Direct Oral Anticoagulant (DOAC) Guideline

Apixaban, dabigatran, edoxaban and rivaroxaban are all approved by NICE for stroke prevention in non-valvular atrial fibrillation (NVAF). Apixaban and rivaroxaban are the DOACs of choice in Gloucestershire.

Apixaban for Non-valvular AF / flutter

Apixaban 5mg TWICE DAILY

Reduce to 2.5mg TWICE DAILY if:

- Creatinine clearance (CrCl) less than 30 mls/min (not recommended if CrCl less than 15 mls/min)

Or:

- 2 or more of the following apply:
  - Age 80 years or over
  - body weight less than 61kg
  - serum creatinine greater than 132 micromol/litre

Rivaroxaban for Non-valvular AF / flutter

Rivaroxaban 20mg ONCE DAILY (with or after food)

Reduce to 15mg ONCE DAILY if:

- CrCl less than 50 mls/min (not recommended if CrCl less than 15 mls/min)

Non-valvular AF Definition: AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis (usually of rheumatic origin).

Additional Notes:

Renal Impairment

It is essential to calculate patients' creatinine clearance (CrCl) using the Cockroft-Gault equation (use **actual** body weight) before DOAC initiation and periodically thereafter (see table above). Estimated glomerular filtration rate (eGFR) can overestimate renal function and increase the risk of bleeding events (see Drug Safety Update). There is risk of DOAC accumulation and subsequent bleeding in renal impairment. Dose reductions are recommended in mild-moderate renal impairment, refer to individual SPCs for dosing advice. Dose adjustment may be necessary if

renal function significantly changes during treatment. All DOACs are unlicensed in severe renal impairment CrCl <15ml/min (with the exception of dabigatran which should be avoided in CrCl <30ml/min). Consider discussion with renal team if CrCl <15 ml/min.

When switching to apixaban from a different anticoagulant, please refer to the switching guideline for timings.

Acute Treatment of VTE

When used to treat VTE, edoxaban and dabigatran must be preceded by 5 days of 'treatment dose' low molecular weight heparin (LMWH).[1,2] Apixaban and rivaroxaban do not require prior LMWH treatment[3,4] and are therefore preferred for acute treatment.

Cancer-Associated Thrombosis (CAT)

In the CARAVAGGIO study, apixaban was shown to be non-inferior to LMWH for CAT and had a similar rate of bleeding.[5] In the Hokusai VTE Cancer study, edoxaban was non-inferior to LMWH but the rate of major bleeding was higher.[6] Gloucestershire Cancer Associated Thrombosis Guideline

Extremes of Body Weight

Obesity:

The International Society on Thrombosis and Haemostasis recommends that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban.[16] This statement relates to the use of DOACs for the treatment of VTE, however the Gloucestershire DOAC Subgroup recommends that this would equally apply to DOAC use in NVAF.

Low Body Weight:

There is a paucity of clinical evidence concerning the use of DOACs in low body weight (<50kg) patients. The DOAC Subgroup suggests using standard doses of apixaban or rivaroxaban. If there is bleeding, consider dose reduction depending on the clinical scenario.

Recurrent Thrombosis while taking a DOAC

If a patient experiences thrombosis while taking a DOAC, compliance must be checked in the first instance.
For rivaroxaban, check that the patient is taking their dose with / after food.
If compliance is confirmed, check that the patient is on the correct dose (if the patient is on a reduced dose and their parameters are close to the cut-off for dose reduction, consider increasing to the full dose).
Consider switching to warfarin if DOAC failure is suspected.

Thrombophilia Testing

DOAC needs to be stopped for 48 hours prior to thrombophilia testing.

Thrombocytopenia

- Platelets greater than 50: DOAC may be continued with caution
- Platelets less than 50: Discuss with Haematology

Previous or High Risk of GI Bleeding

The RE-LY trial demonstrated that dabigatran 110mg bd showed superiority over warfarin for overall major bleeding. However, both doses of dabigatran (150mg and 110mg) had a higher incidence of major GI bleeding in comparison to warfarin.[7] In addition, dabigatran capsules contain tartaric acid, which can contribute to dyspepsia and are therefore best avoided in patients with GI disorders.[2]

In the ROCKET-AF trial there was no significant difference in major bleeding, fewer fatal bleeds but more GI bleeds with rivaroxaban compared with warfarin.[8] Dyspepsia is an established side effect of rivaroxaban, therefore should be used with caution in patients with GI disease even without active ulceration.[4]

The ARISTOTLE trial demonstrated a lower risk of overall major bleeding with apixaban versus warfarin and a comparable rate of GI bleeding.[9]

The ENGAGE-AF TIMI 48 study demonstrated a lower risk of overall major bleeding with edoxaban versus warfarin but an increased risk of GI bleeding with edoxaban 60mg versus warfarin.[10]

The prescribing of an anticoagulant for patients with a high GI bleed risk score should be based on consideration of any options to reduce bleed risk factors, the individual patient's stroke risk and shared patient decision making.

Concomitant Antiplatelet Treatment

Concomitant antiplatelet treatment with all oral anticoagulants increases patients' risk of bleeding; however, combination therapy may be required in patients with a need for anticoagulation (e.g. NVAF) and ischaemic heart disease – notably acute coronary syndrome or those treated with percutaneous coronary intervention (PCI).

General Recommendations:

- Clopidogrel is the P_2Y_{12} inhibitor of choice (avoid prasugrel or ticagrelor in combination with a DOAC)
- The treatment plan (i.e. antiplatelet durations) should be clearly communicated in the Discharge Summary
- Prescribe a proton-pump inhibitor (e.g. lansoprazole) for gastroprotection when a DOAC is prescribed in combination with antiplatelet(s). Avoid combining omeprazole or esomeprazole with clopidogrel.
- The full standard dose of DOACs should be used in combination with antiplatelet therapy unless the patient fulfils dose-reduction criteria (see dosing information on page 1). Where rivaroxaban or dabigatran are used and concerns about bleeding risk prevail over stent thrombosis or ischaemic stroke, the reduced dose should be considered (15mg and 110mg respectively).

In the absence of definitive evidence showing the best antiplatelet/anticoagulation regimen for patients with AF undergoing PCI, the European Cardiology Society makes the following recommendations[15]:

Please note that these recommendations are a guide. The antiplatelet/anticoagulation regimen will be individualised by the Interventional Cardiologist.

AF and acute or chronic coronary syndromes treated with PCI:

Low risk of stent thrombosis (or concerns about bleeding risk prevail over risk of stent thrombosis):

- Triple therapy (aspirin + clopidogrel + DOAC) for ≤ 1 week, followed by
- Dual therapy (clopidogrel + DOAC) for up to 6 months (in chronic coronary syndrome) or up to 12 months (in acute coronary syndrome), followed by
- DOAC monotherapy

Risk of stent thrombosis outweighs bleeding risk (e.g. STEMI, prior stent thrombosis, complex coronary procedures):

- Triple therapy (aspirin + clopidogrel + DOAC) for ≤ 1 month**, followed by
- Dual therapy (clopidogrel + DOAC) for up to 6 months (in chronic coronary syndrome) or up to 12 months (in acute coronary syndrome), followed by
- DOAC monotherapy

**in patients with diabetes mellitus undergoing PCI, prolonging triple therapy for up to 3 months may be of value if thrombotic risk outweighs the bleeding risk

AF and acute coronary syndromes treated without revascularisation:

- Dual therapy (clopidogrel + DOAC) for 6 to 12 months, followed by

- DOAC monotherapy

AF and stable chronic coronary syndromes (i.e. no major acute cardiovascular event within last 12 months):

- DOAC monotherapy

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