (STEMI and NSTEMI) only. The licensed dose is 2.5 mg twice daily. It is usually co-administered with a daily dose of 75 to 100 mg aspirin or a daily dose of 75 to 100 mg aspirin (75 to 100 mg per day) plus clopidogrel (75 mg daily) or standard daily dose of ticlopidine (an antiplatelet agent not available in the UK) [18] and is likely to be initiated in secondary care.

NICE issued a final scope to appraise the clinical and cost effectiveness of rivaroxaban, within its licensed indication, for the prevention of adverse outcomes in patients after the acute management of ACS. The intervention was rivaroxaban (in combination with aspirin or with aspirin and a thienopyridine [clopidogrel])' with two comparators defined as 'clopidogrel with aspirin and aspirin alone for people for whom clopidogrel is considered unsuitable'.

3. The Independent Evidence Review Group Review

In accordance with the process for STAs, the ERG and NICE had the opportunity to seek clarification on specific points in the company's submission, in response to which the company provided additional information. The ERG also modified the company's decision analytic model to produce an ERG base case and to assess the impact of alternative parameter values and assumptions on the model results. The evidence presented in the company's submission and the ERG's review of that evidence is summarised here.

3.1 Clinical evidence provided by the Company

The clinical effectiveness evidence in the company's submission was based primarily on data from the ATLAS-ACS 2-TIMI 51 study [19;20]. This was an international, multicentre (766 sites in 44 countries including the UK), randomised, placebo controlled trial, that was designed to evaluate 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). The trial [19;20] consisted of three phases: 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), patients were stratified on the basis of whether they were planned to have clopidogrel or ticlopidine in addition to aspirin as standard care (stratum 1: aspirin only [n=1053]; stratum 2: aspirin plus clopidogrel or ticlopidine [n=14,473]). All patients who received clopidogrel (approx. 99%) or ticlopidine (approx. 1%) followed national or local guidelines (the daily maintenance dose did not exceed 75 mg a day for clopidogrel or 250 mg twice daily for ticlopidine). Patients were randomised (>24 hours post hospitalisation) to 1 of 3 treatment groups: 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. 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 – this included all randomised patients [with the exception of those from 3 sites where trial misconduct was identified] and the endpoints that occurred until 30 days after treatment discontinuation with censoring of patients thereafter) with sensitivity analyses using variations of the intention-to-treat analysis sets.

During the marketing authorisation process, the European Medicines Agency (EMA) requested that a narrower population of patients with ACS be identified from the ATLAS-ACS 2-TIMI 51 trial [19;20] who derived the most favourable benefit from the addition of rivaroxaban to existing antiplatelet therapy. The population identified by the company, and accepted by the EMA, was adult patients who had ACS with elevated cardiac biomarkers excluding patients with a history of stroke or TIA. The subsequent marketing authorisation was granted for this subgroup of people who thereby form the licensed population.

The main findings of the post-hoc subgroup analysis in the licensed population (all strata, n=12,353; 80% of total population) showed that treatment with rivaroxaban (either 2.5 mg twice daily or 5 mg twice daily) significantly reduced the primary composite efficacy endpoint of CV death, MI or stroke (Table 1). There were differences in the statistical significance between the components of the composite efficacy end points. Rivaroxaban 2.5 mg twice daily significantly reduced the risk of death from CV causes compared with placebo, but did not reduce the risk of MI. In contrast, rivaroxaban 5 mg twice daily significantly reduced the risk of MI, but did not reduce the risk of CV death. Although neither dose indicated a statistically significant change in the incidence of stroke, both midpoint estimates indicated increased risk. A similar pattern was also observed for the total population of the ATLAS-ACS 2-TIMI 51 trial [19;20].

The company did not report any results in relation to treatment compliance or premature discontinuation of study treatments for the licensed population as data were not available at the time of submission. For the total trial population, 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. The most common reasons for discontinuation of study treatment were adverse events and consent withdrawal. Compared with placebo, rivaroxaban increased the rates of non-coronary artery bypass grafting 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 more appropriate than a pooled estimate to represent the licensed dose: hazard ratio (HR) 3.44, 95% CI: 1.97 to 6.01, $p<0.001$.

Table 1: Primary Efficacy Endpoint Analysis in the ATLAS ACS 2–TIMI 51 Trial (mITT analysis excluding 3 sites): Licensed population

Stratum [a]	**Rivaroxaban**			**Placebo**	**2.5 mg bd vs. placebo**		**5 mg bd vs. placebo**		**Combined vs. placebo**	
	2.5 mg bd	**5 mg bd**	**Combined**							
Endpoint					**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All strata (N=12,353)	N=4104	N=4089	N=8193	N=4160						
Primary Endpoint: Composite of CV death, MI, stroke	6.2%	6.1%	6.2%	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	1.7%	2.6%	2.1%	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	4.3%	3.6%	3.9%	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	0.9%	0.9%	0.9%	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

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

[a] Data for strata 1 (aspirin alone) and strata 2 (aspirin plus clopidogrel or ticlopidine) could not be presented as these were considered to be confidential by the company

3.1.1 Critique of the Clinical Evidence and Interpretation

The systematic review process followed by the company was comprehensive and the ERG was confident that all relevant studies (published and unpublished) of rivaroxaban for the prevention of adverse outcomes in patients after the acute management of ACS were included. Although the ERG considered the ATLAS-ACS 2-TIMI 51 trial to be a well-designed, multicentre, randomised, controlled trial of reasonable methodological quality, there were a number of limitations and uncertainties in the evidence base which warranted caution in its interpretation.

- Strength of post-hoc analysis

The main clinical effectiveness data for rivaroxaban were based on 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). The study was not powered for this post-hoc subgroup analysis and the effect of initial randomisation may have been lost. In addition to the known limitations of post-hoc subgroup analyses, [21] Sun et al. [22] also suggest that the credibility of subgroup effects, even when claims are strong, is usually low. However, this post-hoc subgroup analysis was carried out at the request of the EMA to identify a narrower population of patients with ACS who may have a more favourable benefit-risk balance obtained from treatment with rivaroxaban in addition to dual antiplatelet therapy. Moreover, 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 [23]**.** In current 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. In addition, the sensitivity of biomarker assays has increased since the trial was conducted. As a result, if more sensitive assays had been available during the ATLAS-ACS 2-TIMI 51 trial, more patients might have been diagnosed with NSTEMI rather than UA and therefore included in the licensed population.

- Duration of treatment

The mean treatment duration with rivaroxaban 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. However, a more precise continuation rule was not provided by the company.

- Robustness of results

The different components for which the 2.5 mg and 5 mg dose showed statistically significant reductions has been extensively discussed in a US FDA briefing document [24] (albeit in the whole trial population of ATLAS-ACS 2-TIMI 51 rather than the licensed population). This document concluded that 'the proposition that a lower dose of an antithrombotic drug is significantly more effective than a higher dose lacks biological plausibility'. Similarly, the EMA's assessment report [25] concluded that these findings may partly have been due to chance. As a result, the ERG considered the HRs from the combined dose to be more plausible than those of the individual doses for CV death, MI and stroke.

The ERG also considered the validity of the results from the ATLAS-ACS 2-TIMI 51 trial to be questionable as a result of the high discontinuation rates and missing vital status data from the study. Despite the lack of corresponding data for the licensed population, 15.5% (2402/15,526) of the total randomised population prematurely withdrew from the study (rivaroxaban 2.5 mg twice daily, 15.0%; rivaroxaban 5 mg twice daily, 16.3%; placebo, 15.1%). It has been reported that in general the validity of a study may be compromised for losses between 5% and 20% [26]. In addition, 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) [27]; TRACER (vorapaxar), 5.9% (761/12,944) [28]; PLATO (ticagrelor), 3.0% (562/18,624) [29] and TRITON (prasugrel), 5.9% (804/13,619) [30]. At the end of the ATLAS-ACS 2-TIMI 51 trial, vital status was unknown in 495 of the 15,526 patients (3.2%). Due to the missing data on vital status, there is a potential risk that informative censoring has occurred (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), which may be compounded if the reasons for, or frequency of, dropout differs between treatment groups [31]. In this example the concern is that rivaroxaban causes more bleeding, bleeding could lead to discontinuation and that any subsequent CV events, including fatal events, that are at increased risk due to the history of bleeding as reported in the literature would not be recorded [32-34]. Whilst no detailed discussion of this issue was provided in the EMA's assessment report, the ERG considered that the efficacy analyses were at risk of bias because prognoses may differ in those patients who withdrew from the trial. The likely magnitude of any bias introduced by informative censoring in the clinical outcomes and in cost-effectiveness analyses was unknown.

- Applicability of trial results

The population (all randomised patients) in the ATLAS-ACS 2-TIMI 51 study were predominantly men (74.7%) and the mean age was 61.8 years. However, ACS patients in England are usually older, with a mean age of 65 years and 72 years for patients with STEMI and NSTEMI, respectively. [7] In addition, the EMA's assessment report [25] noted that the ACS population in the trial were considered to be at low risk. The trial participants 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.

3.2 Cost-Effectiveness Evidence

The company conducted a systematic review on the cost-effectiveness of interventions for the secondary prevention of ACS. As no relevant studies were identified, the company developed a de novo economic model (constructed in Microsoft Excel®) to estimate the cost-effectiveness of rivaroxaban plus aspirin, with or without clopidogrel, compared to aspirin, with or without clopidogrel.

The model employed a state transition cohort approach which consisted of an observation period intended to replicate the duration of the trial data, and an extrapolation period. The model had a time horizon of 40 years.

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. The extrapolation period started after 96 weeks (the beginning of the 10th cycle) and had a cycle length of 6 months. Half-cycle correction was performed. The model used a NHS and Personal Social Services perspective and discounted future costs and quality adjusted life years (QALYs) at a rate of 3.5%.

The population modelled was the subgroup of patients in the ATLAS-ACS 2-TIMI 51 trial who were biomarker positive and had not experienced a prior stroke or transient ischaemic attack (TIA). The model consisted of a number of health states corresponding to whether no further ACS events occurred, whether the patient suffered a subsequent ACS event or whether a patient died. The subsequent ACS events considered in the model were: MI, ischaemic stroke (IS), haemorrhagic stroke or intracranial haemorrhage (HS/ICH); a bleeding event 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 (MI, IS and HS/ICH); and those deemed to be transient events where the impacts were limited to one model cycle (bleeding and revascularisation). The long term ACS events had two subsequent tunnel states to allow for patients' utility to improve over time and for the cost of treatment and relative risk of suffering from a subsequent event to fall over time. Patients could experience up to three ACS events. The specific ACS events experienced were recorded when patients suffered from two or fewer events; however, when three events occurred, it was assumed that one event of each type (i.e. an MI, an IS and a HS/ICH) had occurred. A one-off cost and utility decrement was applied to patients who entered a transient event state. Transient health states were only applied in the observation period of the model. Patients could die at any time in the model from MI, IS, HS/ICH, other CV or bleeding events and non-CV causes.

Patients were only eligible to receive rivaroxaban in the observation period. The observed continuation rates from the ATLAS-ACS 2-TIMI 51 trial were adjusted downwards using expert opinion to reflect the fact that some patients may stop receiving treatment with rivaroxaban in line with the summary of product characteristics. Discontinuation rates due to subsequent ACS events were derived from the ATLAS-ACS 2-TIMI 51 trial for rivaroxaban and clopidogrel treatments. If the patients did not discontinue treatment due to an ACS event, they continued clopidogrel treatment for one year and aspirin treatment indefinitely.

Transition probabilities in the observation period were based on data from the ATLAS-ACS 2-TIMI 51 trial. For long term ACS events, Weibull curves were fitted to the trial data. This was undertaken independently for both the rivaroxaban 2.5 mg data and for the placebo data. In the observation period it was possible for patients with no prior long term ACS events to transition to the multiple long term ACS event states. For transient ACS events, the total number of events in the observation period were added together and this was then divided by the total number of patients in the trial. The transition probabilities in the extrapolation period were estimated from the trial data assuming that the underlying rates in the last model time cycle were maintained, but then subjected to changes due to patients' ageing. Further details on how changes due to ageing were applied to the transition probabilities are provided in the ERG report [2]. It was assumed that it was not possible for patients

who experienced no further ACS events in the observation period to transition to the multiple long term ACS event states in the extrapolation period.

If a patient experienced a long term ACS event, a relative risk was applied to the probability that the patient would experience another ACS event. The relative risk was calculated using data from ATLAS-ACS 2-TIMI 51 trial on the relative number of ACS events compared to the number of ACS events in the first 6 months and an estimate of a relative risk after one year based on Smolina et al [8]. The relative risk declined over time so different values were calculated for each of the model tunnel states. Full details on how the relative risks were calculated are given in the ERG report [2].

The assumed daily costs of treatments were: rivaroxaban £2.10, clopidogrel £0.06 and aspirin £0.03. The cost of treating subsequent ACS events (long term and transient) were calculated using the NHS reference costs [35] and the cost of follow up was obtained from Heeg et al [36]. The daily cost of rehabilitation from an ACS event was calculated from the NHS reference costs and the duration of rehabilitation was based on clinical opinion. If a patient experienced multiple dissimilar events, it was assumed that the cost of both events applied even though the preceding event would already have been costed if it occurred in a different model cycle. If a patient experienced multiple similar events, it was assumed that the cost of only one event applied. The costs, excluding the drug costs, used by the company in their base case are given in Table 2.

Utility values were obtained from Greenhalgh et al [37]. To calculate the improvement in utility that the patients could experience in the stroke health states over the initial year, data from Ara and Brazier on the utility of stroke patients in the UK at baseline and 12 months after the stroke occurred were used [37;38]. Based on these values it was assumed there was a 33% improvement in a stroke patient's utility over 12 months. The utility of stroke patients 6-12 months after a stroke was assumed to be the average of the value between 0-6 months and the value post 12 months. The company provided the incremental cost-effectiveness ratio (ICER) in terms of cost per QALY gained for a base case analysis and for sensitivity analyses (Table 3).

Table 2: The costs [a], excluding drug costs, and utilities used in the company's base case

ACS event	Acute care (1st 3 months)	Follow – on care (2nd 3 months)	Cost (3rd and 4th 3 months)	Cost (later 3 months)	Utility (1st cycle)	Utility (2nd cycle)	Utility (3rd cycle)
No further ACS event	£0	£0	£0	£0	0.842	N/A	N/A
MI	£3,586	£1,980	£1,440	£540	0.779	0.821	0.821
IS	£7,756	£3,060	£4,200	£1,560	0.703	0.748	0.792
HS/ICH	£12,778	£3,060	£4,200	£1,560	0.703	0.748	0.792
MI+MI	£7,171	£1,980	£1,440	£540	0.607	0.674	0.674
IS+IS	£15,512	£3,060	£4,200	£1,560	0.494	0.559	0.627
HS/ICH + HS/ICH	£25,556	£3,060	£4,200	£1,560	0.494	0.559	0.627
MI+IS	£11,342	£5,040	£5,640	£2,100	0.548	0.614	0.650
MI+HS/ICH	£16,364	£5,040	£5,640	£2,100	0.548	0.614	0.650
IS+HS/ICH	£20,534	£6,120	£8,401	£3,120	0.494	0.559	0.627
3 ACS events	£24,120	£8,101	£9,841	£3,660	0.385	0.459	0.515
PCI/PTCA	£2,082	N/A	N/A	N/A	0.792	N/A	N/A
CABG	£9,619	N/A	N/A	N/A	0.742	N/A	N/A
Major Bleed	£670	N/A	N/A	N/A	0.750	N/A	N/A
Minor Bleed	£68	N/A	N/A	N/A	0.8	N/A	N/A
Bleed requiring medical attention	£130	N/A	N/A	N/A	0.8	N/A	N/A
Fatal MI	£1,500	N/A	N/A	N/A	0	0	0
Fatal IS	£4,500	N/A	N/A	N/A	0	0	0
Fatal HS/ICH	£4,500	N/A	N/A	N/A	0	0	0
Other CV death	£3,000	N/A	N/A	N/A	0	0	0
Non CV death	£300	N/A	N/A	N/A	0	0	0

ACS, acute coronary syndrome; CV, cardiovascular; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; MI, myocardial infarction

[a] All costs are valued in 2012/13 prices

Table 3: Scenario analysis results from the economic model presented by the company

Scenario analysis	Total costs [a]		Total QALYs		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
	Rivaroxaban plus aspirin with or without clopidogrel	Aspirin with or without clopidogrel	Rivaroxaban plus aspirin with or without clopidogrel	Aspirin with or without clopidogrel			
Base case analysis	£14,768	£14,004	9.56	9.44	£764	0.12	£6,203
Probabilistic sensitivity analysis	£14,802	£14,099	9.53	9.40	£703	0.13	£6,298
Transition probabilities were calculated only from those patients who received a thienopyridine	£15,363	£14,480	9.52	9.40	£883	0.12	£7,405
Transition probabilities were non-parametrically estimated	£16,290	£15,431	9.75	9.62	£859	0.13	£6,468
No efficacy adjustments were made for patients discontinuing clopidogrel	£13,794	£13,045	10.09	9.96	£749	0.13	£5,824
Utility values collected in the ATLAS-ACS 2-TIMI 51 trial were used	£14,768	£14,004	9.83	9.71	£764	0.13	£5,935
Utility values return to the baseline utility value after 12-18 months.	£14,768	£14,004	9.61	9.49	£764	0.12	£6,195
A utility of 0.22 is applied to fatal events [37]	£14,768	£14,004	13.39	13.28	£764	0.10	£7,147
Death is assumed to cost £0	£13,522	£12,707	9.56	9.44	£815	0.12	£6,618
Patients are not at an increased risk of a subsequent ACS event following an MI, IS or HS/ICH	£15,960	£15,169	9.81	9.68	£791	0.12	£6,439
Patients do not suffer from an increased risk of death due to age	£31,094	£30,195	14.09	13.91	£899	0.18	£4,928
Patients do not have an increased risk of death due to ageing or from having a prior ACS event	£29,633	£28,705	14.34	14.16	£928	0.18	£6,745

ACS, acute coronary syndrome; HS, haemorrhagic stroke; ICER, incremental cost-effectiveness ratio (in terms of cost per QALY gained); ICH, intracranial haemorrhage; IS, ischaemic stroke; MI, myocardial infarction; QALY, quality adjusted life year

[a] All costs are valued in 2012/13 prices

3.2.1 Critique of the Cost-Effectiveness Evidence and Interpretation

The mathematical model submitted by the company had many limitations, most of which were resolved by the company during the clarification process. Post clarification, the ERG had three key remaining concerns. First, the model structure had the potential to cause inaccuracies as it could not track the time between multiple ACS events. Second, the scenarios surrounding the use of pooled efficacy data, the risk of fatal bleeding events and adjustment for informative censoring were not explored in the company's submission. Finally, the ERG had concerns with the parameterisation of uncertainty in the company's model.

The model's lack of ability to track the time between multiple ACS events caused the potential for inaccuracies in three ways. First, for those patients who transitioned into the multiple event states from the single event states, the cost and QALYs decrement associated with the first event was reapplied. Second, patients who suffer from two events in one time cycle were not distinguished from those patients who suffer multiple events in separate time cycles. Finally, for patients who suffer from multiple events in separate time cycles any improvement over time that they may have experienced was ignored. There are two solutions to this problem: a more complicated state transition cohort model could have been developed so that cost and utilities for each multiple event state can vary by the preceding health state and the time between the events or a patient level simulation approach could have been taken.

In the company's submission, no scenario was presented using the pooled data from the 2.5 mg and 5 mg rivaroxaban twice daily trial arms. This was of concern to the ERG, as the pooled data was the ERG's preferred clinical evidence for the effectiveness of rivaroxaban plus aspirin with or without clopidogrel compared to aspirin with or without clopidogrel for the secondary prevention of ACS. Additionally, the numbers of fatal bleeding events were included in the number of other CV deaths in the model. As such, only crude scenario analyses around the deaths due to bleeding could be undertaken, as the number of fatal bleeding events in each model time cycle could not be identified. The ERG viewed this information to be important to the decision problem as censored patients may have experienced a bleeding event post-censoring.

The ERG had two main concerns with how uncertainty was parameterised in the company's base case probabilistic sensitivity analysis (PSA). First, published standard errors were ignored. Second, the shape and scale parameters used in the Weibull distributions were sampled independently. Uncertainty was parametrised in the company's model using a beta distribution, which was 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. The ERG believed that this was inappropriate, as there were published uncertainty estimates available for the utilities used in the company's model and the NHS reference costs. The ERG also believed that the shape and scale parameters in the Weibull distributions should have been correlated using an appropriate variance-covariance matrix.

The ERG also had concerns about the utility values used in the model for stroke patients, the relative risks applied to patients after a subsequent ACS event, the calculation of life years gained and informative censoring. There was limited empirical evidence to support the improvement of stroke patient's utility over 12 months compared to the values presented in Greenhalgh et al [37]. Therefore, the ERG had concerns about including the improvement in stroke patient's utility values in the model. The relative risks for further ACS events used by the company after a patient experienced a subsequent ACS was higher for some ACS events in the long term tunnel state than the preceding two tunnel states. The ERG believed that this was implausible. The ERG also had concerns about whether the method used to calculate the relative risks was appropriate. In the company's model, the life years gained matrix was calculated using a cycle length of 13 weeks instead of the actual cycle length of 12 weeks. The ERG believed that scenarios to address informative censoring by increasing the number of non-fatal bleeding events should also have been conducted.

3.3 Additional Work Undertaken by the Evidence Review Group

The ERG undertook three main pieces of additional work. First, the PSA was parameterised using the published uncertainty estimates in the cost and utility data. Second, the ERG also considered a range of additional scenarios that were potentially relevant to the decision problem but were not presented by the company. Finally, the ERG conducted a crude sensitivity analysis on the expected number of fatal bleeding events.

The ERG updated the company's base case PSA so that the published uncertainty estimates in the utilities and the costs were used. All random samples were taken from normal distributions with utilities constrained to be equal to or less than one. The ERG chose to keep the assumptions and data used in the company's base case so that the ERG's PSA ICER could be compared to the company's base case deterministic ICER. All parameters were assumed to be normally distributed with the ERG calculating standard errors for each of the NHS reference costs used in the company's model. As the ERG did not have the variance covariance matrix for the shape and scale parameters for the Weibull curves, correlation could not be enforced and the variables left independent.

In addition to the scenario analyses presented by the company (1 to 4 in the following list), the ERG undertook additional analyses (points 5-10):

1. The transition probabilities could be estimated in the observation period (first 10 cycles) using data directly from the ATLAS-ACS 2-TIMI 51 trial. The ERG preferred these data to the Weibull curves, as when the Weibull curves were used the model over predicted the observed ACS events from the ATLAS-ACS 2-TIMI 51 trial.
2. The licence indication for rivaroxaban is primarily for a duration of one year, with use for another year determined on an individual patient basis. The ERG's clinical advisors' believed that given the licence most clinicians would discontinue rivaroxaban treatment after one year.
3. The baseline utility of the population in the model were age adjusted using data from Ara and Brazier [38]. The utilities presented in Table 2 were then used as multipliers to the age adjusted utilities.
4. The initial cost of only one ACS event was applied to the multiple ACS events health states.
5. Utility data published by Greenhalgh et al [37], which showed no improvement over time in stroke patients utility, were used.

6. The relative risks were the same as the company's base case unless they were less than one and half. All relative risks that were less than one and half, were set to one and half.
7. The life years gained matrix, as well as the costs, were adjusted to reflect that the model time cycle in the observation period (after the first two cycles) was 12 weeks, not 13 weeks.
8. The number of non-fatal bleeding events were multiplied by 5 in the rivaroxaban model arm.
9. All relative risks for all future ACS events, after a subsequent ACS event, was one in the extrapolation period.
10. The relative risk of all future ACS events following a subsequent ACS event was set to 5 in the extrapolation period.

As independent Weibull curves were fitted to other CV deaths (which include fatal bleeding events) in the company's model, the ERG could not easily amend the model to assess the sensitivity of the company's base case ICER to the HR for fatal bleeding which could be biased by informative censoring. Further details are provided in the ERG report [2]. The ERG considered a range of additional fatal bleeding events ranging from no additional fatal bleeding events (company's base case) to 20 additional bleeding events, which was considered to be an extreme value. For each integer in this range, ICERs were calculated.

3.3.1 Results of the additional comparisons

The results of the ERG's revised PSA are given in Table 4. As the ERG's probabilistic ICER was close in value to the company's deterministic ICER (£6203), it was assumed that subsequent analyses could be undertaken deterministically.

The first four scenarios presented by the company, the six additional scenarios conducted by the ERG and their corresponding results are presented in Table 4. It can be seen that the ERG's preferred base case ICER is lower than the company's base case ICER at £5,622 per QALY gained compared to £6,203 per QALY gained. None of the analyses conducted by the ERG increased the ICER to be greater than £10,000 per QALY gained.

The result of the ERG's crude exploratory analysis on the number of fatal bleeding events is presented in Fig 1. The results showed that even if rivaroxaban 2.5 mg twice daily 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 gained. This suggested that the impact of any informative censoring was not likely to be large.

Table 4: The results of the ERG's exploratory analyses

Code	Change from company's base case	Total costs [a]		Total QALYs		Incremental costs	Incremental QALYs	ICER (£/QALY)
		Rivaroxaban plus aspirin with or without clopidogrel	Aspirin with or without clopidogrel	Rivaroxaban plus aspirin with or without clopidogrel	Aspirin with or without clopidogrel			
The company's base case		£14,768	£14,004	9.56	9.44	£764	0.12	£6,203
The ERG's PSA	Uncertainty was characterised using published information, where available	£14,806	£14,045	9.54	9.42	£761	0.12	£6,150
1	Transition probabilities are estimated directly from trial data	£16,290	£15,431	9.75	9.62	£859	0.13	£6,468
2	Rivaroxaban is discontinued after one year	£14,629	£14,004	9.56	9.44	£625	0.12	£5,323
3	The utilities are age adjusted, using Ara and Brazier [38]	£14,768	£14,004	9.07	8.95	£764	0.12	£6,536
4	The cost of one ACS event is applied to the multiple ACS event states	£13,592	£12,818	9.56	9.44	£768	0.12	£6,240
5	No improvement over time in the utility of stroke patients	£14,768	£14,004	9.53	9.41	£764	0.12	£6,289
6	The relative risk of a subsequent ACS event is not less than 1.5	£15,007	£14,235	9.59	9.47	£773	0.12	£6,250
7	Costs and QALYs are calculated using a cycle length of 12 weeks in the observation period	£14,804	£14,026	9.49	9.37	£778	0.12	£6,357
8	There are 5 times as many non-fatal bleeding events	£14,874	£14,049	9.56	9.44	£824	0.12	£6,714
9	No increased risk of a further ACS event	£15,960	£15,169	9.80	9.68	£791	0.12	£6,439
10	The relative risk of all further ACS event is 5	£12,293	£11,606	9.04	8.92	£686	0.13	£5,412
ERG base case 1+2+3+4+5+6+7		£14,650	£13,947	9.17	9.05	£703	0.12	£5,622

ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year

[a] All costs are valued in 2012/13 prices

INSERT Fig 1: **The impact of additional fatal bleeding events on the ICER for patients receiving rivaroxaban**

3.4 Conclusions of the Evidence Review Group Report

On the basis of the evidence submitted by the company, the ERG concluded that 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. However, 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 duration of treatment, generalisability to the UK population and the possibility of bias due to informative censoring.

On the basis of the company's economic evaluation, the base case results for the addition of rivaroxaban (2.5 mg twice daily) to existing antiplatelet therapy would result in an ICER of £6,203 per QALY gained. The ERG's base case estimated the ICER to be £5,622 per QALY gained. The ERG explored the potential effects of bias due to informative censoring on the ICER and concluded that if the uncertainties in the clinical data were resolved, the ICER was unlikely to be above £10,000 per QALY gained.

4 Key Methodological Issues

Several important methodological issues were highlighted during the appraisal. First, other dual antiplatelet regimens were absent from the NICE scope and therefore the relative cost-effectiveness of rivaroxaban compared with these interventions could not be estimated. Such interventions included prasugrel and ticagrelor which are recommended in current NICE guidelines for the acute and maintenance phases of ACS [9;12]. Second, there were concerns that missing data from people who withdrew or were lost to follow up from the ATLAS-ACS 2-TIMI 51 trial may result in informative censoring (that is, the patients who drop out, and whose data are therefore censored, have different outcomes to those who remain in the trial) leading to bias. Third, the ERG could not carry out all the exploratory analyses that it deemed potentially relevant due to the model structure. These included amendment to the HRs for fatal bleeds, using pooled efficacy data rather than the 2.5 mg dose alone and adjusting for the possibility of informative censoring.

5 National Institute for Health and Care Excellence Guidance

In March 2015, on the basis of the evidence available, including verbal testimony from invited clinical experts and patient representatives, the Appraisal Committee produced the following final guidance to the NHS in England (TA335) [39]:

- Rivaroxaban is recommended as an option within its marketing authorisation, in combination with aspirin plus clopidogrel or aspirin alone, for preventing atherothrombotic events in people who have had ACS with elevated cardiac biomarkers.

- Clinicians should carefully assess the person's risk of bleeding before treatment with rivaroxaban is started. The decision to start treatment should be made after an informed discussion between the clinician and the patient about the benefits and risks of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone.
- A decision on continuation of treatment should be taken no later than 12 months after starting treatment. Clinicians should regularly reassess the relative benefits and risks of continuing treatment with rivaroxaban and discuss them with the patient.

5.1 Consideration of Clinical and Cost-Effectiveness Issues Included in the Final Appraisal Determination

The full list of the issues considered by the Appraisal Committee can be found in the FAD [39]. The key issues are described in the following sections.

5.1.1 Current Clinical Management

The Appraisal Committee considered the current clinical management of ACS in England and noted that there is some uncertainty as to when and how rivaroxaban would be best incorporated into the treatment pathway. Clinical specialists advised the Appraisal Committee that the mean time to start rivaroxaban in ATLAS-ACS 2-TIMI 51 was 4.6 days, but the majority of patients in England are discharged from hospital by then. In addition, if rivaroxaban was to be started in secondary care this could result in patients staying in hospital longer, which would not happen if it was started in primary care. The Committee heard from its GP members that, after an ACS event, patients would usually be seen by their GP within 1 week of being discharged from hospital. The Committee accepted that the discharge summary which is sent to the patient's GP at the time of discharge would give sufficient information for the GP to start treatment with rivaroxaban. However, the Committee also acknowledged that its introduction might have an effect on the existing pathway.

5.1.2 Uncertainties in the Clinical evidence

The Appraisal Committee noted that in clinical practice, people with ACS are usually older than those patients who were recruited to ATLAS-ACS 2-TIMI 51 study. In addition, the trial participants could be considered as a relatively low-risk population because they had little comorbidity, lower than usual use of PCI and included a relatively small proportion of people aged over 75 years or with impaired renal function. Clinical specialists advised the Appraisal Committee that the average age difference between the trial population and patients seen in clinical practice was not likely to be clinically significant and that patients recruited to the ATLAS-ACS 2-TIMI 51 study were similar in terms of baseline characteristics to those recruited to other trials in ACS. The Committee was persuaded that the issue of generalisability was similar across all trials in this condition, and concluded that the results of ATLAS-ACS 2-TIMI 51 trial were relevant to routine clinical practice.

The Appraisal Committee considered the results of the ATLAS-ACS 2-TIMI 51 trial and noted that the company had presented clinical-effectiveness results for the overall trial population and also for a post-hoc subgroup analysis of patients with elevated cardiac biomarkers (STEMI and NSTEMI) and no history of a stroke or TIA (80% of the total trial population). The Appraisal Committee was aware that this post-hoc subgroup analysis was carried out at the request of the EMA and provided efficacy results that tended to be

more favourable to rivaroxaban than the results from the overall trial population. However, the Appraisal Committee acknowledged that these differences were unlikely to be sufficiently large as to have an impact on the overall decision as to whether rivaroxaban was clinically and cost effective in its licensed indication.

The Appraisal Committee discussed the missing data from people who withdrew or were lost from the ATLAS-ACS 2-TIMI 51 trial and noted the ERG's concerns that missing data may result in informative censoring leading to bias. Whilst extensive efforts had been made by the company to trace trial participants to clarify reasons for withdrawal and to find out if they had died, the Appraisal Committee concluded that the missing data from those who withdrew or were lost from the trial remained of concern, but the magnitude of any bias introduced by informative censoring was unknown.

The Appraisal Committee discussed the concerns about safety and adverse effects associated with rivaroxaban and noted that in the ATLAS-ACS 2-TIMI 51 trial, treatment with rivaroxaban (2.5 mg twice daily) in combination with aspirin plus clopidogrel or aspirin resulted in more non-CABG-related major bleeding than aspirin plus clopidogrel or aspirin alone but also recognised the benefits of rivaroxaban in reducing the risk of MI and CV deaths. The Appraisal Committee concluded that clinicians should carefully assess a person's risk of bleeding before commencing treatment with rivaroxaban and that careful consideration should be given to whether treatment is continued beyond 12 months because experience of treatment with rivaroxaban up to 24 months is limited.

5.1.3 Uncertainties in the Economic Modelling

The Appraisal Committee noted that there were uncertainties surrounding the ICERs due to the risk of bias in the clinical data resulting from missing data and informative censoring. The Appraisal Committee considered that the ICERs presented were within the range that could be considered cost-effective and that the ERG's exploratory analyses suggested that the ICER was unlikely to increase to the extent that it would be considered unacceptable. The Appraisal Committee concluded that rivaroxaban could be considered a cost-effective use of NHS resources.

6 Conclusion

The evidence suggests that in people who have had an ACS with elevated cardiac biomarkers, rivaroxaban in combination with aspirin plus clopidogrel or aspirin alone is a clinically and cost effective option for reducing atherothrombotic events compared with aspirin plus clopidogrel or aspirin alone. However, an important point highlighted by this STA was that the final scope issued by NICE did not include either prasugrel or ticagrelor as comparators. As such, no comparison on the cost-effectiveness of rivaroxaban compared with these interventions could be made.

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Conflicts of Interest

Abdullah Pandor, Daniel Pollard, Tim Chico, Robert Henderson and Matt Stevenson have no potential conflicts of interest that are directly relevant to the content of this article.

Contributions made by each author

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. 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. Abdullah Pandor acts as the guarantor of the manuscript.

References

1. National Institute for Health and Care Excellence (NICE). Guide to the processes of Technology Appraisals. London: NICE, 2014.

2. Pandor A, Pollard D, Stevenson M, Cantrell A, Chico T, Henderson R. Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome: A Single Technology Appraisal. School of Health and Related Research. (ScHARR) 2014.

3. National Institute for Health and Care Excellence (NICE). Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. London : NICE, 2015. https://www nice org uk/guidance/ta335/documents (accessed 10 September 2015)

4. National Institute for Health and Care Excellence (NICE). Unstable angina and NSTEMI: the early management of unstable angina and non-ST segment elevation myocardial infarction (Clinical Guideline No. 94). London: NICE, 2010.

5. Health & Social Care Information Centre. Hospital Episode Statistics, Admitted Patient Care, England 2012-13. Leeds: Health & Social Care Information Centre, 2013.

6. NHS Wales Informatics Service. Patient Episode Database for Wales Statistics. Cardiff: NHS Wales Informatics Service, 2013.

7. Gavalova L, Weston C. Myocardial Ischaemia National Audit Project. How the NHS cares for patients with heart attack. Annual Public Report April 2012 - March 2013. London: University College London, 2013.

8. Smolina K, Wright F, Rayner M, Goldacre M. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circ Cardiovasc Qual Outcomes 2012; 5(4):532-540.

9. National Institute for Health and Care Excellence (NICE). Ticagrelor for the treatment of acute coronary syndromes (Technology Appraisal No. 236). London: NICE, 2011

10. National Institute for Health and Care Excellence (NICE). Secondary prevention in primary and secondary care for patients following a myocardial infarction (Clinical Guideline No. 172). London: NICE, 2013.

11. National Institute for Health and Care Excellence (NICE). Myocardial infarction with STEMI: the acute management of myocardial infarction with STEMI (Clinical Guideline No. 167). London: NICE, 2013.

12. National Institute for Health and Care Excellence (NICE). Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of technology appraisal guidance 182). (Technology Appraisal No. 317). London: NICE, 2014.

13. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006; 333(7578):1091-1094.

14. Norgard N, Dinicolantonio J. Clopidogrel, prasugrel, or ticagrelor? A practical guide to use of antiplatelet agents in patients with acute coronary syndromes. Postgrad Med 2013; 125(4):91-102.

15. Hamm C, Bassand J, Agewall S, Bax J, Boersma E, Bueno H et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011; 32(23):2999-3054.

16. Steg P, James S, Atar D, Badano L, Blomstrom-Lundqvist C, Borger M et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Task

Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J 2012; 33(20):2569-2619.

17. Bayer Pharma AG. Rivaroxaban (Xarelto) - summary of product characteristics. Berlin: Bayer Pharma AG, 2013.

18. Joint Formulary Committee. British National Formulary. London: BMJ Group and Pharmaceutical Press, 2014.

19. Gibson CM, Mega JL, Burton P, Goto S, Verheugt F, Bode C et al. Rationale and design of the Anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome-thrombolysis in myocardial infarction 51 (ATLAS-ACS 2 TIMI 51) trial: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome. American Heart Journal 2011; 161(5):815-821.

20. Mega JL, Braunwald E, Wiviott SD, Bassand J-P, Bhatt DL, Bode C et al. Rivaroxaban in patients with a recent acute coronary syndrome. New England Journal of Medicine 2012; 366(1):9-19.

21. Brookes S, Whitley E, Peters T, Mulheran P, Egger M, Davey Smith G. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. Health Technol Assess 2001; 5(33):1-56.

22. Sun X, Briel M, Busse J, You J, Aki E, Mejza F et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. BMJ 2012; 344:e1553.

23. Thygesen K, Alpert J, Jaffe A, Simoons M, Chaitman B, White H. Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction Third universal definition of myocardial infarction. J Am Coll Cardiol 2012; 60(16):1581-1598.

24. Food and Drug Administration (FDA). FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee Meeting January 16, 2014. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm378911.htm Accessed 3 October 2015.

25. European Medicines Agency (EMA). Assessment Report for Xarelto. Procedure Number: EMEA/H/C/000944/X/00017. London: EMA, 2014.

26. Dumville J, Torgerson D, Hewitt E. Reporting attrition in randomised controlled trials. BMJ 2006; 332:969-971.

27. Alexander JH, Lopes RD, James S, Kilaru R, He YH, Mohan P et al. Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome. New England Journal of Medicine 2011; 365(8):699-708.

28. Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F et al. Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes. New England Journal of Medicine 2012; 366(1):20-33.

29. U.S.Food and Drug Administration. Ticagrelor NDA 22–433 Briefing Document for Cardiovascular and Renal Drugs Advisory Committee Meeting. Available at: http://www.fda.gov/downloads/AdvisoryCommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220197.pdf. Accessed 5 October 2015.

30. U.S.Food and Drug Administration. February 3, 2009, Meeting of the Cardiovascular and Renal Drugs. Briefing Information for the February 3, 2009 Meeting of the Cardiovascular and Renal Drugs Advisory Committee. FDA briefing material. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM181185.pdf. Accessed 5 October 2015.

31. Krantz MJ, Kaul S. The ATLAS ACS 2-TIMI 51 Trial and the Burden of Missing Data (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary

Syndrome ACS 2-Thrombolysis In Myocardial Infarction 51). Journal of the American College of Cardiology 2013; 62(9):777-781.

32. Eikelboom JW, Mehta SR, Anand SS, Xie CC, Fox KAA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006; 114(8):774-782.

33. Ndrepepa G, Schuster T, Hadamitzky M, Byrne RA, Mehilli J, Neumann FJ et al. Validation of the Bleeding Academic Research Consortium Definition of Bleeding in Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention. Circulation 2012; 125(11):1424-1431.

34. Spencer FA, Moscucci M, Granger CB, Gore JM, Goldberg RJ, Steg PG et al. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? Circulation 2007; 116(24):2793-2801.

35. Department of Health (DoH). NHS reference costs 2012-13. London: DoH, 2013. Availiable at: https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013

36. Heeg B, Damen J, Van Hout B. Oral antiplatelet therapy in secondary prevention of cardiovascular events - An assessment from the payer's perspective. Pharmacoeconomics 2007; 25(12):1063-1082.

37. Greenhalgh J, Bagust A, Boland A, Blundell M, Lai M, Dundar Y et al. Ticagrelor for the treatment of acute coronary syndromes: A Single Technology Appraisal. LRiG: University of Liverpool, 2011.

38. Ara R, Brazier JE. Populating an Economic Model with Health State Utility Values: Moving toward Better Practice. Value in Health 2010; 13(5):509-518.

39. National Institute for Health and Care Excellence (NICE). Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. NICE technology appraisal guidance 335. Available at: https://www nice org uk/guidance/ta335/resources/guidance-rivaroxaban-for-preventing-adverse-outcomes-after-acute-management-of-acute-coronary-syndrome-pdf. Accessed 5 October 2015.

Fig 1: **The impact of additional fatal bleeding events on the ICER for patients receiving rivaroxaban**