Evidence Review for Prescribing Clinical Network

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

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Summary page

In NICE technology appraisal guidance [TA335] 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.

The PCN member clinical commissioning groups are required to comply with recommendations in this technology appraisal within 3 months of its date of publication (end June 2015).

The TA335 guidance is summarised in this paper, the full version is available at: https://www.nice.org.uk/guidance/ta335

Place in therapy / treatment pathway NICE treatment pathways available at http://pathways.nice.org.uk/pathways/acute-coronary-syndromes

Clinical effectiveness

NICE concluded that rivaroxaban 2.5mg bd 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.

NICE noted that within the licensed population* the composite risk of myocardial infarction, stroke and death from cardiovascular causes was reduced by 20% when rivaroxaban was added to aspirin plus clopidogrel or aspirin alone.
No specific monitoring for efficacy is required.

*Licensed population is patients with ACS and elevated cardiac biomarkers (ie NSTEMI and STEMI) with no prior history of TIA or stroke.

Safety
There is an increased risk of bleeding when rivaroxaban is added to aspirin plus clopidogrel or aspirin alone. Clinicians should carefully assess the person's risk of bleeding before treatment with rivaroxaban is started.

No specific monitoring for toxicity is required.

Role of the specialist
Initiate treatment in suitable patients
Conduct risk assessment and discuss with the patient
Communicate treatment plan including intended duration with the patient's GP

Role of GP
Following initiation in secondary care, to continue prescribing in primary care. Discontinue treatment following duration requested by the specialist unless the patient experiences side-effects / adverse drug reaction or there is a change in the relative risks and benefits.

Financial implications

Estimated cost per 100 000 population:
£16,100 per 100,000 population, the calculation takes account of the following:

NICE estimates that 152 admissions (for STEMI and NSTEMI) per 100,000 of population and that of these 149 per 100,000 population are eligible for secondary prevention of atherothrombotic events.

The manufacturer's submission estimates that 99% of these patients receive aspirin plus clopidogrel and that the remaining patients receive aspirin alone. However, expert clinical opinion is that these remaining 1% of patients receive either ticagrelor or prasugrel (similar costs), and that the use of clopidogrel in general is decreasing as uptake of these newer agents increases. Due to wide local variation in the use of ticagrelor and prasugrel, NICE recommend that organisations use the template to determine local costs.

The manufacturer expects their market share to increase from 0% to 5% in 2015 and rise to 14% by 2017 and that these switches will be solely from patients receiving aspirin with or without clopidogrel, rather than from patients on ticagrelor or praugrel.

Cost of implementation per 100,000 population using NICE assumptions	Cost (£)	Drug costs per 28 days (£)*
Current treatments (people with STEMI or NSTEMI)		
Aspirin plus ticagrelor	720	55.47
Aspirin plus prasugrel	630	48.43
Aspirin plus clopidogrel	5,330	2.69
Aspirin plus clopidogrel plus rivaroxaban	0	0
Total current cost (£)	**6,680**	
Future treatments (people with STEMI or NSTEMI)		
Aspirin plus ticagrelor	720	55.47
Aspirin plus prasugrel	630	48.43
Aspirin plus clopidogrel	4,570	2.69
Aspirin plus clopidogrel plus rivaroxaban	16,820	61.19
Total future cost (£)	**22,740**	
Net resource impact (£)	**16,060**	

- Drugs at BNF doses and Drug Tariff prices April 2015

Other issues None

Recommendation to PCN
Approval as Amber * on the Traffic Light System
For consultant Cardiologist initiation only

Purpose of the Review

The PCN member clinical commissioning groups are required to comply with recommendations in NICE technology appraisal guidance [TA335] within 3 months of its date of publication, by end June 2015.
In the TA, 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

Review of Evidence
The main evidence in the company's submission for the NICE TA came from ATLAS-ACS 2_TIMI 51. This was an international, multicentre RCT across 44 countries, including the UK. In the licensed population. rivaroxaban 2.5mg bd 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 aspirin alone.

The evidence review group made several comments about the evidence, including the following:

1. The trial population was generally younger and with fewer comorbidities than the UK population.
2. The company presented clinical effectiveness results from the overall trial population and also for a post hoc subgroup analysis (referred to as the 'licensed population' by the company); NSTEMI and STEMI with no history of TIA or stroke (80% of the trial population). This subgroup analysis provided more favourable efficacy results than that provided by the overall trial population.
3. There were numerical inconsistencies between the 2.5mg bd and 5mg bd groups such that for some individual outcomes the 2.5mg bd dose appeared to have greater efficacy than the 5mg bd dose.
4. High discontinuation rates from the trial (15.5% of randomised population) and a proportion of these patients were missing to follow up, with a potential risk for informative censoring leading to bias in the efficacy analyses.

Clinical need and practice

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. 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.

Expert opinion is 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. Due to its different mechanism of action, rivaroxaban could be a useful additional treatment option for some patients receiving clopidogrel plus aspirin or aspirin alone, although during the NICE review it was not possible to identify a particular subgroup of patients for whom it would be most suitable. There is some uncertainty as to when and how it would be best incorporated into the treatment pathway.

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.

Summary of the NICE TA Guidance

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 i.e. post NSTEMI or STEMI in patients with no prior history of stroke or TIA

Clinicians should carefully assess the person's risk of bleeding before treatment with rivaroxaban is started. The decision to start treatment should be made after an informed discussion between the clinician and the patient about the benefits and risks of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone

A decision on continuation of treatment should be taken no later than 12 months after starting treatment. Clinicians should regularly reassess the relative benefits and risks of continuing treatment with rivaroxaban and discuss them with the patient. Careful consideration should be given to whether treatment is continued beyond 12 months as experience of treatment with rivaroxaban up to 24 months is limited.

Most likely cost-effectiveness estimate (given as an ICER)

For the licensed population the incremental cost-effectiveness ratio (ICER) was calculated as £6,203 per quality-adjusted life year (QALY) gained.

Recommendations for PCN
Amber* on Traffic Light System and initiation by Consultant Cardiologist only.

A Transfer of Care sheet to primary care clinicians, containing assurance that bleeding risk assessment and informed discussion between patient and clinician has taken place.

A decision on duration of treatment should be made by the Consultant Cardiologist.

Specific Clinical Questions

1. Who will be responsible for stopping the rivaroxaban?
2. Should it be routinely stopped by the GP at 1 year unless otherwise requested by specialist. Note also that experience of treatment with rivaroxaban up to 24months (but beyond 12 months) is limited- would GPs be prepared to continue prescribing beyond 12 months for these patients if requested by specialist?
3. What subgroup of patients are likely to be treated with rivaroxaban locally?
4. Where does it sit within local treatment pathways?