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RIVAROXABAN for preventing atherothrombotic events in people with coronary and/or peripheral artery disease (CAD and/or PAD)

Note: Rivaroxaban is also licensed, at a higher dose, for stroke prevention in non-valvular atrial fibrillation (NVAF) and treatment / secondary prevention of venous thromboembolism (VTE). Rivaroxaban is licensed at low dose for use following acute coronary syndromes (ACS).

In South London, rivaroxaban plus aspirin is recommended, within its marketing authorisation (unless contra-indicated), as an option for preventing atherothrombotic events in adults with **symptomatic** peripheral artery disease (PAD), and/or with coronary artery disease (CAD) who are **at high risk of ischaemic events,** [1] **but not a high risk of bleeding.**

Coronary Artery Disease (CAD) criteria are:[3]

Myocardial infarction (MI) within the last 20 years,
OR
Multi-vessel coronary disease (≥50% stenosis in ≥2 coronary arteries- *includes re-vascularised arteries*) with symptoms or a history of stable/unstable angina,
OR
Multi-vessel percutaneous coronary intervention (PCI), **OR** Multi-vessel coronary artery bypass grafting (CABG) surgery
AND high risk of ischaemic events

AND /OR

<u>Symptomatic</u> confirmed peripheral artery disease (PAD) definition:[2,3]

Previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularisation of iliac, or infra-inguinal arteries,
OR
Previous limb or foot amputation for arterial vascular disease,
OR
History of intermittent claudication **and 1 or more of**:

- Ankle/arm brachial pressure index (ABPI) <0.9,
  OR
- ≥50% peripheral artery stenosis,
  OR
- Carotid revascularisation or asymptomatic carotid artery stenosis ≥50%

High risk of ischaemic events is defined as:[1]

AND/OR

Aged over 65 years

AND/OR

Atherosclerosis in 2 or more vascular territories:

- coronary
- cerebrovascular
- peripheral arteries

2 or more risk factors:

- Current smoker
- Diabetes mellitus
- Kidney dysfunction (CrCl <60ml/min)
- Heart Failure (if ejection fraction (EF) ≥30% or NYHA class I and II symptoms) ***see contra-indications***
- Previous non-lacunar ischaemic stroke > 1 month ago (***see cautions***)

Dosing: The recommended dose is **2.5mg twice daily.** As specified in the license, for this indication, it **must** be co-prescribed with aspirin 75mg daily[4,5] (and not other antiplatelets).
NB. eGFR (estimated glomerular filtration rate) <15ml/min exclusion criteria in the COMPASS study for renal dysfunction may not give an accurate assessment of renal function, please calculate creatinine clearance (CrCl) using actual bodyweight and a recent serum creatinine: www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation. For patients at high risk of gastrointestinal (GI) bleeding, the co-prescription of a proton pump inhibitor (PPI), or appropriate alternative, may be considered, see: https://cks.nice.org.uk/topics/nsaids-prescribing-issues/[11]

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Patient safety caution when prescribing *– ensure the correct DOAC agent is prescribed. There is a potential risk of prescribing errors due to confusion between rivaroxaban 2.5mg twice daily (ACS/CAD/PAD dose) and apixaban 2.5mg twice daily (VTE treatment or prophylaxis NVAF dose).*

Recommended antithrombotic options for the secondary prevention of CVD in CAD:

1) Aspirin 75mg daily
2) **After ACS event: dual antiplatelet therapy (DAPT) for 12 months** (link: *antiplatelet guideline SEL- under review*) aspirin 75mg with clopidogrel 75mg daily or prasugrel 10mg daily, or ticagrelor 90mg twice daily
3) **For high risk-patients** (see criteria on page 1) **following 12 months of DAPT:**
   a) Aspirin 75mg daily plus ticagrelor 60mg twice daily (for 36 months)
   b) And then/or alternative to option 3a: Aspirin 75mg daily plus rivaroxaban 2.5mg twice daily (if not high bleeding risk) lifelong therapy

Recommended antithrombotic options for the secondary prevention of CVD in PAD:

1) **Clopidogrel 75mg daily:** for asymptomatic PAD, symptomatic PAD without increased risk for CVD and for patients with a high bleeding risk
2) **After angioplasty with stenting:** DAPT for 6 weeks for bare metal stents (BMS), or 6 months for drug-eluting stents (DES): aspirin 75mg with clopidogrel 75mg daily
3) **After the initial period with antiplatelets**, patients with a high thrombotic risk but not a high bleeding risk, may be eligible for rivaroxaban with aspirin as per the compass trial recommendations (in the outpatient setting under vascular advice):
   Rivaroxaban 2.5mg twice daily with aspirin 75mg daily: for symptomatic PAD at increased risk of CVD (eg. multivessel disease, diabetes) but not high bleeding risk- lifelong therapy

Initiation: Treatment should only be started after an informed discussion with the patient about the risks and benefits of rivaroxaban in combination with aspirin; weighing up the risk of atherothrombotic and ischaemic events against the risk of bleeding and considering any cautions/contra-indications to this treatment (*see below*)

Cautions and contra-indications: (*see BNF:* https://bnf.nice.org.uk/drug/rivaroxaban.html#indicationsAndDoses *and SPC:* https://www.medicines.org.uk/emc/product/3410/smpc *for full list*) [4,5]

Contra-indications	Cautions
Patients taking full dose anticoagulation (warfarin, apixaban, dabigatran, edoxaban, rivaroxaban, or heparin) for AF, VTE, antiphospholipid syndrome (APLS) and metallic valves	Any previous haemorrhagic or lacunar stroke, or history of an intracranial bleed and within 1 month of a non-lacunar ischaemic stroke (*seek specific advice from stroke specialists)*
Within one year of an ACS or MI (ie still prescribed dual antiplatelet therapy, DAPT) and for high-risk patients taking prolonged dual antiplatelets such as ticagrelor with aspirin post MI (*see recommendations above*)	Patients taking clopidogrel or other antiplatelets for the secondary prevention of stroke *(discuss management plan with stroke physician before changing therapy)*
Within 3 months of an acute intracranial haemorrhage (ICH)	Low bodyweight <60kg
Within 1 month of a major bleed event	Renal impairment (CrCl <30ml/min)
Patients with severe heart failure (EF <30%) and New York Heart Association (NYHA) symptoms class III or IV were excluded from the COMPASS study	Patients taking clopidogrel (or other antiplatelets) for PAD should be reviewed by a vascular specialist before changing to this combination treatment.
Renal impairment (CrCl <15ml/min)	Modifiable bleeding risk factors **listed on page 3**
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C	Lactose intolerance
Pregnancy and breastfeeding	Elderly and/or frail: consider prognostic benefit in decision making (see bleeding risk review below)
Hypersensitivity to active substance or excipients	
Patients considered at high risk of bleeding- **see criteria below**	

Assessing Bleeding Risk (prior to initiation) European Society of Cardiology (ESC) Chronic Coronary Syndromes (CCS) guidelines (2019) highlight patients considered high risk for bleeding (and contra-indications to treatment):[8]

- History of intracerebral haemorrhage or ischaemic stroke
- History of other intracranial pathology
- Recent gastrointestinal (GI) bleeding or anaemia (due to possible GI blood loss)
- Other GI pathology
- Bleeding diathesis or coagulopathy
- Renal failure requiring dialysis or CrCl <15ml/min
- Liver failure: cirrhotic patients with Child Pugh B and C
  (NB. Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy)[4]
- Extreme old age or frailty[12] (https://www.nice.org.uk/guidance/NG56/chapter/Recommendations#how-to-assess-frailty)

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Efforts should be made to **manage modifiable bleeding risk factors** such as: Uncontrolled hypertension (SBP>160mmHg), other medications that increase GI bleeding risk (eg. antiplatelets and NSAIDs) and alcohol intake (aim for <8units per week). See: https://www.mdcalc.com/has-bled-score-major-bleeding-risk[6]

Course Length: [1,3]

- NICE guidance states that treatment may continue indefinitely/lifelong, however in the COMPASS study the mean period of follow up was for 23 months only. The risks and benefits of continuing therapy should be reviewed at least annually (*see below*).

Monitoring and Side Effects: (see BNF: https://bnf.nice.org.uk/drug/rivaroxaban.html#indicationsAndDoses and SPC: https://www.medicines.org.uk/emc/product/3410/smpc for full list) [4,5]

- Renal function (CrCl), full blood count (FBC) and liver function (LFTs) checked at least annually.
- Patients should also be monitored for signs of bleeding or anaemia.
- Patients should be advised to seek medical advice if they experience persistent or frequent episodes of bleeding (for severe bleeding seek urgent medical advice).

Drug Interactions: (see BNF: https://bnf.nice.org.uk/drug/rivaroxaban.html#indicationsAndDoses and SPC: https://www.medicines.org.uk/emc/product/3410/smpc for full details) [4,5]

Roles and Responsibilities:

Following initiation, the hospital will supply 4 weeks of rivaroxaban (unless a medicines compliance aid is required- *local guidance applies*) and a discharge letter or clinic letter sent to primary care with initiation information and monitoring/follow up requirements.

Initiation information to be completed by the prescriber in secondary care:

- Indication for therapy, including any patient-related risk factors for ischaemic events
- Bleeding risk assessment including follow up monitoring requirements
- Baseline bodyweight, renal function (CrCl), FBC and LFTs
- Recommended course length and/or follow up period for the patient

It is recommended that patients are referred to their local community pharmacy for the New Medicines Service (NMS), that will assist understanding of and adherence to therapy. All medicines compliance aid patients must be discussed with their community pharmacy for new initiations to reduce the risk of missed doses.

For primary care, follow the recommended guidance from initiation and continue to monitor the risk:benefit of therapy for the patient at least annually (*see monitoring and side effects above*) and ensure the patient is supported to adhere to this treatment.

When to refer from primary to secondary care?

Seek advice and guidance from the initiating team or appropriate specialist team for: bleeding (refer to urgent care if severe), renal function decline, abnormal FBC and LFTs, patient tolerability issues and frailty concerns, that may lead to cessation of therapy.

Additional Information

1. Patients taking rivaroxaban should carry an anticoagulation card in addition to the antiplatelet card (available from initiating clinician / anticoagulation clinics) or wear a medic-alert bracelet.
2. Other healthcare professionals should be made aware that rivaroxaban is prescribed, for any patients who are to undergo invasive treatments, including elective surgery and dental treatment.
3. If a patient requires VTE prophylaxis and management of stroke risk reduction for atrial fibrillation (AF) please reassess anticoagulation dosing and the prescription of antiplatelets accordingly.
4. **This therapy should be stopped in patients experiencing acute MI, stroke or significant bleeds until advised by a specialist**. Hospital admissions requiring VTE prophylaxis should also consider temporarily stopping therapy.
5. **Please note: There is a patient safety risk that rivaroxaban 2.5mg twice daily (ACS/CAD/PAD dose) may be confused with apixaban 2.5mg twice daily (VTE treatment or prophylaxis in NVAF dose)- please ensure the indication for rivaroxaban is clear when prescribing this therapy.**

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This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. If rivaroxaban is prescribed for non-approved/unlicensed indications, prescribing responsibility will remain with the initiating clinician/organisation.

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