

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

**Rivaroxaban for preventing atherothrombotic
events in people with coronary or peripheral
artery disease**

1 Recommendations

- 1.1 Rivaroxaban plus aspirin is recommended within its marketing authorisation, as an option for preventing atherothrombotic events in adults with coronary artery disease or symptomatic peripheral artery disease who are at high risk of ischaemic events.
- 1.2 For people with coronary artery disease, high risk of ischaemic events is defined as:
- aged 65 or over, or
 - atherosclerosis in at least 2 vascular territories (such as coronary, cerebrovascular, or peripheral arteries), or
 - 2 or more of the following risk factors:
 - current smoking
 - diabetes
 - kidney dysfunction with an estimated glomerular filtration rate (eGFR) of less than 60 ml/min (note that rivaroxaban is contraindicated if the eGFR is less than 15 ml/min)
 - heart failure
 - previous non-lacunar ischaemic stroke.
- 1.3 Assess the person's risk of bleeding before considering rivaroxaban. Treatment should only be started after an informed discussion with them about the risks and benefits of rivaroxaban, weighing up the risk of

atherothrombotic events against the risk of bleeding. The risks and benefits of continuing treatment with rivaroxaban should be regularly reviewed.

Why the committee made these recommendations

People with chronic coronary artery disease or symptomatic peripheral artery disease can have atherothrombotic events such as myocardial infarction and stroke.

A clinical trial of people at high risk of ischaemic events shows that, compared with aspirin alone, rivaroxaban plus aspirin reduces the risk of having an ischaemic stroke, myocardial infarction or dying from cardiovascular disease. However, it increases the risk of bleeding.

The benefits and risks of rivaroxaban plus aspirin are only known for the specific population in the trial; that is, people a high risk of ischaemic events as defined by the inclusion criteria of the trial. A person’s risk of bleeding should be assessed before rivaroxaban is considered. The decision to start treatment should be taken after an informed discussion about the risks and benefits, weighing up the risk of ischaemic events against the bleeding risk.

The cost effectiveness of rivaroxaban is within the range that is considered an acceptable use of NHS resources. Aspirin plus rivaroxaban is therefore recommended as a treatment option for people at high risk of having atherothrombotic events, who are not identified as having an increased risk of bleeding.

2 Information about rivaroxaban

<p>Marketing authorisation indication</p>	<p>Rivaroxaban (Xarelto, Bayer) co-administered with aspirin, is indicated for ‘the prevention of atherothrombotic events in adult patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischaemic events’.</p>
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Dosage in the marketing authorisation	The recommended dosage for rivaroxaban is 2.5 mg taken orally twice daily in combination with a daily dose of 75 to 100 mg aspirin taken orally.
Price	The list price for 56 tablets of rivaroxaban 2.5 mg is £50.40 (company submission). The treatment period is indefinite.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Bayer, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- It is more clinically plausible to substitute transition probability values used in the economic model that were numerically zero with non-zero values taken from the REACH registry.
- The company's economic model underestimates the effect of varying the stratified mortality outcome 'cardiovascular death' in its sensitivity analyses. The company used the hazard ratio value for 'all cardiovascular death' from the COMPASS trial and assumed the same hazard ratio for all stratified death events in its model. Each mortality hazard ratio was then varied separately in the deterministic and probabilistic sensitivity analyses. Because each death rate only included a small proportion of all cardiovascular deaths, the effect of varying the hazard ratios individually in the sensitivity analyses was underestimated. This issue had no effect on the results of the base-case analysis and only related to the uncertainty in the sensitivity analyses.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 7), and took these into account in its decision making. It discussed the following issues (issues 1, 2 and 3), which were outstanding after the technical engagement stage.

Clinical need and current management

Patients rely on clinicians to discuss with them the benefits and risks of treatment options

- 3.1 The patient expert explained that people with coronary or peripheral artery disease have serious concerns about the risk of having events such as heart attack and stroke. They noted that coronary or peripheral artery disease is a challenging condition requiring significant lifestyle adjustments, including diet and exercise, which can affect the whole family. It is important that people understand why they are being offered a dual therapy and how the drugs work, because this can help with adherence to treatment. The patient expert explained that patients rely on clinicians to discuss with them the best treatment options. All options should be discussed, weighing up the potential benefits and risks of potentially long-term medication. The committee concluded that patients rely on clinicians to present the best treatment options to them, and all potential benefits and risks should be fully discussed.

Patients would welcome an additional treatment option with an acceptable benefit-risk ratio for the prevention of atherothrombotic events

- 3.2 NICE's clinical guideline on [myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease](#) recommends dual antiplatelet therapy for people who have had an acute myocardial infarction. NICE's clinical guideline on [management of stable angina](#) recommends considering aspirin 75 mg daily for secondary prevention of cardiovascular disease. NICE technology appraisal guidance recommends [ticagrelor in combination with aspirin](#) for preventing atherothrombotic events in people who have had a myocardial infarction and are at high risk of a further event. The clinical experts noted that despite widespread use of aspirin in both acute and secondary care the risk of stroke, myocardial infarction and dying from cardiovascular disease remains high for these patients. An additional treatment option that could reduce this risk would be welcomed by patients. The potential clinical

benefit from treatment would need to be assessed, taking into consideration the potential risk of major bleeding events. The committee concluded that people with coronary artery disease or peripheral artery disease would welcome an additional treatment option with an acceptable benefit-risk ratio for the prevention of atherothrombotic events.

Clinical evidence

It is appropriate to consider the overall COMPASS population for decision making

3.3 COMPASS is a double-blind randomised clinical trial comparing rivaroxaban plus aspirin against aspirin alone in people with stable coronary artery disease or peripheral artery disease who are at high risk of ischaemic events. The company presented data for the overall trial population and also for 3 subpopulations that it identified as being at especially high baseline risk of ischaemic events: people with coronary artery disease and peripheral artery disease, people with coronary artery disease and heart failure, and people with coronary artery disease and poor kidney function. The risk of ischemic events is related to the person's medical history and the extent of atheroma. People with heart failure, diabetes, poor kidney function or diffuse atherosclerosis affecting several areas (such as the coronary and peripheral arteries) are at higher risk of events. However other factors also increase risk including diabetes, high BMI and smoking. At technical engagement, it was queried whether the company's subgroups are clinically relevant and represent people at highest risk of atherothrombotic events who are likely to benefit most from treatment with rivaroxaban plus aspirin. The clinical experts agreed that although these subgroups are clinically identifiable and relevant, there are other groups of people who are also at high risk. These include people who have had myocardial infarction or stroke, and those with multi-vessel coronary disease and diabetes. These people could derive similar benefit from rivaroxaban plus aspirin as seen in the 3 subgroups, because there was no between-group heterogeneity in relative treatment effects reported

in COMPASS. The committee acknowledged the company's attempt to predict people with higher baseline risk using the 3 subgroups but noted that although the subgroups are illustrative of people at high risk, they do not identify all people at highest absolute risk of ischaemic events. The clinical experts also highlighted the difficulty in identifying people who are at greatest risk in clinical practice and agreed that, because there is no inter-group difference in treatment effects in COMPASS, the results from the overall population should be considered for decision making.

However, the committee was aware that, within the overall eligible population, clinicians are likely to identify people at highest absolute risk of ischaemic events and offer rivaroxaban to those who are likely to have the highest potential absolute benefit. People at high risk of ischaemic events and no known increased bleeding risk will have the most favourable benefit-risk profile. The committee concluded that the efficacy results from the whole COMPASS population should be considered rather than the 3 subpopulations identified by the company, and it did not consider the subgroups further.

Rivaroxaban plus aspirin reduces the risk of cardiovascular events

- 3.4 The primary efficacy outcome in COMPASS was a composite of 3 major cardiovascular events: myocardial infarction, ischaemic stroke and 'cardiovascular death'. The committee noted that rivaroxaban plus aspirin showed a statistically significant relative risk reduction of 24% in major cardiovascular events compared with aspirin (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.66 to 0.86; $p < 0.001$). Two of the individual components of the primary composite outcome also showed statistically significant relative risk reductions in the treatment arm: 42% for ischaemic stroke (HR 0.58, 95% CI 0.44 to 0.76; $p < 0.001$) and 22% for cardiovascular death (HR 0.78, 95% CI 0.64 to 0.96; $p = 0.02$). The committee concluded that rivaroxaban plus aspirin reduces the risk of cardiovascular events compared with aspirin alone, and that the greatest effect is for ischaemic stroke.

Rivaroxaban plus aspirin increases the risk of major bleeding

3.5 The primary safety outcome in COMPASS was major bleeding based on a modification of the International Society on Thrombosis and Haemostasis (ISTH) criteria. Major bleeding was defined as a composite of fatal bleeding, and/or symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, intramuscular with compartment syndrome, or bleeding into the surgical site requiring re-operation), and/or bleeding leading to hospitalisation (with or without an overnight stay). The risk of major bleeding, as defined by the modified ISTH criteria, increased by 70% in the rivaroxaban plus aspirin group compared with aspirin alone (HR 1.70, 95% CI 1.40 to 2.05; $p < 0.001$). The bleeds in the rivaroxaban plus aspirin group were mostly gastrointestinal, with non-significant differences for the other components of the primary safety outcome. The committee concluded that rivaroxaban plus aspirin increases the risk of major bleeding compared with aspirin alone.

Rivaroxaban should only be used in people at high risk of ischaemic events defined by the inclusion criteria of COMPASS

3.6 The clinical experts highlighted that COMPASS is a highly selected population that includes people at high risk of ischaemic events but excludes people with a known increased bleeding risk. The committee noted that the benefits and risks of rivaroxaban plus aspirin are only known for the specific population of people in COMPASS; that is, people with a high risk of ischaemic events as defined by the inclusion criteria of the trial. The committee recalled that the clinical benefits and risks associated with rivaroxaban plus aspirin are finely balanced (section 3.4 and section 3.5). The committee noted that rivaroxaban plus aspirin is contraindicated in cases of active clinically significant bleeding and in people with lesions or conditions considered to be a significant risk factor for major bleeding. It agreed that a person's risk of bleeding should be assessed before rivaroxaban is considered as a treatment option. The decision to start treatment should be only be taken after an informed

discussion about the risks and benefits of rivaroxaban, weighing up the risk of ischaemic events against the bleeding risk. The committee concluded that rivaroxaban should only be considered a treatment option for people at high risk of ischaemic events as defined by the inclusion criteria of COMPASS.

Comparators

Clopidogrel is not a relevant comparator for the overall COMPASS population

3.7 The company did not present evidence for rivaroxaban plus aspirin compared with clopidogrel. The clinical experts explained that clopidogrel is the preferred antiplatelet treatment for people with peripheral artery disease (based on NICE guidance for the [prevention of occlusive vascular events](#)), but it is not a relevant comparator for the whole COMPASS population. This is because aspirin is the preferred treatment for secondary prevention of cardiovascular disease in people with stable coronary artery disease, and clopidogrel is only recommended when aspirin is unsuitable because of contraindication or hypersensitivity. The committee concluded that clopidogrel is not a relevant comparator for the overall COMPASS population and that it is appropriate to base its recommendation on a comparison of rivaroxaban plus aspirin with aspirin alone.

The indirect comparison of rivaroxaban against ticagrelor does not provide reliable estimates of relative effectiveness or risk of bleeding

3.8 To estimate the relative efficacy of rivaroxaban plus aspirin compared with ticagrelor plus aspirin, the company did an indirect treatment comparison of COMPASS against data from another trial (PEGASUS). The ERG highlighted that the indirect comparison is methodologically sound, but there are important differences between the patients included in the 2 trials. The proportion of people who had had a myocardial infarction was 100% in PEGASUS, but 62% in COMPASS. Also, the time since a myocardial infarction was between 1 and 3 years in PEGASUS, but in

COMPASS people could have had a myocardial infarction at any time within the past 20 years. A clinical expert also noted that people in PEGASUS and COMPASS did not necessarily have the same baseline bleeding risk, and the trials used different methods to define significant bleeding (modified ISTH in COMPASS and TIMI in PEGASUS), making it difficult to compare the rates of bleeding in the 2 trials. The committee noted that the company did not use the results of the indirect comparison in its economic model. It concluded that COMPASS and PEGASUS have too many differences to allow a reliable estimate of the relative efficacy or bleeding risk of rivaroxaban plus aspirin compared with ticagrelor plus aspirin.

The company's economic model

The model is appropriate for decision making

3.9 The company modelled cost effectiveness using a Markov model with 5 states (event-free, non-fatal myocardial infarction, ischaemic stroke, intracranial haemorrhage and death). These were subdivided into acute event (0 to 3 months after an acute event), post-event (3 or more months after an acute event) and second acute event. The efficacy and clinical parameters in the model were derived from COMPASS for the comparison of rivaroxaban plus aspirin against aspirin alone. For the comparison against ticagrelor plus aspirin, the results from the indirect comparison of COMPASS and PEGASUS were not directly used to inform the economic model. Instead, the model used hazard ratios from the COMPASS and PEGASUS trials, which the committee considered appropriate. The committee concluded that the structure of the company's model is appropriate for decision making.

Cost effectiveness estimates

Rivaroxaban plus aspirin is cost effective compared with aspirin alone

3.10 The company's base-case incremental cost-effectiveness ratio (ICER) for rivaroxaban plus aspirin compared with aspirin alone is £14,185 per quality-adjusted life year gained. The committee noted that the ICER is in the range normally considered cost effective and therefore concluded that rivaroxaban plus aspirin is a cost-effective use of NHS resources in people who are at high risk of ischaemic events as defined by the inclusion criteria of COMPASS (see section 3.6).

4 Implementation

- 4.1 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. provide funding to implement this guidance 30 days after publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has coronary artery disease or symptomatic peripheral artery disease and the doctor responsible for their care thinks that rivaroxaban plus aspirin is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication. 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

June 2019

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

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.

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.

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