Northern Treatment Advisory Group

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Rivaroxaban for acute coronary syndromes

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Summary

- Current long-term management following an acute coronary syndrome (ACS) focuses on prevention of further ischaemic events. Medical management consists of dual therapy with aspirin plus another anti-platelet drug such as clopidogrel for one year, followed by continued indefinite treatment with aspirin alone.

- The evidence for adding rivaroxaban 2.5 mg to dual-antiplatelet therapy comes primarily from a single randomised, double-blind, placebo-controlled trial involving over 15,000 people. Over 5,000 of the trial participants were assigned to rivaroxaban 5 mg, which has not been licensed for this indication and will not be considered in detail here.

- The trial found that rivaroxaban 2.5 mg significantly reduced the rate of the primary composite outcome of cardiovascular death, non-fatal MI or stroke compared to placebo. The difference was largely driven by a reduction in the incidence of death from cardiovascular causes. The rate of death from any cause was also significantly reduced with rivaroxaban. The NNT for two years to prevent one primary outcome event was 63.

- The rates of major bleeding, bleeding requiring medical attention and intracranial haemorrhage were all increased by rivaroxaban, but there was no difference in the incidence of fatal bleeding. The NNH for two years to cause one additional major bleed was 84, and the NNH for two years to cause one bleed requiring medical attention was 19. There was no difference in the incidence of non-bleeding adverse events.

- There is no available antidote for rivaroxaban. Bleeding must be managed symptomatically, and on an individual basis.

- The cost of rivaroxaban 2.5 mg is not yet available. The currently available 10 mg, 15 mg and 20 mg tablets all currently cost £764 per year. Using this as an estimate, addition of rivaroxaban 2.5 mg to therapy for ACS would cost between £58,000-£232,000 per year per 100,000 people, based on treating 25-100% of eligible patients. It is not yet known if any subgroup would derive particular benefit from rivaroxaban, or what the optimal duration of therapy is.

- Rivaroxaban is the first anticoagulant to be licensed in ACS. The other newer oral drugs, dabigatran and apixaban, were both found to have unfavourable efficacy and safety profiles in this indication.

Introduction

Acute coronary syndrome (ACS) is an umbrella term used to refer to a group of coronary heart diseases comprising:

- ST segment elevation myocardial infarction (STEMI)
- Non-ST segment elevation myocardial infarction (NSTEMI)
- Unstable angina

All three are caused by disruption of fatty arterial plaques, leading to thrombus formation and disruption of blood flow to the heart muscle.[1]

Initial management of a suspected ACS aims to reduce pain and distress, prevent recurrent ischaemia, and prevent or limit progression to acute myocardial infarction (where appropriate).[2] Long-term management aims to prevent further ACS events, other cardiovascular events such as stroke, or death from cardiovascular causes.[3]

In the UK, all patients with STEMI usually undergo a percutaneous coronary intervention (PCI) to restore blood flow, and receive either a bare metal or drug-eluting stent as part of the procedure.[4] PCI (or coronary artery bypass grafting, CABG) is also an option for those with NSTEMI, although those at lowest risk of future cardiovascular events may be offered medical management instead of revascularisation. Unstable angina is rare in the UK and often does not require revascularisation.

All people who undergo PCI receive 12 months dual antiplatelet therapy with aspirin plus another agent. Clopidogrel remains the most commonly prescribed antiplatelet besides aspirin, but ticagrelor is also licensed and NICE-approved.[4,5] Prasugrel is licensed in adults with ACS who are undergoing PCI, but NICE recommend that it is only used where immediate PCI for STEMI is required, stent thrombosis has occurred during clopidogrel treatment, or where the patient has diabetes.[6]

Coronary heart disease is the most common cause of death in the UK. It has a prevalence of 3.3% in England, and 4.1% in the North of England.[7,8] The incidence and prevalence of ACS are more difficult to estimate, but hospital episode statistics indicate that in 2012-13 there were 33,000 hospital admissions for unstable angina in England, and 76,000 admissions for acute myocardial infarction.[9]

Rivaroxaban (Xarelto®▼, Bayer) is a selective inhibitor of Factor Xa, a component of the clotting cascade. It is licensed, though not yet launched, for the prevention of atherothrombotic events in adults after an acute ACS with elevated cardiac biomarkers.[10] The marketing authorisation requires that it is co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine (NB, ticlopidine was discontinued in the UK several years ago but is still licensed in parts of Europe). Launch is expected in quarter 3 of 2014.[11] Rivaroxaban was rejected by the FDA for this indication in May 2012 and March 2013.

Clinical evidence

One randomised, double-blind, placebo-controlled, phase III trial (n = 15,526) has been published.[12] Participants were adults diagnosed with unstable angina, STEMI or NSTEMI. People aged less than 55 years were included only if they also had either diabetes mellitus or a previous MI. Exclusion criteria included risk factors for bleeding (e.g. platelet count <90 x 10^9/L or haemoglobin count <10g/dL), creatinine clearance less than 30 mL/min, and clinically significant gastrointestinal bleeding

within 12 months before randomisation. Patients were enrolled within seven days of hospital admission for ACS, but only once disease had been stabilised and initial management (including revascularisation) was complete.

Patients were randomised to receive rivaroxaban 2.5 mg or 5 mg twice daily or placebo, in addition to aspirin with or without a thienopyridine according to local or national guidelines. Patients with previous stroke or transient ischaemic attack (TIA) were excluded from the dual antiplatelet stratum. The primary endpoint was a composite of death from cardiovascular causes, non-fatal MI, or stroke of any type. The mean and maximum treatment durations were 13 and 31 months respectively, and results were presented as Kaplan-Meier estimates of outcomes after 24 months.

There were significantly fewer primary endpoint events with rivaroxaban 2.5 mg than placebo (see table 1). The difference was largely driven by a reduction in death from cardiovascular causes. From these data, the number needed to treat (NNT) for two years to prevent one additional cardiovascular death, MI or stroke is 63.

Table 1: primary outcome of the pivotal trial, and its components, in the modified intention-to-treat population[12]

	Events recorded		**Hazard ratio (95% CI)**	**NNT**
	Placebo (n=5,113)	**Rivaroxaban 2.5 mg (n=5,114)**		
Primary endpoint*	376	313	0.84 (0.72 to 0.97), p=0.02	63
Death from cardiovascular causes	143	94	0.66 (0.51 to 0.86), p=0.002	82
Non-fatal MI	229	205	0.9 (0.75 to 1.09), p=0.27	-
Stroke	41	46	1.13 (0.74 to 1.73), p=0.56	-
Death from any cause	153	103	0.68 (0.53 to 0.87), p=0.002	63

*Primary endpoint is the composite of death from cardiovascular death, non-fatal MI, or stroke.

NNT – Number needed to treat, i.e. number of people who would need to be treated with rivaroxaban for 2 years to prevent one outcome.

Rivaroxaban 5 mg has not been licensed for ACS, and so is not considered in detail here. Although this dose was associated with a significant improvement in the primary endpoint compared to placebo (313 vs. 376 events, p=0.03), neither death from cardiovascular causes (4.0% vs. 4.1%, p=0.63) nor death from any cause (4.4% vs. 4.5%, p=0.66) were significantly altered. This is in contrast to the rivaroxaban 2.5 mg group, in which the risk of death was significantly reduced compared to placebo (see table 1). The trial authors suggest that this difference may be due to a higher rate of fatal bleeding observed in the rivaroxaban 5 mg arm.

The trial had 90% power to detect a 22.5% reduction in relative risk between either dose of rivaroxaban and placebo. The observed relative risk reduction was 15%, meaning the trial may have been under-powered.

Drop-out was greater than 25% in each treatment arm, and the primary reasons for discontinuation were death and withdrawal of consent.[3] It is unclear how many people withdrew consent due to adverse effects.

The trial used a modified intention-to-treat (mITT) population which only followed patients until 30 days after treatment discontinuation. A standard intention-to-treat analysis, including data from all patients from randomisation until trial end, gave similar results.

At the end of the trial, information on vital status was missing for 8.4% of trial participants. Although this is concerning, the EMA found that in order to change the trial result, outcomes for the missing patients would have to be so different to those with full follow-up as to be implausible.[3] In contrast, the FDA declined approval of rivaroxaban for ACS in May 2012 due to concerns regarding the missing data, as well as use of the mITT analysis, polypharmacy and bleeding risk.[13] Approval was declined again in March 2013 although the reasons on that occasion are not yet clear.[11]

In addition to the above problems, a number of factors limit the applicability of the trial data to UK clinical practice:

- The mean age of participants was 62 years and approximately one third were over 65, contrasting with a mean age of 71 for patients with acute MI in England.[9]
- Roughly 75% were male, compared to roughly 60% of patients in England.[9]
- Due to the trial exclusion criteria, patients were likely to be at lower risk of bleeding than is typical in the UK.
- Mean duration of treatment was 13 months and the maximum was 31, meaning patients may have remained on clopidogrel therapy longer than is typical in the UK. Usual UK practice is to give aspirin and clopidogrel for one year, and aspirin alone indefinitely thereafter.
- There are no trial data available on combining rivaroxaban with other drugs used in ACS such as ticagrelor or prasugrel.
- The licensed indication includes the use of rivaroxaban an aspirin without a thienopyridine, a combination used by only 7% of participants in the pivotal trial. Rivaroxaban tended to be more effective than placebo in these patients, but the difference was not significant (HR 0.69, 95% CI 0.45 - 1.05).[12] There were insufficient patients in this group to determine whether there was any difference in bleeding risk.

Finally, trial conduct and reporting make it difficult to determine the optimum duration of rivaroxaban therapy post-ACS. In particular, the use of Kaplan-Meier estimates to two years to report the primary outcome means that no data are available on the efficacy and safety of rivaroxaban use for any other period of time.

Safety

The primary safety endpoint was major bleeding not related to CABG, defined as symptomatic cranial haemorrhage or clinically overt haemorrhage associated with a drop in haemoglobin of at least 5g/dL.[12] Other bleeding events were also recorded Major bleeding was significantly more common with rivaroxaban 2.5 mg than placebo, as were bleeding requiring medical attention and intracranial haemorrhage

(see table 2). There was no significant difference in the incidence of fatal bleeding or minor bleeding.

Rates of adverse events unrelated to bleeding were comparable between rivaroxaban and placebo. The most commonly reported events were co-morbidities that were not unexpected given the trial population, such as chest pain, heart failure and hypertension.[14]

Table 2: bleeding events in the pivotal trial[12]

	Events recorded		Hazard ratio (95% CI)	NNH
	Placebo (n=5,113)	**Rivaroxaban 2.5 mg (n=5,114)**		
Major bleeding not associated with CABG	19	65	3.46 (2.08 to 5.77), p<0.001	84
Minor bleeding	20	32	1.62 (0.92 to 2.82), p=0.09	-
Bleeding requiring medical attention	282	492	1.79 (1.55 to 2.07), p<0.001	19
Intracranial haemorrhage	5	14	2.83 (1.02 to 7.86), p=0.04	500
Fatal bleeding	9	6	0.67 (0.24 to 1.89), p=0.45	-

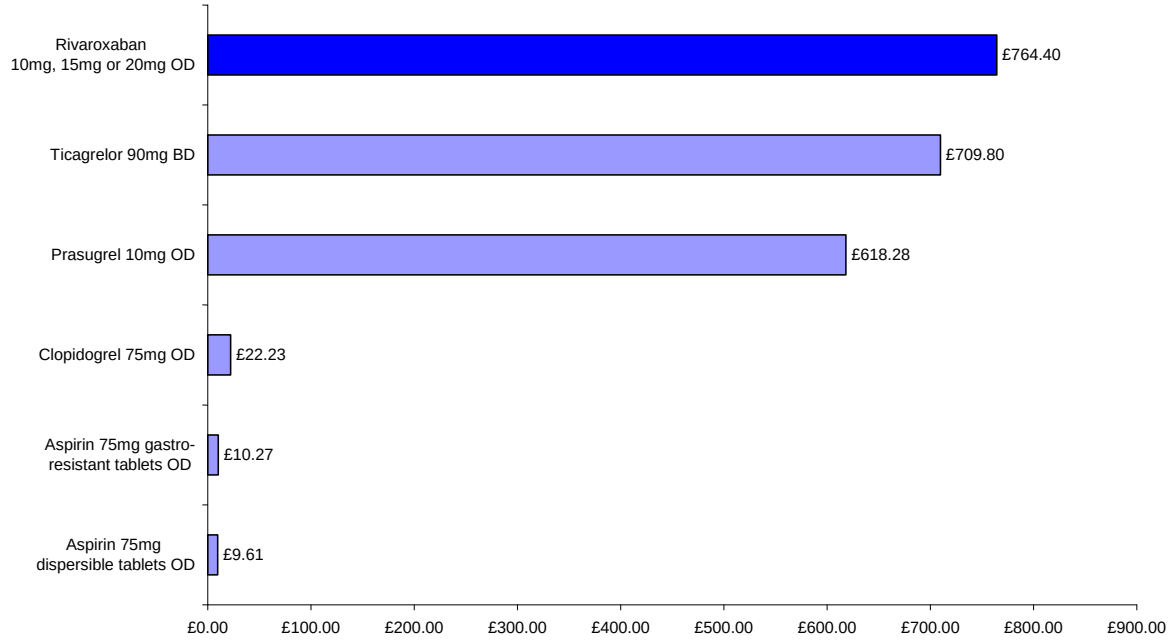
NNH – Number needed to harm, i.e. number of people who would need to be treated with rivaroxaban for 2 years to cause one additional bleeding event.

Cost analysis

Rivaroxaban 2.5 mg tablets are not yet available, and the manufacturer has declined to provide a price. All strengths currently available (10 mg, 15 mg & 20 mg) cost £2.10 per tablet (£764 per year). The following estimates assume that rivaroxaban 2.5 mg will also cost £764 per year.

Rivaroxaban is administered at a dose of 2.5 mg twice daily for ACS, in contrast to other indications which require once daily dosing. It is licensed for use in ACS in addition to existing treatments, therefore the cost of prescribing will be in addition to the current spend. Current standard care costs £31.84 per patient per year for aspirin plus clopidogrel, or £719.41 for aspirin plus ticagrelor

Figure 1: annual cost per patient of drugs for ACS (Drug Tariff, May 2014)



NICE estimate that 304 people per 100,000 population are diagnosed with ACS each year. It is currently unclear if any particular sub-group of people with ACS would derive particular benefit from addition of rivaroxaban, therefore table 3 below estimates the cost of treating between 25% and 100% of the eligible population. It also estimates the number of cardiovascular deaths, MIs and strokes that may be prevented, and major bleeds that may be caused, based on the outcomes of the pivotal trial. It should be noted that risks and benefits may be different in the general population than among the carefully selected trial participants.

The cost of management for bleeding events is difficult to estimate, and has not been included here. However it should be noted that, given the NNTs presented above, treating 25% of the eligible population (approximately 76 people) with rivaroxaban will likely prevent one cardiovascular death, MI or stroke (NNT 63), but cause four bleeds which require medical attention (NNH 19).

Table 3: estimated costs per 100,000 population of adding rivaroxaban to therapy for ACS, assuming all eligible people receive aspirin plus clopidogrel

Outcome	Percentage of eligible population treated with rivaroxaban			
	25%	50%	75%	100%
Annual cost of aspirin 75 mg (dispersible) plus clopidogrel 75 mg per person	£31.84	£31.84	£31.84	£31.84
Annual cost of aspirin plus clopidogrel per 100,000 population	£9679.36	£9679.36	£9679.36	£9679.36
Annual cost of rivaroxaban 2.5 mg per person (estimated)	£764	£764	£764	£764
Additional cost of rivaroxaban per 100,000 population	£58,094	£116,189	£174,283	£232,378
Total cost of aspirin + clopidogrel + rivaroxaban per 100,000 population	£67,774	£125,868	£183,963	£242,057
CV events* prevented	1 to 2	2 to 3	3 to 4	4 to 5
Cost to prevent one CV event*	£48,157	£48,157	£48,157	£48,157
Major bleeds caused	0 to 1	1 to 2	2 to 3	3 to 4

*CV events – composite of cardiovascular death, MI or stroke.

Patient impact

Since anticoagulants have not routinely been added to therapy post-ACS, the patient impact of rivaroxaban is difficult to predict. Safety concerns, particularly the risk of bleeding, are likely to be a major factor. Counselling will be required on the appropriate management of any bleeding events.

The problem of polypharmacy should also be considered, since the target population are likely to already be receiving several medicines. In the pivotal trial two-thirds of patients were taking a beta-blocker, nearly 40% had an ACE-inhibitor or angiotensin-receptor blocker, and over 80% were taking a statin.

Points to consider

The evidence for addition of rivaroxaban 2.5 mg to standard therapy for secondary prevention of atherothrombotic events following ACS is based on a single pivotal trial. The trial found that rivaroxaban significantly reduced the incidence of the composite outcome of cardiovascular death, non-fatal MI and stroke compared to placebo. The number needed to treat for two years to prevent one primary outcome event was 63.

Addition of rivaroxaban to therapy also significantly increased the rate of major bleeding, and the number needed to treat for two years to cause one additional major bleed was 84.

There is no antidote available for rivaroxaban, and bleeding must be managed on an individual basis.[10] Symptomatic treatment such as mechanical compression, surgical haemostasis, fluid replacement, haemodynamic support and blood products may be required.

The APPRAISE-2 trial was designed to assess apixaban 5 mg, another Factor Xa inhibitor, for secondary prevention in ACS. That trial found no significant reduction in recurrent ischaemic events, but there was an increase in the number of major bleeding events. The investigators in the rivaroxaban trial speculate that the difference in observed outcomes is due in part to differences in trial populations, specifically the exclusion of patients with previous transient ischaemic attack or ischaemic stroke.[12]

Dabigatran, a direct thrombin inhibitor, has also been shown to be unsuitable in ACS. A meta-analysis published in 2012 found that when data from all available trials were aggregated dabigatran was associated with an increased risk of MI and ACS.[15]

Rivaroxaban is therefore the only one of the newer oral anticoagulants to be shown to be useful in this indication. The EMA felt that the pivotal trial must therefore be robust and compelling, and that the presented data met that requirement.[3] The FDA disagreed, and have twice rejected rivaroxaban in this indication. A final FDA decision has not yet been made.[11]

ACS has an incidence of approximately 304 per 100,000 population. It is not clear if any sub-group of people would derive particular benefit from rivaroxaban, nor is the optimal length of therapy known. Providing aspirin plus clopidogrel for all people with ACS currently costs roughly £9,700 per 100,000 people, and it is estimated that addition of rivaroxaban for 25-100% of eligible people would cost an additional £58,000-232,000 per year.

Author's declaration. The lead author has no relevant interests to declare.

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