NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA335; Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome

Original publication date:	March 2015
Review date	March 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for 335, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

Evidence published since NICE technology appraisal 335 supports the committee's considerations and addresses some of the uncertainties identified in the appraisal. There has not been any evidence identified that suggests a review of this guidance is necessary.

3. Summary of new evidence and implications for review

The clinical evidence in the original appraisal came from 1 randomised controlled trial (ATLAS-ACS 2-TIMI 51). Since the appraisal, 1 new trial has been identified which investigates part of the indication explored in TA335 (COMPASS comparing rivaroxaban with aspirin; Eikelboom et al. (2017)). Two new meta-analyses have been identified which compared new oral anticoagulants (including rivaroxaban) with single or dual antiplatelet therapies in patients with acute coronary syndrome (Fanaroff et al. (2017); Kahn et al. (2018)). Further literature that is relevant to uncertainties in the original appraisal has also been identified. The additional evidence supports the conclusions drawn by the committee in the original appraisal that the rivaroxaban treatment regimen significantly reduces the risk of adverse cardiovascular outcomes after acute coronary syndrome, but that it also increases risk of bleeding. The new clinical evidence is unlikely to lead to a change in the recommendations of the original guidance.

The net price of rivaroxaban has decreased since the original appraisal. As the original guidance was positive this is unlikely to lead to a change in the recommendations.

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Has there been any change to the price of the technology since the guidance was published?

The list/acquisition price for a 56-tablet pack of 2.5mg rivaroxaban has changed from £58.88 to £50.40 (BNF; accessed 15 Jan 18).

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

There are no changes or proposed changes to the marketing authorisation.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The original guidance compared rivaroxaban administered with aspirin plus clopidogrel or aspirin alone, with aspirin plus clopidogrel or aspirin alone. The main source of evidence for the appraisal came from 1 randomised controlled trial (ATLAS-ACS 2-TIMI 51), which compared a rivaroxaban treatment regimen with standard care (clopidogrel plus aspirin or aspirin alone) in patients with acute coronary syndrome (ACS; unstable angina, non-ST-segment-elevation myocardial infarction [NSTEMI] or ST-segment-elevation myocardial infarction [STEMI]).

In the original guidance the committee identified the following uncertainties:

1. High discontinuation rates from the trial. The committee acknowledged that discontinuation rates were high but considered that this was also an issue in other trials in acute coronary syndrome and in clinical practice.
2. Missing data from the trial. The committee raised concerns that bias may be introduced by informative censoring, and that the magnitude of this bias was unknown.
3. Safety profile of rivaroxaban treatment regimen compared with other antiplatelet regimens (e.g. ticagrelor and prasugrel).
4. Uncertainties arising from the economic model structure. In the original appraisal the ERG highlighted that their exploratory analyses were limited by the inflexible model structure. Exploratory analyses affected by the model structure included amendments to the hazard ratio for fatal bleeds and adjusting for the possibility of informative censoring. However, the ERG did a 'crude' analysis which showed that the ICER was not sensitive to changes in the number of patients who experienced a fatal bleed.

Since the original guidance was published, 1 new published randomised controlled trial has been identified (COMPASS). The trial explored whether rivaroxaban (2.5mg twice daily) plus aspirin (100mg once daily) was more effective than aspirin alone (100mg once daily) for secondary cardiovascular

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prevention in patients with stable cardiovascular disease. Results were reported for patients with coronary artery disease, of which acute coronary syndrome is a subset. Rivaroxaban lowered the risk of cardiovascular death, stroke or myocardial infarction (composite endpoint; HR: 0.74, 95% CI: 0.65, 0.86) in patients with coronary artery disease. However rivaroxaban increased risk of major bleeding in the full trial population (HR: 1.70, 95% CI: 1.40, 2.05). These findings are consistent with the findings of the ATLAS-ACS 2-TIMI 51 trial in the overall trial population which informed the original guidance.

Since the original guidance, there have not been any published or ongoing trials identified which compare rivaroxaban in combination with clopidogrel plus aspirin with clopidogrel plus aspirin.

Two indirect comparisons have been published since the original guidance, which explore the efficacy and safety of the rivaroxaban treatment regimen. Fanaroff et al. (2017) conducted a network meta-analysis of oral antithrombotic agents in patients with ACS or prior myocardial infarction. This study found that low dose rivaroxaban in combination with clopidogrel and aspirin was associated with lower all-cause mortality (OR: 0.67, 95% CI: 0.49, 0.90), but that triple antithrombotic therapy was associated with a 2 to 6 fold increase in major bleeding.

Kahn et al. (2018) conducted a network meta-analysis exploring the addition of new oral anticoagulants (including rivaroxaban) to single and dual agent antiplatelet therapy. The study found that adding new oral anticoagulants to single antiplatelet therapy did not significantly decrease major adverse cardiovascular events and did not significantly increase risk of clinically important bleeding. In contrast, adding new oral anticoagulants to dual antiplatelet therapy increased the risk of bleeding but only showed a model decrease in the risk of major adverse cardiovascular events.

Since the original guidance was developed, 3 new studies have been identified that address other areas of uncertainty from the appraisal. Little et al. (2016) investigated the impact of missing data on the results from the ATLAS-ACS 2-TIMI 51 study. Based on sensitivity analyses and data from a follow-up study, the findings of ATLAS-ACS 2-TIMI 51 appear to be robust to missing data, addressing this uncertainty.

Chatterjee et al. (2014) conducted a meta-analysis of 18 randomised controlled trials to explore treatment discontinuations in new oral anticoagulants (including rivaroxaban). The study found that all cause discontinuation in acute coronary syndrome was higher for new oral anticoagulants than for placebos (RR: 1.04, 95% CI: 1.07, 1.83). This finding supports the committee's original considerations about discontinuation rates affecting other trials in the disease area.

Ye et al. (2014) published an indirect comparison of rivaroxaban 2.5mg with dual antiplatelet therapy and with ticagrelor, prasugrel and apixaban. The network meta-analysis extracted data from 5 randomised controlled trials (including ATLAS-ACS 2-TIMI 51). There were no significant differences in major bleeding between rivaroxaban 2.5mg and prasugrel (OR: 0.39, 95% CI: 0.06, 2.41) or rivaroxaban 2.5mg and ticagrelor (OR: 3.36, 95% CI: 0.42, 25.52). This additional

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evidence addresses uncertainty about the safety profile of rivaroxaban in comparison to other antithrombotic regimens. The evidence identified is unlikely to lead to a change in the recommendations made in the original guidance.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments

The manufacturer search strategy referred to in the ERG report was adapted and re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from March 2014 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues relevant to the committee's recommendations were raised in the original guidance.

GE paper sign off: **Meindert Boysen, 01 March 2018**

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome.

6. Current 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.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

“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.”

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Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at a future date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

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Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

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Appendix C – other relevant information

1. Relevant Institute work

Published

Ticagrelor for the treatment of acute coronary syndromes (2011) NICE technology appraisal guidance TA236

Ticagrelor for preventing atherothrombotic events after myocardial infarction (2016) NICE technology appraisal guidance TA420

Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (2014) NICE technology appraisal guidance TA317

Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes (2002) NICE technology appraisal guidance TA47

Bivalirudin for the treatment of ST-segment-elevation myocardial infarction (2011) NICE technology appraisal guidance TA230

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (2010) NICE technology appraisal guidance TA210

Drug-eluting stents for the treatment of coronary artery disease (2008) NICE technology appraisal guidance TA152

Guidance on the use of coronary artery stents (2003 updated 2008) NICE technology appraisal guidance TA71

Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction (2002) NICE technology appraisal guidance TA52

Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction (2003 updated 2011) NICE technology appraisal guidance TA73

Myocardial infarction with ST-segment elevation (2013) NICE clinical guideline CG167

Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013) NICE clinical guideline CG172

Hyperglycaemia in acute coronary syndromes (2011) NICE clinical guideline CG130

Chest pain of recent onset (2010 updated 2016) NICE clinical guideline CG95

Unstable angina and NSTEMI (2010 updated 2013) NICE clinical guideline CG94

In progress

Acute Coronary Syndromes. NICE guideline. Publication expected May 2020.

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Suspended/terminated

Cangrelor for reducing atherothrombotic events in people undergoing percutaneous coronary intervention or awaiting surgery requiring interruption of anti‑platelet therapy (terminated appraisal) (2015) NICE technology appraisal guidance TA351

2. Details of new products

None.

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"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)." "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."	There are no changes or proposed changes to the marketing authorisation. Ticlopidine is still not listed in the British National Formulary (BNF). BNF (accessed 15 Jan 18) gives the NHS indicative price for a 56 tablet pack of 2.5mg rivaroxaban as £50.40.

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4. Registered and unpublished trials

Trial name and registration number	Details
NCT01776424 A Randomized Controlled Trial of Rivaroxaban for the Prevention of Major Cardiovascular Events in Patients With Coronary or Peripheral Artery Disease (COMPASS - Cardiovascular OutcoMes for People Using Anticoagulation StrategieS).	Start date: February 2013 Estimated primary completion date: July 2017 Estimated completion date: June 2021 Estimated number of participants: 27395 Status: active not recruiting Phase III

5. Relevant services covered by NHS England specialised commissioning [including the Cancer Drugs Fund]

No relevant information was found.

6. Implementation

None.

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Appendix D – References

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