Non-vitamin K oral anticoagulant options for patients with non-valvular atrial fibrillation and renal impairment

This guideline was developed by a multidisciplinary expert panel, Kalra PA, Cowie M et al, and was commissioned and funded by Bayer. See inside for full disclaimer. Prescribing information can be found on the outside back cover.

Patient with renal impairment requiring anticoagulant therapy

- Baseline information:
  - age
  - body weight
  - sex
  - full blood count
- Calculate CrCl using actual body weight* (this dosing guide is based on CrCl and not eGFR calculated using the MDRD equation)
- For full prescribing requirements, refer to SPCs†–4

<table>
<thead>
<tr>
<th>CrCl (ml/min)*</th>
<th>≥80</th>
<th>50–79</th>
<th>30–49</th>
<th>15–29</th>
<th>&lt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>150 mg BD or dose reduction to 110 mg BD recommended if:</td>
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<tr>
<td></td>
<td>■ age ≥80 years</td>
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<td></td>
<td>■ concomitant verapamil</td>
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<tr>
<td></td>
<td>150 mg BD or dose reduction to 110 mg BD for consideration if:†</td>
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<tr>
<td></td>
<td>■ age 75–80 years</td>
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<tr>
<td></td>
<td>■ CrCl 30–50 ml/min</td>
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<tr>
<td></td>
<td>■ increased bleeding risk</td>
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<tr>
<td><strong>Rivaroxaban</strong></td>
<td>20 mg OD</td>
<td></td>
<td>15 mg OD</td>
<td></td>
<td>Not recommended if CrCl 15–29 ml/min and to be used with caution</td>
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<tr>
<td><strong>Apixaban</strong></td>
<td>5 mg BD</td>
<td></td>
<td></td>
<td></td>
<td>Not recommended</td>
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<tr>
<td></td>
<td>Reduce dose to 2.5 mg BD if ≥2 of:</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>■ age ≥80 years</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>■ weight ≤60 kg</td>
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<tr>
<td></td>
<td>■ serum creatinine ≥1.5 mg/dl (133 μmol/l)</td>
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<tr>
<td><strong>Edoxaban</strong></td>
<td>60 mg OD§</td>
<td></td>
<td></td>
<td></td>
<td>Not recommended</td>
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<tr>
<td></td>
<td>Reduce dose to 30 mg OD§ if ≥1 of:</td>
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<td></td>
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<tr>
<td></td>
<td>■ weight ≤60 kg</td>
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<td></td>
<td>■ concomitant use of P-gp inhibitors¹</td>
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</tbody>
</table>

Monitoring and dosing review

- Monitor renal function according to the latest CrCl (advice based on expert opinion):
  - if latest CrCl 30–60 ml/min, measure renal function at least every 6 months
  - if latest CrCl <30 ml/min, measure renal function every 3 months
  - also consider measuring CrCl if patients develop intercurrent illness such as diarrhoea, vomiting, or fever

| Reduced dose dependent on CrCl alone |
| Reduced dose dependent on various patient factors |

Drugs ordered chronologically by date of marketing authorisation.

*CrCl, as an indicator of renal function, was calculated using the Cockroft-Gault equation with actual body weight in phase 3 trials, therefore the dosing in SPCs is based on CrCl–4
†Selected based on an individual assessment of the thromboembolic and bleeding risk
§Should only be used in patients with a high creatinine clearance after a careful evaluation of individual thromboembolic and bleeding risk
¹Ciclosporin, dronedarone, erythromycin, or ketoconazole
CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease; SPC=summary of product characteristics; BD=twice daily; OD=once daily; P-gp=P-glycoprotein
Drug selection and dosing

NICE and European guidance recommend anticoagulant therapy to prevent stroke in patients with non-valvular atrial fibrillation (AF), including non-vitamin K oral anticoagulants (NOACs: dabigatran etexilate, rivaroxaban, apixaban, or edoxaban) and vitamin K antagonists (warfarin):5,6–15

- treatment choice should take into account clinical features, such as stroke and bleeding risks (using CHA2DS2-VASc and HAS-BLED scores), and patient preference5,6,13
- for patients taking warfarin, optimal time in therapeutic range is associated with a lower risk of adverse events independent of underlying renal function, but patients with non-valvular AF and severe chronic kidney disease (CKD) (estimated glomerular filtration rate <30 ml/min/1.73 m²) have worse control of international normalised ratio while on warfarin16
- the evidence suggests that NOACs are a suitable alternative to warfarin in a CKD population with CrCl 30–50 ml/min, but they are at least partly excreted via the kidneys, so healthcare professionals can find it challenging to decide on dosing taking into account factors such as age, weight, renal function, co-morbidities, concomitant drug treatment, and the relevant summary of product characteristics (SPC)5,8–12,15,17

Select drug treatment through shared decision-making with the patient:
- use patient-focused information and websites, such as the AF Association website (www.heartrhythmalliance.org/afa/uk/), to discuss options with the patient

Use the dosing guide to aid in the choice of NOAC and determine the appropriate dosing regimen for the selected drug:1–4
- if creatinine clearance (CrCl) <30 ml/min, use with caution or consider seeking specialist advice
- check for drug interactions with existing concomitant drugs and when additional medications are prescribed1–4

Seek specialist advice for specific populations such as patients undergoing dialysis and post-renal transplant patients

Patient counselling

Educate the patient on how to take their NOAC and when they should contact a healthcare professional:
- dabigatran 110 mg and 150 mg capsules should be swallowed whole with a glass of water, to facilitate delivery to the stomach1
- rivaroxaban 15 mg and 20 mg tablets should be taken with food2
- 2.5 mg and 5 mg apixaban tablets should be swallowed with water3
- emphasise the importance of compliance at every opportunity
- advise patients who have had an injury, particularly a head injury, to go to the emergency department
- advise patients who have significant bruising or bleeding to seek urgent hospital advice
- remind patients to always carry their anticoagulant alert card and to show it to every doctor or dentist before treatment
- avoid co-administration of non-steroidal anti-inflammatory drugs in patients on NOACs if possible18

Key additional considerations in the management of patients on NOACs

NOACs may need to be stopped before some procedures, including surgery19,20
- patients undergoing surgery in secondary care should be counselled on stopping and restarting drugs at their preoperative assessment
- dental extractions can generally be performed safely in an outpatient facility by applying local haemostatic measures, without interrupting anticoagulation or by just skipping the morning dose of the NOAC5
- it is recommended that oral anticoagulation is not interrupted for most minor surgical procedures and those procedures where bleeding is easily controllable5

References


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**Useful resources**

- AF Association: [www.heartrhythmalliance.org/afa/uk/](http://www.heartrhythmalliance.org/afa/uk/)
- British Society of Haematology (BSH) guideline on *Peri-operative management of anticoagulation and antiplatelet therapy*
- European Heart Rhythm Association practical guide to NOACs

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**about this dosing guide …**

This NOAC dosing guide has been commissioned by Bayer, who also provided funding for its development. Bayer reviewed and approved the scope and pre-meeting documents, suggested the Chair and experts for the group, and put the dosing guide through full medical approval to ensure its compliance with appropriate regulations. The views and opinions of the contributors expressed in this document are not necessarily those of Bayer, or of *Guidelines*, its publisher, advisers, or advertisers.

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Conflicts of interest — The group members have received an honorarium from Bayer to attend a meeting to develop this dosing guide. Some of the group members have also received consultancy fees from other pharmaceutical companies, which might include Bayer, for activities other than the development of this dosing guide.

PP-XAR-GB-0968                  Date of preparation: November 2019
Xarelto® (rivaroxaban) 2.5, 10, 15 and 20 mg film-coated tablets

Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5mg/10mg/15mg/20mg rivaroxaban tablet.
Indication(s): 2.5mg Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Xarelto, co-administered with acetylsalicylic acid, is indicated 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.
10mg Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients).
15mg/20mg Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation who require oral anticoagulation & undergo PCI (with stent placement).

Dosage & Administration:

Posology & method of administration: 2.5mg – Oral b.i.d. dose; patients should also take a daily dose of 75 – 100 mg ASA or a daily dose of 75 – 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. Start Xarelto as soon as possible after stabilisation, including revascularisation for ACS; at the earliest 24 hours after admission & at discontinuation of parenteral anticoagulation.
If dose is missed take next dose, do not double the dose. 10mg – hip or knee replacement surgery: Oral o.d. dose; initial dose taken 6 to 10 hours after surgery provided haemostasis established. DVT & PE: When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg o.d.
In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg o.d., a dose of 15 mg o.d. should be considered. 15mg/20mg – with food: SPAF: 20 mg orally o.d. DVT & PE: 15 mg b.i.d. for 3 weeks followed by 20 mg o.d. for continued treatment & prevention of recurrent DVT & PE.

All strengths – Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants.

Special populations: Patients undergoing cardioversion: Xarelto can be initiated or continued in patients who may require cardioversion.
In patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement: There is limited experience of a reduced dose of 15 mg Xarelto once daily (or 10 mg Xarelto once daily for patients with a body weight <60kg) in patients undergoing PCI with stent placement. Refer to SmPC for further information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants.

Renal impairment: mild (creatinine clearance 50–80 ml/min) – no dose adjustment; 2.5mg/10mg – moderate (creatinine clearance 30–49 ml/min) – no dose adjustment; 15mg/20mg/25mg – moderate (creatinine clearance 30–49 ml/min) & severe (creatinine clearance 15-29 ml/min) – SPAF: reduce dose to 15 mg o.d., DVT & PE: 15 mg b.i.d. for 3 weeks, thereafter 20 mg o.d. Consider switching from 20mg to 15mg o.d. if patient’s bleeding risk outweighs risk for recurrent DVT & PE; All strengths – Severe impairment: limited data indicate rivaroxaban concentrations are significantly increased, use with caution. Creatinine clearance <15 ml/min - not recommended. Hepatic impairment: Do not use in patients with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C.

Paediatrics: Not recommended.

Contra-indications: Hypersensitivity to active substance or any excipient; active clinically significant bleeding; lesion or condition considered to confer a significant risk for major bleeding (refer to SmPC); concomitant treatment with any other anticoagulants except under specific circumstances of switching an anticoagulant or when unfractioanted heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding.

Effects on ability to drive & use machines: Concomitant use with strong CYP3A4 inducers should be avoided unless patient is closely observed for signs & symptoms of thrombosis. Pregnancy & breast feeding: Concomitant use with strong CYP3A4 inducers should be avoided.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in Google Play or Apple App Store. Adverse events should also be reported to Bayer plc.
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