Direct Oral Anticoagulant (DOAC) Guideline

Background

Apixaban, dabigatran, edoxaban and rivaroxaban are all approved by NICE for stroke prevention in non-valvular atrial fibrillation. Apixaban is the first DOAC to come off patent and, as such, is currently the most cost-effective option.

Increasing the use of apixaban in place of the other DOACs will release substantial savings which can be reinvested in identifying and treating additional patients with atrial fibrillation (AF).

The One Gloucestershire Medicines Optimisation Group supports the promotion of apixaban and has provided the following guidance for prescribers:

Indication for Anticoagulation	DOAC of choice
Venous Thromboembolism (VTE) Treatment	
Acute treatment of VTE	**Apixaban** or rivaroxaban
Cancer-associated thrombosis	**Apixaban**
Non-valvular AF / flutter	
First line	**Apixaban**
Second line	Rivaroxaban Edoxaban Dabigatran
Other conditions	
High-risk acute coronary syndrome (in combination with aspirin +/- clopidogrel)	Rivaroxaban 2.5mg bd (Consultant Cardiologist initiation only)
Combined coronary artery disease / peripheral artery disease (CAD/PAD) – in combination with aspirin	Rivaroxaban 2.5mg bd
VTE prophylaxis following orthopaedic surgery	**Apixaban**, rivaroxaban, or dabigatran
Moderate to severe mitral stenosis	DOAC not suitable
Mechanical prosthetic heart valve	DOAC not suitable
Antiphospholipid syndrome	DOAC not suitable

Apixaban Dosing Information for Non-valvular AF / flutter

Apixaban 5mg bd

Reduce to 2.5mg bd if:

- CrCl < 30 mls/min (apixaban not recommended if CrCl < 15 mls/min)

Or:

- In combination with dual antiplatelet therapy (DAPT) – full dose may be used with single antiplatelet

Or:

- 2 or more of the following apply:
  - Age 80 years or over
  - body weight ≤60kg
  - serum creatinine ≥133 micromol/litre

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

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]

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.
- DOAC dosing with concomitant antiplatelet(s) [11-15]:

DOAC	Max. dose with concomitant **dual** antiplatelet therapy (DAPT) e.g. DOAC + aspirin + clopidogrel	Max. dose with concomitant **single** antiplatelet therapy e.g. DOAC + clopidogrel
Apixaban	2.5mg BD	5mg BD
Dabigatran	110mg BD	110mg BD
Edoxaban	30mg OD	30mg OD
Rivaroxaban	15mg OD	15mg OD

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.

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:

- 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

Renal Impairment

It is essential to calculate patients' creatinine clearance (CrCl) using the Cockroft-Gault equation (use actual body weight) before DOAC initiation and annually thereafter. 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.

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.[17]

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