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HEALTH TECHNOLOGY BRIEFING APRIL 2019

Rivaroxaban for reducing the risk of major thrombotic vascular events in symptomatic peripheral arterial disease patients with a recent lower extremity revascularisation procedure

NIHRIO ID	12541	**NICE ID**	9557
Developer/Company	Bayer AG	**UKPS ID**	638690

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Rivaroxaban is in clinical development for reducing the risk of major thrombotic vascular events in patients with symptomatic peripheral arterial disease (PAD) who have undergone a recent lower extremity revascularisation procedure. PAD is a common condition in which a build-up of fatty deposit in the arteries (atherosclerosis) reduces blood supply to the limbs. Many people with PAD have no symptoms but some people develop pain in their legs which may require surgery (revascularisation). People with PAD that undergo this procedure have significantly increased risks of major thrombotic vascular events like heart attack and stroke.

Rivaroxaban is an already approved oral medicine used for the prevention of thrombotic vascular events in different types of artery diseases including PAD. It acts by blocking specific pathways involved in the process of blood clots within blood vessels, reducing the risk of a major vascular event. Aspirin alone is the current standard treatment in patients with PAD undergoing revascularization procedures but its risk reduction may not be adequate. If licensed rivaroxaban will potentially be an option as an add-on therapy in this patient group.

PROPOSED INDICATION

To reduce the risk of major thrombotic vascular events in symptomatic peripheral artery disease (PAD) patients with a recent lower extremity revascularisation procedure - add-on therapy to standard of care.[a]

TECHNOLOGY

DESCRIPTION

Rivaroxaban (Xarelto, BAY-59-7939) is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.[1] Thrombin is central to the process of blood clotting. By blocking factor Xa, the levels of thrombin decrease, which reduces the risk of blood clots forming in the veins and arteries, and also treats existing clots.[2]

Different mechanisms have been proposed to explain the vascular protection associated with rivaroxaban. It significantly reduces the formation, progression and destabilisation of cholesterol plaques through an anti-inflammatory mechanism, blocking macrophage activation and it inhibits thrombotic formation over unstable plaques. It also promotes viability, growth and migration of endothelial cells, protects them from the proinflammatory effects of factor Xa, improving endothelial function and facilitates vascular neoformation.[3]

Rivaroxaban is in clinical development for reducing the risk of major thrombotic vascular events in subjects with symptomatic PAD undergoing peripheral revascularization procedures of the lower extremities. In the phase III clinical trial (VOYAGER PAD; NCT02504216), rivaroxaban is administered as an oral tablet at a dose of 2.5mg twice daily. The treatment duration was not reported.[4]

INNOVATION AND/OR ADVANTAGES

Rivaroxaban is already licensed for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.[1] However, in patients with PAD undergoing revascularization procedures, the current standard of care is aspirin alone, which may not be adequate as it only reduces the risk of cardiovascular events by about 25%.[5]

The addition of rivaroxaban (2.5 mg twice daily) to aspirin has the potential to further reduce the risk for cardiovascular death, myocardial infarction, stroke, acute limb ischaemia, and amputation in PAD patients undergoing revascularization.[5]

Antiplatelet therapies (such as aspirin) and rivaroxaban have complementary mechanisms of action and when combined have been shown to improve outcomes in patients with acute coronary syndrome.[1,a]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Rivaroxaban is currently licenced in the EU/UK for:[1,6]

- Prophylaxis of venous thromboembolism following knee replacement surgery
- Prophylaxis of venous thromboembolism following hip replacement surgery
- Initial and continued treatment of deep vein thrombosis and pulmonary embolism

[a] Information provided by Bayer plc on UK PharmaScan

- Prophylaxis of recurrent deep vein thrombosis and pulmonary embolism
- Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischemic attack, age > 75 years or diabetes mellitus
- Prophylaxis of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers (in combination with aspirin alone or aspirin and clopidogrel)
- Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events (in combination with aspirin)

The most common side effects with rivaroxaban (seen in between 1 and 10 patients in 100) are bleeding in various parts of the body, anaemia, dizziness, headache, hypotension (low blood pressure), haematoma (collection of blood under the skin), pain in the stomach and belly, dyspepsia (indigestion), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, ecchymosis (bruising), pain in the arms and legs, 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 a surgical wound.[2]

Rivaroxaban is in phase III clinical development for thromboprophylaxis in paediatric patients and in phase II for thrombosis prophylaxis in bariatric surgery.[7]

PATIENT GROUP

DISEASE BACKGROUND

Peripheral artery disease (PAD) also referred to as atherosclerotic arterial occlusive disease of the lower extremities,[8] is an atherosclerotic process that causes stenosis and occlusion of non-cerebral and non-coronary arteries.[9] It is usually caused by a build-up of fatty deposits called atheroma in the walls of the leg arteries.[10]

The development of atherosclerotic PAD is a multifactorial process involving both modifiable and non-modifiable risk factors. About 65% of patients also have clinically relevant cerebral or coronary artery disease, and a large prospective cohort study showed that patients with PAD have a six-fold higher risk of death from cardiovascular disease than those without PAD. Other major risk factors includes: age, smoking, diabetes, chronic renal insufficiency, hypertension and hyperlipidaemia.[9]

Many people with PAD have no symptoms. However, some develop a painful ache in their legs when they walk, which usually disappears after a few minutes' rest, a condition termed as intermittent claudication. The pain can range from mild to severe, and usually goes away after a few minutes when upon rest. Both legs are often affected at the same time, although the pain may be worse in one leg.[10] Other symptoms include; hair loss on legs and feet, numbness or weakness in the legs, brittle, slow-growing toenails, leg ulcers, change in leg skin colour, shiny skin, muscle wasting and erectile dysfunction. PAD is not immediately life-threatening, but the process of atherosclerosis that causes it can lead to serious and potentially fatal problems.[10]

Lower extremity revascularisation procedures are sometimes used in the management of intermittent claudication in patients with PAD, and may include angioplasty and stenting, and bypass surgery and graft types.[11]
Recent clinical trial data showed that 11% to 12% of patients with stable, symptomatic PAD suffered cardiovascular death, myocardial infarction (MI), or stroke, and 2% to 4% were hospitalized for acute limb ischemia (ALI) over 36 months of follow-up. After PAD revascularization, corresponding risks are even higher, with reported rates of nonfatal MI, ischaemic stroke, or cardiovascular death 36 months

after procedure of 14% among patients with intermittent claudication and 34% among those with critical limb ischaemia.[8]

A prior history of peripheral revascularization is a strong predictor of ALI and compared with patients with stable PAD, those with a history of limb revascularization >30 days before enrolment have a significantly higher risk of MI. These risks are further elevated after repeat limb revascularization, supporting the need for more aggressive secondary prevention measures, including intensive antithrombotic therapy, to prevent recurrent events in this high-risk population.[8]

CLINICAL NEED AND BURDEN OF DISEASE

A cohort study carried out using Health Improvement Network in the UK observed a decline in incidence of PAD between 2000 and 2014 across all age groups except the group aged 50–59 years, in which the incidence remained largely similar over time. The incidence of symptomatic PAD per 10,000 person-years decreased over time, from 38.6 (men: 51.0; women: 28.7) in 2000 to 17.3 (men: 23.1; women: 12.4) in 2014. The prevalence of symptomatic PAD decreased from 3.4% (men: 4.5%; women: 2.5%) in 2000 to 2.4% (men: 3.1%; women: 1.7%) in 2014.[12]

There is limited evidence on the prevalence of PAD in the general population. However, about 20% of the UK population aged 55–75 years have evidence of lower extremity PAD, equating to a prevalence of 850,000 people, of whom 5% have symptoms (i.e. 42,500 people).[b]

In England, in 2017-2018 there were 15,535 (13,486 males and 6,578 females) hospital admissions with a primary diagnosis of atherosclerosis of arteries of extremities (ICD-10 code I70.2), resulting in 128,080 bed days and just 3,628 day cases.[13] Assuming that all those admitted to hospital had a peripheral infra-inguinal revascularization and scaling this up to the UK, the eligible population that may benefit from rivaroxaban can be estimated to be 18,487.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The starting point for managing PAD involves risk factor modification. Support and treatment are offered to reduce the risk of life threatening cardiovascular events and prevent progression of disease. This may include smoking cessation, controlling diabetes, improving diet, reducing body weight, increasing exercise, lipid modification and statin therapy, management of high blood pressure, and antiplatelet therapy.[14,15] Antiplatelet agents are mostly used after peripheral percutaneous revascularisation.[15]

CURRENT TREATMENT OPTIONS

Antiplatelet agents are used for secondary prevention of cardiovascular events in patients with symptomatic PAD.[16]

The 2017 European Society of Cardiology guidelines on the diagnosis and treatment of PAD recommends:[16]

- Single antiplatelet therapy (SAPT) is indicated only if lower extremity artery disease patients are symptomatic or have undergone revascularisation
- Clopidogrel is the preferred antiplatelet drug in lower extremity artery disease patients

[b] Information provided by Bayer plc on UK PharmaScan

- Chronic anticoagulation therapy is given only if there is a concomitant indication and may be combined with SAPT when there is a recent revascularisation procedure

PLACE OF TECHNOLOGY

If licensed, rivaroxaban will offer a treatment option as add-on therapy to standard of care to reduce the risk of major thrombotic vascular events in symptomatic PAD patients with a recent lower extremity revascularisation procedure.

CLINICAL TRIAL INFORMATION

Trial	**VOYAGER PAD, NCT02504216, EduraCT 2014-005569-58**, adults aged 50 years and older; rivaroxaban vs placebo; phase III
Sponsor	Bayer plc
Status	Ongoing
Source of Information	Trial registry[4,17]
Location	23 EU countries incl UK, USA, Canada, countries in Asia and South America
Design	Randomised, placebo-controlled, parallel assignment
Participants	N=6565; aged 50 years and older; peripheral artery disease (PAD); documented moderate to severe symptomatic lower extremity atherosclerotic PAD; technically successful peripheral revascularization distal to the external iliac artery for symptomatic PAD within the last 10 days prior to randomisation
Schedule	Randomised to: • Rivaroxaban 2.5 mg orally twice daily (5 mg cumulative daily dose) • Rivaroxaban-placebo orally twice daily
Follow-up	Approximately 2 years
Primary Outcomes	Time frame: Approximately 2 years • Time from randomisation to the first occurrence of any of the following major thrombotic vascular events: MI (Myocardial infarction), ischemic stroke, CV (Cardiovascular) death, ALI (Acute limb ischaemia), and major amputation • Time from randomisation to first occurrence of major bleeding events according to the Thrombolysis in Myocardial Infarction (TIMI) classification
Secondary Outcomes	Time frame: Approximately 2 years • Time from randomisation to first occurrence of MI, ischemic stroke, coronary heart disease mortality, ALI, and major amputation of a vascular aetiology • Time from randomisation to first occurrence of an unplanned index limb revascularization for recurrent limb ischemia • Time from randomisation to first occurrence of hospitalisation for a coronary or peripheral cause (either lower limb) of a thrombotic nature • Time from randomisation to the first occurrence of MI, ischemic stroke, all-cause mortality, acute limb ischemia, and major amputation of a vascular aetiology • Time from randomisation to first occurrence of myocardial infarction, all-cause stroke, cardiovascular death, acute limb ischemia, and major amputation of a vascular aetiology

	• Time from randomisation to first occurrence of all-cause mortality • Time from randomisation to first occurrence of venous thromboembolic (VTE) events
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as October 2019

ESTIMATED COST

Rivaroxaban is already marketed in the UK; a pack of 56 x 2.5mg tablets costs £50.40.[18]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease (ID1397). Expected publication date: August 2019.
- NICE technology appraisal guidance. Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (TA223). May 2011.
- NICE technology appraisal guidance. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (TA210). December 2010.
- NICE clinical guideline. Peripheral arterial disease: diagnosis and management (CG147). February 2018.
- NICE quality standard. Peripheral arterial disease (QS52). January 2014.
- NICE interventional procedures guidance. Percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting) for peripheral artery disease (IPG433). November 2012.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- American Family Physician. Lower extremity peripheral artery disease: diagnosis and treatment. 2019.[19]

- The task force for the diagnosis and treatment of peripheral arterial diseases of the European society of cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular surgery (ESVS). 2017.[15]
- American College of Cardiology and American Heart Association. 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: Executive Summary. 2016.[20]
- Scottish Intercollegiate Guidelines Network. Antithrombotics: indications and management (SIGN129). 2013.[21]
- The British Medical Journal. Diagnosis and Management of Peripheral Arterial Disease. 2012.[9]

REFERENCES

1 Electronic Medicines Compendium (emc). *Xarelto 2.5 mg film-coated tablets.* Available from: https://www.medicines.org.uk/emc/product/3410/smpc#PHARMACOLOGICAL_PROPS [Accessed 19 March 2019].

2 European Medicines Agency. *Xarelto.* Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/xarelto [Accessed 19 March 2019].

3 Gradolí J, Vidal V, Brady AJ, Facila L. Anticoagulation In Patients With Ischaemic Heart Disease And Peripheral Arterial Disease: Clinical Implications Of COMPASS Study. *European Cardiology Review*. 2018;13(2):115-8. Available from: https://doi.org/10.15420/ecr.2018.12.2

4 ClinicalTrials.gov. *Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities (VOYAGER PAD). Trial ID: NCT02504216*. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT02504216 [Accessed 19 March, 2019].

5 Fredenburgh JC, Gross PL, Weitz JI. Emerging anticoagulant strategies. *Blood*. 2017;129(2):147-54. Available from: https://dx.doi.org/10.1182/blood-2016-09-692996.

6 British National Formulary (BNF). *RIVAROXABAN.* Available from: https://bnf.nice.org.uk/drug/rivaroxaban.html [Accessed 02 April 2019].

7 ClinicalTrials.gov. *Rivaroxaban.* Available from: https://clinicaltrials.gov/ct2/results?term=rivaroxaban%2C+janssen&recrs=abdf&phase=012 [Accessed 02 April 2019].

8 Hess Connie N, Norgren L, Ansel Gary M, Capell Warren H, Fletcher John P, Fowkes FGR, et al. A Structured Review of Antithrombotic Therapy in Peripheral Artery Disease With a Focus on Revascularization. *Circulation*. 2017 2017/06/20;135(25):2534-55. Available from: https://doi.org/10.1161/CIRCULATIONAHA.117.024469.

9 Peach G, Griffin M, Jones KG, Thompson MM, Hinchliffe RJ. Diagnosis and management of peripheral arterial disease. *BMJ : British Medical Journal*. 2012;345:e5208. Available from: https://dx.doi.org/10.1136/bmj.e5208.

10 National Health Service. *Peripheral arterial disease (PAD).* Available from: https://www.nhs.uk/conditions/peripheral-arterial-disease-pad/ [Accessed 02 April 2019].

11 National Institute for Health and Care Excellence. *Managing intermittent claudication in people with peripheral arterial disease.* Available from: https://pathways.nice.org.uk/pathways/lower-limb-peripheral-arterial-disease/managing-intermittent-claudication-in-people-with-peripheral-arterial-disease.pdf [Accessed 18 April 2019].

12 Cea-Soriano L, Fowkes FGR, Johansson S, Allum AM, García Rodriguez LA. Time trends in peripheral artery disease incidence, prevalence and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK. *BMJ Open*. 2018;8(1):e018184. Available from: https://dx.doi.org/10.1136/bmjopen-2017-018184.

13 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18.* 2017. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Accessed 17 December 2018].

14 National health Service. *Treatment- Peripheral arterial disease (PAD).* Available from: https://www.nhs.uk/conditions/peripheral-arterial-disease-pad/treatment/ [Accessed 02 April 2019].

15 Naylor AR, Vlachopoulos C, Espinola-Klein C, Tepe G, Desormais I, Collet J-P, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *European Heart Journal*. 2017;39(9):763-816. Available from: https://doi.org/10.1093/eurheartj/ehx095.

16 Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018 Mar 1;39(9):763-816. Available from: https://dx.doi.org/10.1093/eurheartj/ehx095.

17 EU Clinical Trials Register. *Efficacy and safety of rivaroxaban in reducing the risk of major thrombotic vascular events in subjects with peripheral artery disease undergoing peripheral revascularization procedures of the lower extremities. Trial ID: 2014-005569-58*. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-005569-58/GB [Accessed 02 April 2019].

18 British National Formulary (BNF). *Rivaroxaban tablet.* Available from: https://bnf.nice.org.uk/medicinal-forms/rivaroxaban.html [Accessed 02 April 2019].

19 Firnhaber JM, Powell CS. Lower Extremity Peripheral Artery Disease: Diagnosis and Treatment. *Am Fam Physician*. 2019 Mar 15;99(6):362-9. Available from: https://www.aafp.org/afp/2019/0315/p362.html.

20 Gerhard-Herman Marie D, Gornik Heather L, Barrett C, Barshes Neal R, Corriere Matthew A, Drachman Douglas E, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017 2017/03/21;135(12):e726-e79. Available from: https://doi.org/10.1161/CIR.0000000000000471.

21 Scottish Intercollegiate Guidelines Network. *Antithrombotics: indications and management-A national clinical guideline.* 2013. Available from: https://www.sign.ac.uk/assets/sign129.pdf [Accessed 03 April 2019].

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