Prescribing safety warning *Potential for* ***DOAC selection error*** *involving* ***rivaroxaban 2.5mg bd*** *(for prophylaxis of atherothrombotic events following ACS/CAD/PAD) and* ***apixaban 2.5mg bd*** *(for VTE prophylaxis/NVAF).* ***Ensure correct DOAC prescribed for the indication.***

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 Surrey Heartlands, rivaroxaban 2.5mg BD 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 at a high risk of bleeding.**

Coronary Artery Disease (CAD) criteria[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

At high risk of ischaemic events[1] (defined as)

- Aged over 65 years **and/or**
- Atherosclerosis in 2 or more vascular territories (e.g., coronary, cerebrovascular, or peripheral arteries) **and/or**
- 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***)

SYMPTOMATIC 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%

AND

At high risk of ischaemic events[1]

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[3] 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, should be considered, see: https://cks.nice.org.uk/topics/nsaids-prescribing-issues/[11]

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Recommended antithrombotic options for the secondary prevention of CVD in CAD:
(In post ACS patients initially up to 12months of DAPT= Aspirin **PLUS** either Clopidogrel **OR** Prasugrel **OR** Ticagrelor 90mg BD followed by)

1) **Aspirin 75mg OD** for life (if Aspirin not tolerated or previous Stroke/TIA, offer Clopidogrel 75mg OD for life) **OR**
2) For high ischaemic risk **EITHER**:
   a. Start with Aspirin 75mg OD **PLUS** Ticagrelor 60mg BD (for up to 36 months) then continue with option 2b
      OR
   b. Commence Aspirin 75mg OD **PLUS** Rivaroxaban 2.5mg BD (if not high bleed 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.
2) **Rivaroxaban 2.5mg twice daily with Aspirin 75mg daily:** For symptomatic PAD at increased risk of CVD but not high bleed risk - Lifelong therapy

Caution: After angioplasty with stenting, patients will require an initial period of DAPT before continuing with either option 1 or 2. Please seek specialist vascular advice for duration and composition of DAPT.

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
Any previous haemorrhagic or lacunar stroke or within 1 month of any stroke	History of an intracranial bleed (see information below regarding intracerebral haemorrhage)
Patients requiring full dose anticoagulation (warfarin, apixaban, dabigatran, edoxaban, rivaroxaban, or heparin) for AF, VTE, antiphospholipid syndrome (APLS) and metallic valves	Patients taking clopidogrel or other antiplatelets for the secondary prevention of stroke *(discuss management plan with stroke physician before changing therapy)*
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 60mg BD with aspirin post MI (*see recommendations above*)	Low bodyweight <60kg
Within 3 months of an acute intracranial haemorrhage (ICH)	Modifiable bleeding risk factors **listed on page 3**
Within 1 month of a major bleed event	Patients taking clopidogrel (or other antiplatelets) for PAD should be reviewed by a vascular specialist before changing to this combination treatment.
Patients with severe heart failure (EF <30%) and New York Heart Association (NYHA) symptoms class III or IV were excluded from the COMPASS study	Renal impairment (CrCl <30ml/min)
Renal impairment (CrCl <15ml/min)	Lactose intolerance
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Elderly and/or frail: consider prognostic benefit in decision making (see bleeding risk review below)
Pregnancy and breastfeeding	
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:

If initiation is by specialist in secondary care, 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

Ensure that the patient/carer is counselled on discharge, with specific reinforcement of advice to discontinue any previously prescribed, **but no longer required**, anticoagulant/antiplatelet treatment.

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, initiate for patients with CAD/PAD that fit in to the criteria above following a risk:benefit conversation with the patient. 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.

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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 prophylaxis and NVAF treatment dose)- please ensure the indication for rivaroxaban is clear when prescribing this therapy.**

GLOSSARY

DOAC Direct acting Oral Anticoagulant
ACS Acute Coronary Syndrome
CAD Coronary Artery Disease
PAD Peripheral Artery Disease
NVAF Non-Valvular Atrial Fibrillation
VTE Venus Thromboembolism

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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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