NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome

This guidance was produced using the single technology appraisal (STA) process.

1 Guidance

1.1 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 an acute coronary syndrome with elevated cardiac biomarkers.

1.2 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

1.3 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.

2 The technology

2.1 Rivaroxaban (Xarelto, Bayer), co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers. The licenced dose is 2.5 mg twice daily. Patients should also take a daily dose of 75–100 mg aspirin or a daily dose of 75– 100 mg aspirin in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. Ticlopidine is not listed in the British National Formulary (BNF).

2.2 Treatment with rivaroxaban should be evaluated regularly in the individual patient, weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis because experience up to 24 months is limited. Treatment with rivaroxaban should be started as soon as possible after stabilisation of the acute coronary syndrome event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

2.3 The summary of product characteristics includes the following adverse reactions for rivaroxaban: anaemia, dizziness, headache, fainting, bleeding events, tachycardia (rapid heartbeat), low blood pressure, haematoma, stomach pain, dyspepsia (heartburn), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, bruising, pain in the extremities, fever, and swelling, especially of the ankles and feet. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The list price of rivaroxaban is £58.88 per 2.5 mg, 56 capsule pack (excluding VAT, company submission) The recommended dose is 2.5 mg twice daily which equates to a price of £2.10 per day. Total acquisition costs depend on the duration of therapy. Assuming a treatment duration of 12 months, total acquisition costs are £766.50. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by the company that manufactures rivaroxaban and a review of this submission by the Evidence Review Group (ERG; section 9).

3.1 The main evidence in the company's submission came from ATLAS-ACS 2-TIMI 51. This was an international, multicentre (766 sites in 44 countries including the UK), randomised controlled trial (RCT) designed to evaluate whether rivaroxaban in addition to standard-care antiplatelet therapy reduced the risk of cardiovascular death, myocardial infarction or stroke in patients with recent acute coronary syndrome (unstable angina, non-ST segment elevation myocardial infarction [NSTEMI] or ST segment elevation myocardial infarction [STEMI]). The company also provided supportive evidence from the ATLAS-ACS TIMI 46 trial, which compared rivaroxaban once-daily dosing with twice-daily dosing within the same total daily dose range (5–20 mg). This study was a safety and efficacy study to determine the most favourable dose and dosing regimen of rivaroxaban for ATLAS-ACS 2-TIMI 51.

3.2 The ATLAS-ACS 2-TIMI 51 trial had 3 phases: a 6-day screening phase; a double-blind treatment phase; and a follow-up phase. Patients were enrolled into the trial within 7 days of being admitted to hospital for acute coronary syndrome. After stabilisation of the acute coronary syndrome (and after completion of any initial management strategies such as revascularisation), patients were stratified on the basis of whether they were 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]). Patients were then randomised to 1 of 3 treatment groups; rivaroxaban 2.5 mg, rivaroxaban 5 mg or placebo (all taken twice daily). The dosage of clopidogrel or ticlopidine followed national or local prescribing information. Enrolment was neither capped nor fixed and depended on regional medical practice. The daily maintenance dose was not to exceed 75 mg a day for clopidogrel or 250 mg twice daily for ticlopidine. Approximately 99% of the patients in stratum 2 had clopidogrel. The duration of treatment was not fixed because the trial was event-driven (that is, the time needed to obtain at least 983 primary efficacy end-point events across both strata and at least 728 primary efficacy events in stratum 2). The mean duration of treatment was 13.1 months.

3.3 The company considered the baseline patient characteristics of those enrolled into ATLAS-ACS 2-TIMI 51 to be generally similar between the treatment groups. The mean age of the trial population was 61.8 years; 9.0% were aged over 75 years, and 74.7% were men. In the trial population, the index acute coronary syndrome event was 50.9% STEMI, 25.6% NSTEMI and 23.6% unstable angina. The company stated that baseline patient characteristics were representative of a moderate to high-risk population of patients with acute coronary syndrome, with the majority of all

patients randomised having cardiovascular risk factors such as hypertension (67.4%), diabetes (32.0%), a history of myocardial infarction (26.9%) or hypercholesterolaemia (48.6%). Of the 60.5% of patients who had a revascularisation procedure for the index event; the vast majority of these were percutaneous coronary intervention. In the trial population 7.1% of patients had impaired renal function with creatinine clearance less than 50 ml/min.

3.4 The efficacy analysis was based on the modified intention-to-treat (mITT) analysis set, which included all randomised patients (except those from 3 excluded sites where trial misconduct was identified) and the end point 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 the study drug prematurely), or 30 days after randomisation (for patients who were randomised but never treated). The exclusion of the data from the 3 sites was considered to be acceptable by the European Medicines Agency (EMA). The company presented the efficacy results for the 2.5 mg rivaroxaban twice-daily and 5 mg twice-daily doses separately and combined by strata (stratum 1, stratum 2 and combined [ALL strata]).

3.5 The primary efficacy end point in ATLAS-ACS 2-TIMI 51 was the composite of death from cardiovascular causes (cardiovascular [CV] death), myocardial infarction (MI) or stroke (ischaemic, haemorrhagic or stroke of uncertain cause). A range of secondary composite end points were also included. These were:

- composite of death from any cause, MI or stroke
- net clinical outcome (composite of CV death, MI, ischaemic stroke and non-CABG TIMI major bleeding [major bleeding

assessed using 'Thrombolysis in Myocardial Infarction' criteria not related to coronary-artery bypass grafting])

- composite of CV death, MI, stroke or severe recurrent ischaemia needing revascularisation
- composite of CV death, MI, stroke or severe recurrent ischaemia leading to hospitalisation.

3.6 The results for the primary efficacy end point for the total trial population in ATLAS-ACS 2-TIMI 51 are provided in table 1.

Table 1 Effect of rivaroxaban compared with placebo on the primary efficacy end point (total population, mITT analysis [excluding 3 sites])

Stratum	2.5 mg rivaroxaban bd vs placebo		5 mg rivaroxaban bd vs placebo		Combined rivaroxaban dose vs placebo	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
ALL strata (n=15,342)	0.84 (0.72–0.97)	0.02	0.85 (0.73–0.98)	0.028	0.84 (0.74–0.96)	0.008
Stratum 1* (n=1050)	0.74 (0.45–1.22)	0.234	0.64 (0.38–1.07)	0.089	0.69 (0.45–1.05)	0.084
Stratum 2** (n=14,292)	0.85 (0.72–0.99)	0.039	0.87 (0.74–1.01)	0.075	0.86 (0.75–0.98)	0.024
bd, twice daily; CI: confidence interval; HR: hazard ratio, mITT, modified intention to treat * stratum 1: aspirin alone ** stratum 2: aspirin plus clopidogrel or ticlopidine						

3.7 In its submission, the company provided results on the primary efficacy end point across a number of subgroups for the whole trial population only (combined 2.5 mg twice daily and 5 mg twice daily doses of rivaroxaban). These included age, sex, creatinine clearance, previous MI, stroke or transient ischaemic attack (TIA) and index event (STEMI, NSTEMI or unstable angina). The company stated that in general, rivaroxaban treatment was consistently associated with improved outcomes across all major subgroups (with the exception of the subgroup analysis of prior

history of stroke or TIA [eligible to be enrolled in stratum 1 only]). The company stated that during the marketing authorisation process, the EMA requested that a narrower population of patients with acute coronary syndrome be identified with a more favourable benefit–risk balance obtained from treatment with rivaroxaban in addition to dual antiplatelet therapy. The population identified by the company, and accepted by the EMA, was patients who had acute coronary syndrome with elevated cardiac biomarkers (that is patients with STEMI and NSTEMI), excluding patients with a history of stroke or TIA.

3.8 The company presented a post hoc subgroup analysis of patients in ATLAS-ACS 2-TIMI 51 who had acute coronary syndrome with elevated cardiac biomarkers, excluding those with a history of stroke and TIA. The company referred to this subgroup as the licensed population because it is the population of patients for whom the drug is indicated in the marketing authorisation. It consisted of 12,353 patients in ATLAS-ACS 2-TIMI 51 (ALL strata, 80% of the total trial population). Results for the primary efficacy end point and components for the licensed population in ATLAS-ACS 2-TIMI 51 are provided in table 2. Table 2 presents only the results for ALL strata because the results for strata 1 (aspirin alone) and strata 2 (aspirin plus clopidogrel or ticlopidine) are considered to be confidential by the company and so cannot be reported. The company explained that its submission focused on the results for the 2.5 mg twice-daily dose because this is the licensed dose.

Table 2 Effect of rivaroxaban compared with placebo on the primary efficacy end point and components (licensed population, mITT analysis [excluding 3 sites])

	2.5 mg Rivaroxaban bd vs placebo		5 mg Rivaroxaban bd vs placebo		Combined rivaroxaban dose vs placebo	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
ALL strata n=12,353						
Primary end point	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	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	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	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, twice daily; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; mITT, modified intention to treat						

3.9 The company did not report any results in relation to treatment compliance or premature discontinuation of study treatments for the licensed population because data were not available at the time of submission. For the total trial population, among patients who had at least 1 dose of a study drug, premature discontinuation of treatment occurred in 26.9% (1376/5115) of patients having the 2.5 mg twice-daily dose of rivaroxaban, 29.4% (1504/5110) of patients having the 5 mg twice-daily dose of rivaroxaban and 26.4% (1351/5125) of patients having placebo. 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 mg twice daily 10.9%; placebo 7.3%), consent withdrawal (rivaroxaban 2.5 mg twice daily 4.7%; rivaroxaban 5 mg twice daily 4.3%; placebo 4.3%) and 'other' (rivaroxaban 2.5 mg twice daily 11.5%; rivaroxaban 5 mg twice daily 11.3%; placebo 11.8%).

3.10 Of the 15,526 patients randomised to ATLAS-ACS 2-TIMI 51, 13,124 (84.5%) patients were alive at the end of the trial follow-up period and 537 patients (3.5%) had died. The remaining 1865 (12.0%) of patients were categorised as having 'incomplete follow-up'. 11,026 (71.0%) of randomised patients completed both the double-blind treatment period and the follow-up period. At the end of the trial, of the 1294 patients who withdrew consent, vital status was unknown for 1117 (86.3%) patients. During discussions with the US Food and Drug Administration (FDA), concerns were raised about the level of missing data as a result of the incomplete follow up of patients who withdrew from the trial. The company therefore made extensive efforts to obtain vital status information on patients who withdrew consent. This reduced the proportion of patients with unknown vital status to 3.2% (495 patients) in the intention to treat (ITT) analysis set and 1.8% (278 patients) in the mITT analysis set.

3.11 Health-related quality of life was assessed in ATLAS-ACS 2-TIMI 51 using the EuroQoL (EQ-5D) utility index. EQ-5D data were collected from sites in 8 countries including the UK at baseline, 4 weeks, 24 weeks, 48 weeks, 72 weeks and 96 weeks. Health-related quality of life data were collected for all of the participants in the trial. The company stated that the utility values obtained from the trial were not used in the economic model.

3.12 The primary safety analysis set was the treatment-emergent safety analysis set, which included all patients who were randomised and who had at least 1 dose of the study drug. For each patient, all events were included from the first dose of the study drug up to the date of the last dose of study drug plus 2 days. This analysis set was used for the primary safety end point of non-CABG TIMI major

bleeding events, key adverse event summaries and for the benefit–risk analysis.

3.13 The company presented results on the primary safety end point and other bleeding-related end points based on the whole trial population and for the licensed population (that is, adult patients after an acute coronary syndrome with elevated cardiac biomarkers without a history of stroke or TIA). The total number of patients included in the safety analysis from ATLAS-ACS 2-TIMI 51 in the licensed population was 12,325 (ALL strata n=4096; rivaroxaban 2.5 mg twice daily n=4072; rivaroxaban 5 mg twice daily n=4157; placebo). The results for the licensed population showed a dose-dependent increase in the rate of non-CABG TIMI major bleeding events for rivaroxaban added to antiplatelet therapy compared with antiplatelet therapy alone. In 'ALL strata' in the treatment-emergent safety analysis set, the primary safety end point occurred in 1.3% of patients in the rivaroxaban 2.5 mg twice-daily group, 1.6% of patients in the rivaroxaban 5 mg twice-daily group and 0.4% of patients in the placebo group. The hazard ratio (HR) for the primary safety end point was 3.44 (95% confidence interval [CI]: 1.97, 6.01) for the 2.5 mg rivaroxaban twice-daily group, 4.4 (95% CI 2.55 to 7.60) for the rivaroxaban 5 mg twice-daily group and 3.91 (95% CI 2.32 to 6.59) for the rivaroxaban combined-dose group.

Cost effectiveness

3.14 The company submitted a de novo Markov cohort model comparing rivaroxaban 2.5 mg twice daily with standard care (clopidogrel plus aspirin or aspirin alone) in adults who had a recent acute coronary syndrome with elevated cardiac biomarkers and who had not had a previous stroke or TIA. The model used a time horizon of 40 years that was divided into 2 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 2 cycles had a cycle length of 4 weeks and 8 weeks respectively and the remaining cycles used a cycle length of 12 weeks. The company based the analysis from an NHS and personal social services perspective, and costs and benefits were discounted at an annual rate of 3.5%. Half-cycle correction was performed on the Markov trace.

3.15 The company's model consisted of a number of health states corresponding to whether or not the hypothetical patient had another acute coronary syndrome event. The acute coronary syndrome events considered in the model were: MI, ischaemic stroke, haemorrhagic stroke or intracranial haemorrhage (HS/ICH); a bleeding event measured on the TIMI scale; and revascularisation. These acute coronary syndrome events fell into 2 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 1 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, ischaemic stroke or HS/ICH or other CV death, which included deaths related to bleeding. Patients could also die from non-CV causes at any time point in the model.

3.16 The long-term acute coronary syndrome events included the MI, ischaemic stroke and HS/ICH conditions. The long-term events had 2 subsequent tunnel states to allow for the patient's health-related quality of life to improve over time, and for the cost of treatment and the relative risk of having a subsequent event to fall over time.

Patients could have up to 3 acute coronary syndrome events; the specific types of event were recorded when patients had 2 or fewer events. When 3 events happened, it was assumed that there was 1 event of each type (that is an MI, an ischaemic stroke and a HS/ICH).

3.17 The health states corresponding to bleeding and revascularisations were assumed to be transient health states and when a patient entered 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 2 interventions were comparable after rivaroxaban treatment was discontinued for all patients at the end of the second year.

3.18 The population modelled was the subgroup of patients who had acute coronary syndrome with elevated cardiac biomarkers and had not experienced a prior stroke or TIA in the ATLAS-ACS 2-TIMI 51 trial. The data were not pooled from both rivaroxaban trial arms; the model was based on the subgroup data from patients who had 2.5 mg rivaroxaban twice daily only. Data from both trial strata were used to inform the model. In accordance with ATLAS-ACS 2-TIMI 51, it was assumed that in the base case 93% of patients had clopidogrel plus aspirin and 7% of patients had aspirin alone. A scenario analysis was presented considering only those patients who had clopidogrel and aspirin.

3.19 In the base case the transition probabilities for future acute coronary syndrome-related events in the observation period (2 years) were determined by fitting a Weibull distribution to the trial data. This was undertaken for both the rivaroxaban 2.5 mg twice-daily arm and for the placebo arm. The company stated that

because patient numbers diminished over time, particularly visible towards the end of ATLAS-ACS 2-TIMI 51, it was difficult to estimate transition probabilities directly from the data for the later cycles within the observation period. The company commented that by fitting a Weibull distribution to the ATLAS-ACS 2-TIMI 51 trial data, it was able to remove the data fluctuations caused by a decline in the numbers of observations over the trial.

3.20 The company's model assumed that patients could discontinue treatment in the observation period after they had an acute coronary syndrome event. The probability of discontinuation following an event was obtained from ATLAS-ACS 2-TIMI 51. This was calculated by using the total trial population, not the licensed population.

3.21 The UK marking 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'. To reflect this, the company adjusted the proportion of patients who continued on rivaroxaban treatment in the second year (that is from 48-60 weeks on wards). The proportion of patients selected was to allow an overall continuation rate of 19% after 12 months and that this would decline to 0% at the end of the second year. No treatment effect or cost was applied to those patients who discontinued rivaroxaban treatment.

3.22 In the model patients had clopidogrel 75 mg once a day, aspirin 75 mg once a day and rivaroxaban 2.5 mg twice daily as appropriate. Because rivaroxaban entered the treatment pathway after stabilisation of an acute coronary syndrome event, any further differences in costs between the intervention and the comparator

were a result of acute coronary syndrome events and discontinuations related to an acute coronary syndrome event.

3.23 Costs of acute coronary syndrome events were determined by the NHS reference costs (2012–13) of treating the event and the cost of follow up for the patient. An assumption was made that if a patient had multiple acute events in the long term, then the cost of hospitalisation and the follow up of two events were applied. This was the case irrespective of the time between the events. It was assumed that, on average, patients experienced 5, 14 and 28 days rehabilitation after MI, ischaemic stroke and HS/ICH respectively. These rehabilitation costs occurred in the first 3 months after the event. Transient event costs were also included in the model.

3.24 The utility values associated with long-term health states were obtained from the literature, primarily from NICE's technology appraisal guidance on ticagrelor for the treatment of acute coronary syndromes. A study by Ara and Brazier was used to calculate the improvement in health-related quality of life that patients would experience in the stroke health states. The study was used to obtain the utility values of patients with stroke in the UK at baseline and at 12 months after the stroke occurred. Based on the utility values from these 2 time points, a 33% improvement in health-related quality of life over 12 months was calculated for patients who had strokes. To calculate the utility values for patients who had a stroke 6 months after a previous stroke, the average of the stroke first 6 months and the stroke (post 12 months) health states was taken. Utility values were assumed to be the same for both rivaroxaban and standard care following any event. For multiple event states, the utility values of two events that had occurred were multiplied together. The company stated that this allowed for

worsening health-related quality of life following multiple events to be taken into account. The utility value for the event-free health state was assumed to remain constant over time. The resulting utility estimates were 0.842 for no event, 0.779 for non-fatal MI, 0.821 for after MI, 0.703 for non-fatal stroke, and 0.703 for after stroke.

3.25 For the licensed population, the company reported a deterministic incremental cost-effectiveness ratio (ICER) of £6203 per quality-adjusted life year (QALY) gained (incremental costs £764, incremental QALYs 0.12) for a life time horizon of 40 years for rivaroxaban compared with clopidogrel plus aspirin or aspirin alone.

3.26 The company conducted a series of 1-way deterministic sensitivity analyses. Changes to the cost parameters, discount rates, utility values and risk estimates for MI impacted on the base case ICER, but no factor increased the ICER to over £10,000 per QALY gained. The company's probabilistic analysis showed that rivaroxaban had a 99.9% probability of being cost effective compared with clopidogrel plus aspirin or with aspirin alone if the maximum acceptable amount for an additional QALY was £20,000.

Evidence Review Group comments

3.27 The ERG stated that the company undertook a comprehensive systematic review of rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome. The ERG considered ATLAS-ACS 2 TIMI 51 to be a well-designed, multicentre RCT of reasonable quality.

3.28 The ERG questioned the generalisability of the population enrolled in ATLAS-ACS 2-TIMI 51 to the population seen in clinical practice in England. The ERG noted that of all patients randomised in

ATLAS-ACS 2-TIMI 51, 74% were men and the mean age was 61.8 years. The ERG commented that patients with acute coronary syndrome in England are usually older, with a mean age of 65 years and 72 years for patients with STEMI and NSTEMI respectively. It highlighted that the EMA's assessment report noted that patients in the trial were considered to be at low risk. Patients in the trial had little comorbidity, lower than usual use of percutaneous coronary intervention and included a relatively small proportion of people aged over 75 years or who had impaired renal impairment with creatinine clearance less than 50 ml/min. As a result, the findings from ATLAS-ACS 2-TIMI 51 may not be applicable to an older population or to those with a greater incidence of renal impairment and a higher baseline bleeding risk.

3.29 The ERG commented that mean treatment duration with rivaroxaban in ATLAS-ACS 2-TIMI 51 was 13.1 months. As a result, the evidence on efficacy and safety of rivaroxaban 2.5 mg twice daily beyond this time is limited. The ERG noted that this is reflected in the summary of product characteristics, 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.

3.30 The ERG stated that the test 'elevated cardiac biomarker' is less sensitive than if a patient exhibits a rise or fall in their cardiac biomarkers (preferably troponins), because many patients have persistently elevated biomarkers outside the context of acute coronary syndrome. In current practice, the diagnosis of NSTEMI requires evidence of myocardial ischaemia with a rise or fall in the blood level of a cardiac biomarker (troponin). In addition, the sensitivity of biomarker assays has increased since the trial was

conducted. If more sensitive assays had been available during ATLAS-ACS 2-TIMI 51, more patients might have been diagnosed with NSTEMI rather than unstable angina and therefore included in the licensed population.

3.31 The ERG noted that there were numerical inconsistencies between the 2 dose groups (2.5 mg twice daily and 5 mg twice daily) for the components of the composite efficacy end points in the licensed population (see table 2). When the components of the primary efficacy end points were analysed individually, 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 or stroke. In contrast, rivaroxaban 5 mg twice daily significantly reduced the risk of MI, but did not reduce the risk of CV death or stroke. The ERG noted that the numerical inconsistencies between the 2 dose groups had been extensively discussed in a US FDA briefing document (albeit in the whole trial population of ATLAS-ACS 2-TIMI 51, rather than the licensed population). This briefing document states that 'the proposition that a lower dose of an antithrombotic drug is significantly more effective than a higher dose lacks biological plausibility'. The ERG also noted that the EMA's assessment report concluded that these findings may partly have been due to chance. The ERG therefore considered the hazard ratios from the combined dose to be more plausible than those of the individual doses.

3.32 The ERG considered the validity of the results from the ATLAS-ACS 2-TIMI 51 study to be questionable as a result of the high discontinuation rates from the trial. The ERG noted that 15.5% of the total randomised population (n=15,526) withdrew from the trial (2.5 mg rivaroxaban twice daily 15%; 5 mg rivaroxaban twice

daily 16.3%; placebo 15.1%). The ERG highlighted that the rates of premature withdrawal in the ATLAS-ACS 2-TIMI 51 trial were higher than other similar randomised trials in patients with acute coronary syndrome: APPRAISE-2 (apixaban, 1.8% [131/7392]); TRACER (vorapaxar, 5.9% [761/12,944]); PLATO (ticagrelor, 3.0% [562/18,624]) and TRITON (prasugrel, 5.9% [804/13,619]).

3.33 The ERG commented that because data were missing for people who withdrew from the trial (proportion of patients with unknown vital statistics 3.2% [ITT analysis, 495/15,526]) there was a potential risk that this may have led to informative censoring. That is, patients who drop out (and therefore are censored) are more or less likely to experience the primary outcome of interest compared with those remaining in the study, and this happens in a non-random manner. This may be compounded if the reason for, or frequency of, discontinuation differs between treatment groups. The ERG highlighted that no detailed discussion was provided in the EMA's assessment report regarding this issue. 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 ERG highlighted that the likely bias introduced by informative censoring in the clinical outcomes and cost-effectiveness analyses was unknown.

3.34 The ERG stated that the structure of the company's model led to the potential for systematic errors to occur, because the time between multiple events is not tracked. This causes the potential for systematic errors in 3 ways. First, patients who had 2 events in 1 time cycle were not distinguished from those patients who had multiple events in separate time cycles. Second, for patients who had multiple events in separate time cycles any improvement over

time that they may have experienced was ignored. Finally, for those patients who transition into the multiple event states from the single event states, the first event was not tracked. The ERG commented that there were 2 solutions to this problem. First, a more complicated state transition cohort model could be developed so that cost and utilities for each multiple event state can be varied by the preceding health state and by the time between the events. Second, a patient-level simulation approach could be taken.

3.35 The ERG stated that the population modelled by the company was the patient subgroup who had elevated cardiac biomarkers and had not experienced a prior stroke or TIA. Therefore, all issues with the generalisability of the results of ATLAS-ACS 2-TIMI 51 (see sections 3.3 and 3.28) and informative censoring (see sections 3.10 and 3.33) also apply to the economic model results.

3.36 The ERG stated that the approach used by the company to calculate the transition probabilities for the transient health states was inappropriate because the cost and QALYs of the events that occurred in the second year were not appropriately discounted. Also, there was no clear adjustment for the number of additional patients who were assumed to discontinue rivaroxaban in year 2 or for those patients who were assumed to discontinue clopidogrel or rivaroxaban treatment after an acute coronary syndrome event.

3.37 The ERG commented that it was not clear in the submission how the patients who continued rivaroxaban treatment after 1 year were selected from the rest of the patient population. The ERG stated that it was unknown whether the base-case parameters for the change in efficacy and costs represent patient discontinuation in the second year of treatment.

3.38 The ERG had concerns with the methodology used by the company to calculate the utility values for patients who had a stroke. The ERG stated that it was unclear why the values from Ara and Brazier were appropriate to calculate the improvement in health-related quality of life of patients who experienced a stroke, but not considered appropriate to be used as the utility values in the economic model.

3.39 The ERG had concerns about how the improvement in utility values over time was modelled in the multiple event states. If a hypothetical patient transitioned into the multiple event states from a single event state, their utility in the multiple event state could be understated, because improvement in utility after the first event had been ignored. The ERG stated that that this problem was again related to the inability of the model to distinguish when events had occurred. The ERG noted that this was not the only assumption that the company could have made to calculate the utility value in the multiple event states. It could have assumed that the lowest utility value of the 2 events applied to the patients or, if the model could track the chronicity of events, it could have assumed that the utility of the most recent event applied.

3.40 The ERG expressed concerns about the appropriateness of the methods used to model the costs of rivaroxaban, clopidogrel and aspirin and the efficacy data (shape and scale parameters of the Weibull curve) in the probabilistic sensitivity analysis. The ERG recalculated the probabilistic sensitivity analysis and found that the results were generally more favourable to rivaroxaban, producing more incremental QALYs at a lower incremental cost.

3.41 The ERG commented that there were a number of key parameters that could not be adjusted within the model, which may have

changed the ICER to a greater extent. These included: amendments to the hazard ratio for fatal bleeds; using pooled efficacy data rather than the 2.5 mg rivaroxaban twice-daily dose alone; and adjusting for the possibility of informative bias.

3.42 The ERG conducted an exploratory probabilistic sensitivity analysis in which published levels of uncertainty around the utility value estimates and the reference costs, rather than an arbitrary range, were taken into account. The resulting probabilistic ICER was £6150 per QALY gained for rivaroxaban plus clopidogrel plus aspirin or rivaroxaban plus aspirin, compared with clopidogrel plus aspirin or aspirin alone. The ERG noted that its probabilistic ICER was similar to the company's deterministic ICER.

3.43 The ERG addressed its concerns about informative censoring (see section 3.33) by conducting a 'crude' exploratory sensitivity analysis, to explore the effects on the ICER of increasing the number of patients who experienced a fatal bleeding event with rivaroxaban (assuming that the event occurred immediately on taking rivaroxaban). 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. Because there were 21 fatal bleeding events in the combined rivaroxaban treatment arms of the total population in ATLAS-ACS 2-TIMI 51, the ERG considered that 20 additional fatal bleeding events was an unfavourable scenario for the rivaroxaban 2.5 mg twice-daily dose. The result of the ERG's exploratory analysis showed 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 gained.

3.44 The ERG also undertook a series of exploratory scenario analyses. When the following changes to the model were implemented, the ERG's preferred deterministic base-case ICER was £5622 per QALY gained (compared with the company's deterministic base-case ICER of £6203 per QALY gained):

- The transition probabilities were estimated from the trial data rather than using the Weibull curves.
- The treatment duration of rivaroxaban was limited to 1 year.
- Age-adjusted utility values for the whole population from Ara and Brazier's formula were used to adjust the no-event health state.
- Only 1 cost was applied to the multiple event states. Where there were 2 different costs added together in the company's base case, the maximum of the 2 costs was applied.
- No improvement over time in the stroke utility was modelled.
- The relative risk of having a subsequent event, given that an event had already occurred, was amended.
- The life-years gained matrix and the costs were adjusted for the 12-week cycle length in the observation period.

3.45 Full details of all the evidence are in the committee papers.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rivaroxaban, having considered evidence on the nature of acute coronary syndrome and the value placed on the benefits of rivaroxaban by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee discussed the clinical management of acute coronary syndrome in England. The Committee understood that treatment options for people with ST segment elevation myocardial infarction (STEMI) include percutaneous coronary intervention followed by dual antiplatelet therapy, prasugrel in combination with aspirin (for people who have had percutaneous coronary intervention or in whom it is planned), ticagrelor in combination with low-dose aspirin, or clopidogrel in combination with low-dose aspirin. It also understood that people with non-ST segment elevation myocardial infarction (NSTEMI) are offered treatments depending on their Global Registry of Acute Coronary Events (GRACE) or thrombolysis in myocardial infarction (TIMI) score and that these include a range of options from aspirin alone to percutaneous coronary intervention, depending on the risk of future events. The Committee heard from the clinical experts that ticagrelor and prasugrel have potential advantages over clopidogrel because of their faster antiplatelet action, although they are associated with higher bleeding risk. The Committee also heard from the clinical experts that the use of clopidogrel in clinical practice was generally decreasing as uptake of the newer agents increased, but that there was variation in practice with different centres often having their own local protocols for the treatment of acute coronary syndrome. The Committee heard from the clinical experts that because of its different mechanism of action, rivaroxaban could be a useful additional treatment option for some patients receiving clopidogrel plus aspirin or aspirin alone, although it was not possible to identify a particular subgroup of patients for whom it would be most suitable. However, the clinical experts highlighted that there is some uncertainty as to when and how it would be best incorporated into the treatment pathway. They explained that the mean time to start rivaroxaban in

ATLAS-ACS 2-TIMI 51 was 4.6 days, but the majority of patients in England have been discharged from hospital by then. The clinical experts further explained that if rivaroxaban was 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 acute coronary syndrome event, patients would usually be seen by their GP within 1 week of being discharged from hospital. The Committee considered that a 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. The Committee recognised that rivaroxaban may be a useful additional treatment option for selected patients and noted that in the trial it was started between 1– 7 days after acute coronary syndrome, but acknowledged that its introduction might have an effect on existing patient pathways.

4.3 The Committee discussed the clinical need for treatment in people with acute coronary syndrome. The Committee heard that the symptoms of acute coronary syndrome vary according to the type and severity of the disease. It was highlighted that common symptoms of acute coronary syndrome are chest pain, breathlessness and anxiety, and that the experience is painful and frightening. It was also highlighted that acute coronary syndrome may have a negative impact on the quality of life of the person and their family, as a result of worries over their future health and capability. The Committee heard from the patient expert about the importance of having timely diagnosis and effective treatments available for acute coronary syndrome. The Committee also heard that people were generally prepared to accept a certain risk of bleeding associated with antiplatelet therapy or anticoagulant

treatment such as rivaroxaban if the treatment lowered their risk of further cardiovascular events sufficiently, but the patient expert stressed the need for efficient symptom management with regular reviews. The Committee acknowledged the impact on patients and families of the symptoms of acute coronary syndrome and the increased risk of further events that followed it. The Committee concluded that an additional treatment to reduce the risk of further cardiovascular events would be useful, but that the additional bleeding risk should be taken into account for any individual when considering starting treatment.

Clinical effectiveness

4.4 The Committee considered the clinical-effectiveness data from the ATLAS-ACS 2-TIMI 51 trial comparing rivaroxaban in combination with aspirin plus clopidogrel or aspirin alone against aspirin plus clopidogrel or aspirin alone. It noted that this formed the basis of the clinical-effectiveness evidence in the company's submission. The Committee considered that the ATLAS-ACS 2-TIMI 51 trial was of good quality but noted that a key issue highlighted by the ERG was the generalisability of the results to people diagnosed with acute coronary syndrome in England. The Committee noted that people with acute coronary syndrome in clinical practice are usually older than those patients who were recruited to ATLAS-ACS 2-TIMI 51. The Committee also noted that patients in the trial could be considered a relatively low-risk population because they had little comorbidity, lower than usual use of percutaneous coronary intervention and included a relatively small proportion of people aged over 75 years or with impaired renal function. The Committee heard from the clinical experts 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 ATLAS-ACS 2-TIMI 51 were similar in terms of baseline characteristics to those recruited to other trials in acute coronary syndrome. 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 were relevant to routine clinical practice.

4.5 The Committee considered the results of the ATLAS-ACS 2-TIMI 51 trial. The Committee 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 Committee was aware from the company that this post hoc subgroup analysis was carried out at the request of the European Medicines Agency (EMA). The Committee noted that this post hoc subgroup analysis (referred to as the licensed population by the company) provided efficacy results that tended to be more favourable to rivaroxaban than the results from the overall trial population. However, it 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.

4.6 The Committee discussed the numerical inconsistencies between the 2 dose groups in the trial (2.5 mg twice daily and 5 mg twice daily) for the individual components of the composite efficacy end point that had been identified by the ERG (see section 3.31). It was aware that for some individual outcomes the 2.5 mg twice-daily dose appeared to have a greater efficacy than the 5 mg twice-daily dose. The ERG considered that it was unlikely that the 2.5 mg

twice-daily dose would be more clinically effective than 5 mg twice daily and suggested that the results from both doses combined were more plausible than those of the individual doses. The Committee heard from the company that the summary of product characteristics for rivaroxaban specified the 2.5 mg twice-daily dose and that the EMA had based its decision for this dose based on the balance of risk and benefits of the 2.5 mg twice-daily dose, compared with those of the 5 mg twice-daily dose. The Committee noted the lower bleeding risk associated with the 2.5 mg twice-daily dose compared with the 5 mg twice-daily dose. While it acknowledged that there were numerical inconsistencies in the efficacy results between the 2.5 mg and 5 mg twice-daily arms, it concluded that the efficacy data from the 2.5 mg twice-daily rivaroxaban arm were the most relevant for decision-making because it is the licensed dose of rivaroxaban for this indication.

4.7 The Committee discussed the high discontinuation rates from the trial (see section 3.10). The Committee was aware that 15.5% of the total randomised population prematurely discontinued from the trial and that the discontinuation rate was higher in ATLAS ACS 2 TIMI 51 than in other similar randomised trials in patients with acute coronary syndrome. The Committee heard from the clinical experts that high discontinuation rates were common in trials in patients with acute coronary syndrome and that this is replicated in the adherence rates seen in clinical practice, because current treatment protocols mean that people who had acute coronary syndrome are already taking 5 separate medications. The clinical experts highlighted that clinicians are mindful of the effect on patient adherence of adding any additional treatments to those already prescribed. The Committee acknowledged that the discontinuation rates in ATLAS-ACS 2-TIMI 51 were high but that

this was a concern for other trials carried out in people with acute coronary syndrome, and that it was also an issue that is seen in clinical practice.

4.8 The Committee discussed the missing data from people who withdrew or were lost from the trial (see section 3.10). The Committee was aware of the ERG's concerns that missing data may result in informative censoring (that is, patients who drop out, and whose data are therefore censored, have different outcomes to those who remain in the trial) leading to bias. The Committee was aware from the company that extensive efforts had been made to trace trial participants, to clarify reasons for withdrawal and to find out if they had died. The company stated that this had reduced the proportion of patients for whom vital status was unknown to 3.2% of people who had been recruited to the trial. The company explained that it had been unable to obtain the data for the remaining participants for whom vital status was unknown, because of restrictions imposed by the countries in which the people lived. The clinical experts acknowledged that this was a problem for many multinational trials in people with acute coronary syndrome but expressed their concern about the level of missing data, given the bleeding risks associated with rivaroxaban added to antiplatelet therapy. The Committee understood that the EMA's assessment report had not discussed this issue in detail but acknowledged the clinical experts' concerns regarding the missing data. The 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.

4.9 The Committee considered the effectiveness of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone in the licensed population (that is, people with elevated cardiac biomarkers and without a history of stroke or TIA). The Committee noted that rivaroxaban 2.5 mg twice daily in combination with aspirin plus clopidogrel or with aspirin alone reduced the composite risk of myocardial infarction, stroke and death from cardiovascular causes by 20% compared with aspirin plus clopidogrel or with aspirin alone (see table 2: ALL strata, 2.5 mg twice-daily rivaroxaban dose). The Committee understood that this composite reduction in risk was driven by reductions in cardiovascular death and myocardial infarction. The Committee concluded that rivaroxaban 2.5 mg twice daily in combination with aspirin plus clopidogrel or with aspirin alone was more effective than aspirin plus clopidogrel or aspirin alone for preventing myocardial infarction and death from cardiovascular causes in people with acute coronary syndrome and elevated cardiac biomarkers.

4.10 The Committee discussed the concerns about safety and adverse effects associated with rivaroxaban. The Committee was aware that the results for the licensed population showed that there was a dose-dependent increase in the rate of non-CABG TIMI major bleeds [major bleeding assessed using 'Thrombolysis in Myocardial Infarction' criteria not related to coronary-artery bypass grafting] for rivaroxaban added to antiplatelet therapy compared with antiplatelet therapy alone. It noted that in the 2.5 mg rivaroxaban twice-daily arm of the ATLAS-ACS 2-TIMI 51 study, there was a 3 times greater risk of non-CABG TIMI major bleeding with rivaroxaban in combination with aspirin plus clopidogrel or aspirin compared with these antiplatelet therapies alone. The Committee

acknowledged that all antiplatelet and anticoagulant treatments have an associated risk of bleeding but noted the comments it had heard from the clinical and patient experts that the risk of bleeding was a key consideration when deciding on a particular treatment. The Committee was aware that no data had been presented by the company or other stakeholders comparing the risk of bleeding with rivaroxaban in combination with antiplatelet agents compared with other treatment regimens with antiplatelet agents such as ticagrelor and prasugrel, because these were not included in the final scope. The Committee was therefore unable to compare the effectiveness and safety profile of a treatment strategy in which rivaroxaban is added to clopidogrel and aspirin at least 24 hours after admission to hospital, with strategies in which ticagrelor and prasugrel are added to aspirin from the start of treatment. The Committee concluded that treatment with rivaroxaban resulted in more non-CABG-related major bleeding than aspirin plus clopidogrel or aspirin alone, but also recognised the particular importance of the effects of rivaroxaban in reducing the risk of myocardial infarction and death from cardiovascular causes. The Committee also concluded that clinicians should undertake a careful assessment of whether the bleeding risk is outweighed by the benefits of rivaroxaban in preventing further ischaemic events for individual patients when deciding whether to start or continue treatment. The Committee noted that the summary of product characteristics states that treatment should be regularly evaluated and, in particular, 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.

Cost effectiveness

4.11 The Committee considered the company's economic model and the review and exploratory sensitivity analyses performed by the ERG. The Committee noted that the ICERs presented by the company in its base-case analysis and in the ERG's exploratory sensitivity analyses were all lower than £10,000 per QALY gained. The Committee was aware of the ERG's concerns about the structure of the company's economic model and, in particular, that the model is relatively inflexible. This meant that the ERG could not carry out all the exploratory analyses that it deemed potentially relevant. These included amendments to the hazard ratio for fatal bleeds and adjusting for the possibility of informative censoring. The Committee noted that, to explore its concerns about informative censoring, the ERG had undertaken a 'crude' exploratory analysis to explore the effects on the ICER of increasing the number of patients who experienced a fatal bleed with rivaroxaban. The Committee was aware that the analysis showed that even if rivaroxaban 2.5 mg twice daily caused as many as 20 more fatal bleeds than observed in the trial, the estimated ICER remained below £10,000 per QALY gained. The Committee concluded that despite the inflexibility of the company's economic model and the resulting constraints on the ERG's ability to undertake further exploratory analyses, the ICERs presented were a suitable basis for decision-making on the cost effectiveness of rivaroxaban in addition to clopidogrel plus aspirin or with aspirin alone.

4.12 The Committee considered the ICER for the 2.5 mg dose of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone in patients with acute coronary syndrome with elevated cardiac biomarkers (STEMI or NSTEMI) and no history of stroke or

TIA. The Committee noted that the company's base-case ICER was £6203 per QALY gained, and the ERG's preferred base-case estimate was £5622 per QALY gained. It accepted that there is uncertainty about the validity of the results based on ATLAS-ACS 2-TIMI 51 because of the risk of bias resulting from missing data and informative censoring. However, the Committee considered 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. It concluded that rivaroxaban can be considered a cost-effective use of NHS resources.

4.13 The Committee was aware that there is an increased risk of bleeding when rivaroxaban is added to aspirin or aspirin plus clopidogrel and it would be important for clinicians to carefully assess a person's individual bleeding risk and for patients to have an informed discussion with their clinician about the potential risks and benefits before starting treatment with rivaroxaban. The Committee noted that the summary of product characteristics states that after initiation, there should be regular assessment of the risks and benefits of continuing treatment with rivaroxaban and extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited. The Committee concluded that it was appropriate that a formal assessment of whether to continue treatment should be made no later than 12 months after starting rivaroxaban.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Rivaroxaban for preventing adverse outcomes in patients after the	Section

	acute management of acute coronary syndrome	
Key conclusion		
1.1 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 an acute coronary syndrome with elevated cardiac biomarkers. 1.2 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. 1.3 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. The Committee concluded that rivaroxaban 2.5 mg twice daily in combination with aspirin plus clopidogrel or with aspirin alone was more effective than aspirin plus clopidogrel or aspirin alone for preventing myocardial infarction and death from cardiovascular causes in people with acute coronary syndrome and elevated cardiac biomarkers. The Committee concluded that treatment with rivaroxaban resulted in more non-coronary artery bypass grafting (non-CABG) major bleeding than aspirin plus clopidogrel or aspirin alone, but also recognised the particular importance of the effects of rivaroxaban in	1.1-1.3 4.9-4.12

reducing the risk of myocardial infarction and death from cardiovascular causes. The Committee also concluded that clinicians should undertake a careful assessment of whether the bleeding risk is outweighed by the benefits of rivaroxaban in preventing further ischaemic events for individual patients when deciding whether to start or continue treatment. The Committee noted that the summary of product characteristics states that treatment should be regularly evaluated and, in particular, 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. The Committee considered 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. It concluded that rivaroxaban can be considered a cost effective use of NHS resources.	
Current practice	

Clinical need of patients, including the availability of alternative treatments	The Committee understood that, in England, treatment options for people with ST segment elevation myocardial infarction (STEMI) include percutaneous coronary intervention followed by dual antiplatelet therapy, prasugrel in combination with aspirin (for those who have undergone percutaneous coronary intervention or in whom it is planned), ticagrelor in combination with low-dose aspirin, or clopidogrel in combination with low-dose aspirin. The Committee heard from the clinical experts that ticagrelor and prasugrel have potential advantages over clopidogrel because of their faster antiplatelet action, although they are associated with higher bleeding risk. The Committee heard from the patient expert about the importance of having timely diagnosis and effective treatments available for acute coronary syndrome. The Committee also heard that people were generally prepared to accept a certain risk of bleeding associated with antiplatelet therapy or anticoagulant treatment such as rivaroxaban if the treatment lowered their risk of further cardiovascular events sufficiently, but the patient expert stressed the need for efficient symptom management with regular reviews.	4.2-4.3

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the clinical experts that because of its different mechanism of action, rivaroxaban could be a useful additional treatment option for some patients having clopidogrel plus aspirin or aspirin alone, although it was not possible to identify a particular subgroup of patients for whom it would be most suitable.	4.2

What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the clinical experts that there is some uncertainty as to when and how rivaroxaban would be best incorporated into the treatment pathway. The clinical experts explained that the mean time to start rivaroxaban in ATLAS-ACS 2-TIMI 51 was 4.6 days, but the majority of patients in England have been discharged from hospital by then. The clinical experts further explained that if rivaroxaban was 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 acute coronary syndrome event, patients would usually be seen by their GP within 1 week of being discharged from hospital. The Committee considered 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.	4.2
Adverse reactions	The Committee was aware that treatment with rivaroxaban resulted in more non-CABG-related major bleeding than aspirin plus clopidogrel or aspirin alone.	4.10
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The Committee considered the clinical-effectiveness data from the ATLAS-ACS 2-TIMI 51 trial comparing rivaroxaban in combination with aspirin plus clopidogrel or aspirin alone against aspirin plus clopidogrel or aspirin alone. It noted that this formed the basis of the clinical-effectiveness evidence in the company's submission. The Committee considered that the ATLAS-ACS 2-TIMI 51 trial was of good quality.	4.4
Relevance to general clinical practice in the NHS	The Committee concluded that the results of the ATLAS ACS 2-TIMI 51 trial were broadly relevant to routine clinical practice.	4.4

Uncertainties generated by the evidence	The Committee discussed the missing data from people who withdrew or were lost from the trial. The Committee was aware of the ERG's concerns that missing data 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. The Committee was aware from the company that extensive efforts had been made to trace trial participants, to clarify reasons for withdrawal and to find out if they had died. The company stated that this had reduced the proportion of patients for whom vital status was unknown to 3.2% of people who were recruited to the trial. The 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.	4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No subgroups were identified.	

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that rivaroxaban 2.5 mg twice daily in combination with aspirin plus clopidogrel or with aspirin alone was more effective than aspirin plus clopidogrel or aspirin alone for preventing myocardial infarction and death from cardiovascular causes in people with acute coronary syndrome and elevated cardiac biomarkers.	4.9
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the company's economic model and the review and exploratory sensitivity analyses performed by the ERG.	4.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee was aware of the ERG's concerns about the structure of the company's economic model and, in particular, that the model is relatively inflexible. This meant that the ERG could not carry out all the exploratory analyses that it deemed potentially relevant. These included amendments to the hazard ratio for fatal bleeds and adjusting for the possibility of informative censoring.	4.11

Incorporation of health-related quality of life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	Not applicable. The Committee did not draw any specific conclusions about the health-related quality of life benefits and utility values.	
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee did not identify specific groups of people for whom the technology is particularly cost effective.	
What are the key drivers of cost effectiveness?	Not applicable. The Committee did not draw any specific conclusions about the key drivers of cost effectiveness.	

Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that the company's base case ICER was £6203 per QALY gained, and the ERG's preferred base case estimate was £5622 per QALY gained. It accepted that there is uncertainty about the validity of the results based on ATLAS-ACS 2-TIMI 51 because of the risk of bias resulting from missing data and informative censoring. However, the Committee considered 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 the ICER to the extent that it would become unacceptable.	4.12
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No equality issues relevant to the Committee's recommendations were raised.	

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of technology appraisal guidance 182). NICE technology appraisal guidance 317 (2014).
- Myocardial infarction – secondary prevention: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 172 (2013).
- Myocardial infarction with ST-segment elevation: the acute management of myocardial infarction with ST-segment elevation. NICE clinical guideline 167 (2013).
- Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisal guidance 236 (2011).
- Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE clinical guideline 94 (2010).

7 Review of guidance

7.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, Appraisal Committee
November 2014

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Consultant radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Professor Thanos Athanasiou
Professor of Cardiovascular Sciences and Cardiac Surgery, Imperial College London; Consultant Cardiothoracic Surgeon, Imperial College Healthcare NHS Trust

Dr Simon Bond

Senior Statistician, Cambridge Clinical Trials Unit

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

Professor Aileen Clarke

Professor of Public Health & Health Services Research, University of Warwick

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Dr Brian Hawkins

Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Alec Miners

Senior Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Mohit Misra

GP, Queen Elizabeth Hospital, London

Ms Sarah Parry

Clinical Nurse Specialist, Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees

Lay member

Dr Ann Richardson

Lay member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire Clinical Commissioning Group

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Peter Sims

GP, Devon

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker and Mary Hughes
Technical Leads

Nicola Hay
Technical Adviser

Bijal Joshi
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield:

- Pandor A, Pollard D, Stevenson M, et al., Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome: a single technology appraisal (August 2014)

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Bayer (rivaroxaban)

II. Professional/specialist and patient/carer groups:

- British Heart Foundation
- Pumping Marvellous
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- National Institute for Health Research Health Technology Assessment Programme
- School of Health and Related Research Sheffield (ScHARR)

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on rivaroxaban by attending the initial Committee

discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr James Cotton, Consultant Cardiologist, nominated by organisation representing British Cardiovascular Intervention Society – clinical expert
- Professor Carlo Di Mario, Consultant Cardiologist, nominated by organisation representing Bayer – clinical expert
- Mr Nick Hartshorne-Evans, nominated by organisation representing Pumping Marvellous Foundation – patient expert
- Ms Jayne Knowles-Smith, nominated by organisation representing Pumping Marvellous Foundation – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bayer