Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

Published: July 2018

Rivaroxaban with or without aspirin in people with stable peripheral or carotid artery disease

A large, multicentre randomised control trial looked at the use of a combination of low-dose rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) in people with stable peripheral arterial disease (PAD) or carotid artery disease (CAD). Combination therapy reduced the composite primary outcome of cardiovascular death, stroke or myocardial infarction and increased the risk of major bleeds compared with aspirin (100 mg once daily) alone.

Rivaroxaban 2.5 mg twice daily is not licensed for the prevention of occlusive vascular events in people with PAD or CAD. Clopidogrel is the standard antiplatelet used in PAD and cerebrovascular disease and by not having a comparison with clopidogrel in the study, the relevance of the results to UK practice is limited at present. NICE has issued guidance on clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events and peripheral arterial disease: diagnosis and management.

Overview and current advice

Peripheral arterial disease (PAD) and carotid artery disease (CAD) are caused by atherosclerosis. PAD mainly occurs in arteries that supply blood to the legs and people with PAD are at risk for major adverse limb events such as severe limb ischaemia and amputation (Gerhard-Herman et al. 2017). The carotid arteries supply blood to the brain and people with CAD are at risk of a stroke or a transient ischemic attack (TIA). PAD is strongly associated with cardiovascular disease at other sites, mainly coronary and cerebrovascular. The modifiable and non-modifiable risk factors for PAD are shared with those for cardiovascular disease. Many individuals with PAD will have evidence of cardiovascular disease, and people diagnosed with PAD are at high risk of further cardiovascular events such as stroke and myocardial infarction (NICE guideline peripheral arterial disease: diagnosis and management).

The NICE guideline on peripheral arterial disease: diagnosis and management, recommends that all people with PAD are offered information, advice, support and treatment regarding the secondary prevention of cardiovascular disease, in line with published NICE guidance on myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease.

For people who have had an occlusive vascular event, or who have established PAD, NICE has issued guidance on clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. The guidance recommends clopidogrel as an option to prevent occlusive vascular events for people who have had an ischaemic stroke or who have PAD or multivascular disease (people with cardiovascular disease who have disease in more than one vascular site).
Rivaroxaban is a direct oral anticoagulant that did not have a licence for preventing occlusive vascular events in PAD or CAD at the time of writing this medicines evidence commentary (July 2018). NICE has issued a number of technology appraisals (see TA170, TA261, TA287, TA256 and TA335) for its licensed indications which include treatment and secondary prevention of recurrence of deep vein thrombosis and pulmonary embolism, and prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (see the summary of product characteristics and key therapeutic topic on anticoagulants for more information). The dose of rivaroxaban investigated in the study described in the new evidence section below (2.5 mg twice daily) is only licensed for the prevention of atherothrombotic events in adults after an acute coronary syndrome with elevated cardiac biomarkers in combination with aspirin alone or with aspirin and clopidogrel or ticlodipine (summary of product characteristics: Xarelto 2.5 mg).

The NICE Pathway on lower limb peripheral arterial disease and stroke brings together all related NICE guidance and associated products on PAD and stroke in a set of interactive topic-based diagrams. The Clinical Knowledge Summaries information on peripheral arterial disease and stroke and TIA gives a general overview of prescribing considerations.

New evidence

The study by Anand et al. 2018 aimed to identify whether low-dose rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily or rivaroxaban 5 mg twice daily was more effective than aspirin 100 mg once daily in reducing major adverse cardiovascular events and major adverse limb events in people with stable PAD or CAD who were in the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial. COMPASS was a multicentre, double-blind, randomised controlled trial (RCT) comparing low-dose rivaroxaban plus aspirin or rivaroxaban with aspirin for prevention of cardiovascular death, myocardial infarction, and stroke in people with stable coronary artery disease or PAD who were receiving other proven therapies (Bosch et al. 2017). COMPASS enrolled 27,395 participants from 602 centres in 33 countries into the overall trial.

The study by Anand et al. 2018 included 7,470 participants recruited from 558 centres across 33 countries, including the UK. Participants either had a history of PAD of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease) or carotid artery disease (previous carotid artery revascularisation or asymptomatic carotid artery stenosis of at least 50%), or coronary artery disease with an ankle–brachial index (ABI) of less than 0.90. The mean age of the participants was approximately 67 years and 72% were male; 81% of participants met the inclusion criteria for symptomatic PAD including 55% with symptomatic PAD of the lower extremities and 26% with carotid artery disease. In addition, 19% of participants were classed as having asymptomatic PAD and were included in the study as they met the inclusion criteria of coronary artery disease (ABI of less than 0.90). There was a history of coronary artery disease in 66% of the population. Participants were also taking other medicines such as lipid lowering treatment, angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers, beta-blockers and proton pump inhibitors (PPIs). Around 30% of participants in each group were taking non-study PPIs. Participants who were not already taking a PPI were also randomly assigned to receive pantoprazole or an equivalent placebo. The number of participants taking the study PPI in each study group was not reported by Anand et al. 2018.

Participants with a high risk of bleeding, stroke within 1 month, a history of haemorrhagic or lacunar stroke, severe heart failure with a known ejection fraction of less than 30%, or estimated glomerular filtration rate of less than 15 mL/min were excluded. Also, people who needed dual antiplatelet therapy, other non-aspirin antiplatelet therapy, oral anticoagulant therapy, strong inhibitors of CYP3A4, strong inducers of CYP3A4, or other medicines with known interactions with rivaroxaban were excluded from the trial.
After a 30-day run-in period (during which participants took aspirin 100 mg daily), participants were randomised to receive either oral rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily (n=2,492), rivaroxaban 5 mg twice daily (n=2,474), or aspirin 100 mg once daily (n=2,504). The rivaroxaban-based groups were compared with the aspirin control group. The median duration of follow-up was 21 months. The characteristics of those with PAD were reported to be well balanced between the 3 treatment groups.

The primary outcome was the composite of cardiovascular death, myocardial infarction or stroke, which occurred in 5% (126/2492) of the low-dose rivaroxaban plus aspirin group compared with 7% (174/2504) of the aspirin group (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.57 to 0.90, p=0.0047). Rivaroxaban alone compared with aspirin alone did not significantly reduce the primary composite endpoint (6% [149/2474] versus 7%, HR 0.86, 95% CI 0.69 to 1.08, p=0.19). There was no statistically significant difference reported in the individual outcomes of myocardial infarction, cardiovascular death or death when low dose rivaroxaban plus aspirin or rivaroxaban alone was compared with aspirin. However, a statistically significant difference in the number of people with stroke was found when low-dose rivaroxaban plus aspirin was compared with aspirin alone (1% [25/2492] versus 2% [47/2504], HR 0.54, 95% CI 0.33 to 0.87, p-value not reported).

Fewer participants in the low-dose rivaroxaban plus aspirin group compared with the aspirin alone group had major adverse limb events (1% [30/2492] versus 2% [56/2504], HR 0.54, 95% CI 0.35 to 0.84, p=0.0054) or major amputations (less than 1% [5/2492] versus 1% [17/2504], HR 0.30, 95% CI 0.11 to 0.80, p=0.011). There was no statistically significant difference between the 2 groups for chronic limb ischaemia (HR 0.67, 95% CI 0.35 to 1.26, p=0.21). A similar trend was seen in the rivaroxaban alone group compared with aspirin alone group for these outcomes. However there was no statistically significant difference for major amputations between the 2 groups.

The primary safety outcome was major bleeding, measured by using the modified International Society on Thrombosis and Hemostasis (ISTH) criteria for major bleeding, defined as the composite of bleeding that was fatal, symptomatic bleeding into a critical organ, surgical site requiring reoperation, or requiring hospitalisation (including presentation to an acute care facility without an overnight stay). A statistically significant increase in major bleeding was seen in the low-dose rivaroxaban plus aspirin group compared with the aspirin alone group (3% [77/2492] versus 2% [48/2504], HR 1.61, 95% CI 1.12 to 2.31, p=0.0089). A similar finding was reported in participants in the rivaroxaban alone group when compared with aspirin alone (3% [79/2474] versus 2%, HR 1.68, 95% CI 1.17 to 2.40, p=0.0043). The most common site of bleeding for all groups was gastrointestinal.

**Commentary**

Commentary provided Professor Gerry Stansby, Professor of Vascular Surgery, Newcastle upon Tyne

People with PAD are more likely to suffer a cardiovascular death, stroke or myocardial infarction than they are to lose their limb from amputation. This is a reflection of the fact that the vast majority of them will have widespread atherosclerosis, either symptomatic or asymptomatic at other sites including the heart and brain. In the management of PAD the long-term reduction of generalised cardiovascular risk is more important than a focus on risk to the lower limbs alone. Any new strategy such as the combination of a low-dose direct oral anticoagulant with aspirin is of potential interest. However it is important to be aware that risk reduction in both PAD and cerebrovascular disease also critically involves the use of antihypertensives, statins and smoking cessation, and that all antiplatelets and anticoagulants will increase the risk of clinically significant bleeding. Rivaroxaban 2.5 mg twice daily did not have a licence for preventing occlusive vascular events in PAD or CAD at the time of writing this commentary (July 2018).

Clopidogrel 75 mg daily has been used for some time as the main antiplatelet agent in PAD and cerebrovascular disease rather than aspirin 75 mg daily. In the CAPRIE study, on which NICE
guidance in relation to antiplatelet therapy in PAD was largely based, clopidogrel was shown to be significantly better than aspirin at reducing the risk of a first occurrence of ischaemic stroke, myocardial infarction or vascular death in people with atherosclerotic vascular disease manifested as either recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease. The use of clopidogrel is both effective and cost-effective and represents the current gold standard against which newer strategies should be compared, not aspirin.

In most large RCTs of antiplatelet agents the rates of clinical major bleeding are relatively low, which may be due to the exclusion of people at higher risk of bleeding in the studies. It is therefore important not to underestimate the potential risks of bleeding, principally gastrointestinal bleeding, with wider clinical use outside the trial context. This may offset the value and cost effectiveness of a strategy of using combination therapy with an anticoagulant and antiplatelet. In the study by Anand et al. 2018, major bleeding was increased in the rivaroxaban based groups compared with aspirin alone group despite some participants also taking non-study and study PPIs. It is unclear in the study if the use of PPIs may have affected the risk of bleeding in all the treatment groups. There is now an increasing use of PPIs in people taking long-term aspirin therapy because of bleeding risk, but not usually with clopidogrel. An increase in the use of aspirin, particularly if combined with low-dose rivaroxaban, and the use of PPIs alongside aspirin will have cost implications and potentially issues with compliance.

The COMPASS trial has provided some interesting results. However, by not having a comparison with clopidogrel its relevance to current UK practice is limited at present.

Declaration of interests:
Professor Gerry Stansby declared no interests.

Study sponsorship
The study was sponsored by Bayer AG, the manufacturer of rivaroxaban.

References

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