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Rivaroxaban (Xarelto) in combination with aspirin for prevention of major cardiovascular events in coronary or peripheral artery disease

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LAY SUMMARY

Coronary artery disease (CAD) is the most common type of heart disease. CAD occurs when the arteries that supply blood to the heart become narrowed by the build-up of fat (cholesterol) and other material (known as plaque) on the inner walls of the arteries. As a result, the heart cannot get enough blood and oxygen supply it needs. This can lead to chest pain (angina) or a heart attack.

Peripheral artery disease (PAD) is caused by plaque building in peripheral arteries (i.e. arteries outside of the heart), such as in the legs. This limits blood flow, resulting in leg pain which may at first be only when walking or exercising, but may become a constant pain as the disease progresses. In patients with CAD or PAD, there is a risk of the plaques coming away from the artery wall and blocking major blood vessels supplying the heart or brain. This may result in a "cardiovascular event" such as a heart attack or stroke. These may be fatal, or result in disability.

The best way to help prevent a cardiovascular event is to exercise regularly, avoid smoking, eat a healthy diet, maintain a healthy weight, and avoid drinking too much alcohol, although medications may also be prescribed. Rivaroxaban and aspirin are drugs that reduces blood clots in blood vessels and are currently being given to some patients with CAD and PAD. The combination of rivaroxaban with aspirin is being developed as a more effective treatment. If licensed, this combination will offer a new option for the prevention of major cardiovascular events.

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TARGET GROUP

Prevention of major adverse cardiovascular events (MACE) (including myocardial infarction, stroke, cardiovascular death), prevention of acute limb ischaemia and mortality, in patients with established coronary artery disease (CAD) or peripheral artery disease (PAD).

TECHNOLOGY

DESCRIPTION

Rivaroxaban (Xarelto; BAY-59-7939) is a Factor Xa inhibitor. The drug blocks Factor Xa, an enzyme that is involved in the production of thrombin. Thrombin is central to the process of blood clotting. The activated Factor X (Factor Xa) is a central component of the prothrombinase complex, which converts large amounts of prothrombin (Factor II) to thrombin, described as the "thrombin burst". By blocking Factor Xa, the levels of thrombin decreases, which reduces the risk of blood clots forming in the veins and arteries, and also treats existing clots.[1]

Rivaroxaban is licensed in the EU for the following indications:[2]

- Prevention of venous thromboembolism (VTE, the formation of blood clots in the veins) in patients who are undergoing surgery to replace a hip or knee
- Prevention of stroke caused by a blood clot in the brain and systemic embolism (a blood clot in a blood vessel) in patients with non-valvular atrial fibrillation (irregular rapid contractions of the upper chambers of the heart)
- Treatment of deep-vein thrombosis (DVT, a blood clot in a deep vein, usually in the leg) and pulmonary embolism (a clot in a blood vessel supplying the lungs), and to prevent DVT and pulmonary embolism from re-occurring
- Prevention of atherothrombotic events (problems caused by blood clots and hardening of the arteries) after an acute coronary syndrome. Acute coronary syndrome is a group of conditions that includes unstable angina (a severe type of chest pain) and heart attack. It is used together with antiplatelet medicines, which prevent the blood from clotting.

The most common side effects of rivaroxaban (seen in between 1 and 10 patients in 100) are anaemia, dizziness, headache, bleeding in various parts of the body, hypotension (low blood pressure), haematoma (collection of blood under the skin), pain in the stomach and belly, dyspepsia (heartburn), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, ecchymosis (bruising), pain in the extremities, decreased kidney function, fever, peripheral oedema (swelling, especially of the ankles and feet), decreased general strength and energy, increased levels of some liver enzymes in the blood and oozing of blood or fluid from the surgical wound in patients undergoing surgery.[2] For further details about adverse events associated with different dosages of rivaroxaban, see the electronic Medicines Compendium (eMC) website.[3]

In the phase III clinical trial (COMPASS, NCT01776424), rivaroxaban is given orally as 2.5mg tablet twice daily in combination with aspirin given orally as a 100mg tablet once daily. The subjects are treated on an ongoing basis.[4]

Rivaroxaban is also in phase III stage of development in a large number of trials, mainly involving the reduction of the risk of thrombotic vascular events or cardiovascular events in subjects with a range of cardiovascular conditions, or for use related to surgical procedures.[1]

Rivaroxaban is also in pre-registration stage of development for venous thromboembolism and acute coronary syndrome.[1]

Rivaroxaban in combination with aspirin is also in phase III stage of development for use following successful transcatheter aortic valve replacement surgery, and for subjects with atrial fibrillation who undergo percutaneous coronary intervention.[5] Low-dose rivaroxaban in combination with aspirin alone or aspirin and clopidogrel is licensed for the prevention of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers.[6]

INNOVATION and/or ADVANTAGES

If licensed, rivaroxaban in combination with aspirin will offer an additional treatment option for prevention of MACE in patients with CAD or PAD.

DEVELOPER

Bayer Plc

PATIENT GROUP

BACKGROUND

Stable coronary artery disease (CAD) causes reduced stress and exercise tolerance due to narrowing of major coronary arteries from atherosclerotic plaque formation.[7] It is characterised by episodes of reversible myocardial demand/supply mismatch, related to ischaemia or hypoxia, which are usually inducible by exercise, emotion or other stress and reproducible - but, which may also be occurring spontaneously. Such episodes of ischaemia/hypoxia are commonly associated with transient chest discomfort (angina pectoris). Stable CAD also includes the stabilised, often asymptomatic, phases that follow acute coronary syndrome.[8]

Peripheral artery disease (PAD) is caused by plaque building in peripheral arteries, limiting blood flow to the extremities.[7,9] One of the most common and earliest manifestations of PAD is intermittent claudication (lower leg pain elicited by exertion and relieved by rest). As the disease progresses, insufficient oxygen and nutrients to the tissue can result in complications such as chronic leg pain, skin ulceration, gangrene and eventually amputation. Patients with PAD may experience loss of autonomy, disability, emotional distress and poor quality of life.[9]

In patients with established atherosclerotic vascular disease, plaque rupture may lead to secondary cardiac events such as myocardial infarction or stroke, which can result in death or permanent disability.[7] Prognosis can vary considerably within the population of patients with CAD; conventional risk factors for the development of CAD (such as obesity, smoking, sedentary lifestyle, diabetes) have an adverse influence on prognosis, although appropriate treatment can reduce these risks.[8]

CLINICAL NEED and BURDEN OF DISEASE

There were 1,839,330 patients on the coronary heart disease (CHD) register in England in 2015/16 and 352,545 on the PAD register in the same period.[10] It is estimated that 182,094 people had CAD with concomitant PAD.[11] Population excluding overlap therefore equals (1,839,330 + 352,545) – 182,094 = 2,009,781.

Key exclusion criteria in the trial included the need for dual antiplatelet therapy or oral anticoagulation, severe heart failure and severe renal impairment. These are estimated to be 1.4%,

7.1%, 2.5% and 3.5% of CAD patients respectively. This reduces the eligible population to an estimated 1,718,363.[7,11,12] Using a population for England of 57,555,947 this equates to 3,037 patients per 100,000 population.

The company anticipates that rivaroxaban will be considered only in patients who have the most advantageous benefit:risk profile, and have assumed this group represents about 25% of the total eligible population under the anticipated license i.e. 437,100 patients in England.[a]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Ticagrelor for preventing atherothrombotic events after myocardial infarction (TA420). December 2016.
- NICE technology appraisal. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. (TA385). February 2016.
- NICE technology appraisal. Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (TA335). March 2015.
- NICE technology appraisal. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (TA210). December 2010.
- NICE technology appraisal. Drug-eluting stents for the treatment of coronary artery disease (TA152). July 2008.
- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). July 2014, updated September 2016.
- NICE clinical guideline. Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (CG172). November 2013.
- NICE clinical guideline. Peripheral arterial disease: diagnosis and management (CG147). August 2012. Due for update February 2018.
- NICE evidence summary. Symptoms of peripheral arterial disease: ramipril (ESUOM45). June 2015.
- NICE quality standard. Cardiovascular risk assessment and lipid modification (QS100). September 2015.
- NICE quality standard. Secondary prevention after a myocardial infarction (QS99). September 2015.
- NICE public health guidance. Cardiovascular disease prevention (PH25). June 2010.
- NICE public health guidance. Cardiovascular disease: identifying and supporting people most at risk of dying early (PH15). September 2008.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Vascular Services (Adults). A04/S/a.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of cardiovascular disease (SIGN 149). July 2017.[13]

[a] Information supplied by company

- European Society of Cardiology. Stable Coronary Artery Disease (Management of): ESC Clinical Practice Guidelines. 2013.[8]

CURRENT TREATMENT OPTIONS

The best way to help prevent a cardiovascular event is to exercise regularly, avoid smoking, eat a healthy diet, maintain a healthy weight, and avoid drinking too much alcohol.[14]

In addition to lifestyle changes, as secondary prevention for patients with cardiovascular disease NICE also recommends lipid modification therapy:

- statin treatment (starting with atorvastatin)
- ezetimibe monotherapy if statin therapy is contraindicated
- evolocumab or alirocumab if statin treatment is insufficient to reduce low-density lipoprotein concentrations to specified thresholds[15]

Antiplatelet therapy may also be offered to patients with PAD; the two therapies offered most commonly are low-dose aspirin and clopidogrel.[14] Despite increased risk of bleeding associated with long-term use of low-dose aspirin, this treatment regimen has proved to be effective in reducing the risk of serious vascular events in patients with acute or previous vascular disease. In patients with PAD, however, it is not clear whether the benefit of preventive aspirin treatment outweighs the increased frequency of bleeding events.[7]

EFFICACY and SAFETY

Trial	COMPASS, NCT01776424; rivaroxaban + aspirin vs rivaroxaban + placebo vs aspirin + placebo; phase III
Sponsor	Bayer Plc
Status	Published
Source of Information	Abstract[16], Trial registry[4]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled
Participants	n=27,395; coronary or peripheral artery disease (CAD or PAD); patients with CAD must be aged ≥65 yrs or aged <65 yrs with documented atherosclerosis or revascularisation involving at least 2 vascular beds, or at least 2 additional risk factors
Schedule	Randomised to: • rivaroxaban 2.5mg, twice daily, orally, tablet and aspirin 100mg, once daily, orally; • rivaroxaban 2.5mg, twice daily, orally, tablet and aspirin placebo, once daily, orally; • rivaroxaban placebo, twice daily, orally, table and aspirin 100mg, once daily, orally Subjects who are not on a proton pump inhibitor (PPI) also randomised to pantoprazole or pantoprazole placebo.
Follow-up	Mean duration of treatment was 23 mths, maximum duration 47 mths.

	Follow-up 5 years.[b]
Primary Outcomes	• Time from randomisation to first occurrence of either myocardial infarction (MI), stroke or cardiovascular death [Time Frame approx. 5 yrs] • Time from randomisation to the first occurrence of major bleeding (modified International Society on Thrombosis and Haemostasis) [Time Frame approx. 5 yrs]
Secondary Outcomes	• Time from randomisation to first occurrence of either coronary heart disease death, MI, ischaemic stroke, acute limb ischaemia [Time Frame approx. 5 yrs] • Time from randomisation to first occurrence of either cardiovascular death, MI, ischaemic stroke, acute limb ischaemia [Time Frame approx. 5 yrs] • Time from randomisation to first occurrence of all-cause mortality [Time Frame approx. 5 yrs]
Key Results	The study was stopped for superiority of the rivaroxaban+aspirin group after a mean follow-up of 23 mths. The primary outcome occurred in fewer patients in the rivaroxaban+aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; P<0.001; z=−4.126), but major bleeding events occurred in more patients in the rivaroxaban+aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban+aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group. Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg once daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events.
Adverse effects (AEs)	Patients assigned to rivaroxaban+aspirin had more major bleeding events than those assigned to aspirin alone. Other adverse effects were not specified in the abstract.

ESTIMATED COST and IMPACT

COST

Rivaroxaban is already marketed in the UK; the NHS indicative price for a pack of 56 x 2.5mg tablets is £50.40 (£0.90 per tablet).[17]

[b] Information supplied by company

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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