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Guideline on selecting appropriate Non-vitamin K Antagonist Oral Anticoagulants (NOACs)/ Direct Oral Anticoagulants (DOACs)

Scope of guideline

The aim of this guideline is to aid clinical decision making to select the most appropriate non vitamin K antagonist oral anticoagulant (NOAC)/direct oral anticoagulant (DOAC) tailored for the individual patient and highlights what clinical aspects need to be considered before initiating NOAC/DOAC therapy.

Introduction

A decision to start oral anticoagulation, whether it is a vitamin K antagonist (VKA) or a NOAC/DOAC, should be made based on an informed discussion with the patient. The risks and benefits in relation to the patients' clinical features, patient preference and sustained adherence with treatment should be considered to ensure medicines optimisation as recommended by NICE.[1]

NOACs/DOACs are a preferable option in comparison to vitamin K antagonists (VKA) (in accordance with licensed specification) in the following groups of patients:

- Intolerance to warfarin such as alopecia, rash, skin necrosis, etc.
- Unable to adhere to the monitoring requirements associated with VKAs.
- Unable to achieve adequate INR control defined as follows:
  - 2 INR values higher than 5 or 1 INR value higher than 8 in the past 6 months
  - 2 INR values less than 1.5 in the last 6 months
  - Target therapeutic range (TTR) <65% despite adherence to treatment.

The different NOACs/DOACs available and their licensed indications are shown in table 1. Table 3 shows a summary of the primary efficacy and safety endpoints for the NOACs/DOACs in VTE as well as AF in comparison to warfarin.

Table 1: Indications of the different NOACs/DOACs

NOAC/ DOAC	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation	Treatment of deep vein thrombosis and / or pulmonary embolism	Secondary prevention of deep vein thrombosis and / or pulmonary embolism	Prevention of venous thrombo-embolism after total hip (35 days) or knee (14 days) replacement in adults	Acute management of acute coronary syndrome
Apixaban	✓	✓	✓	✓	✗
Dabigatran	✓	✓	✓	✓	✗
Edoxaban	✓	✓	✓	✗	✗
Rivaroxaban	✓	✓	✓	✓	✓

Important: *Doses vary depending on indication and may need to be adjusted for renal impairment, interactions, weight, and co-morbidities. Refer to SPC for further details.*

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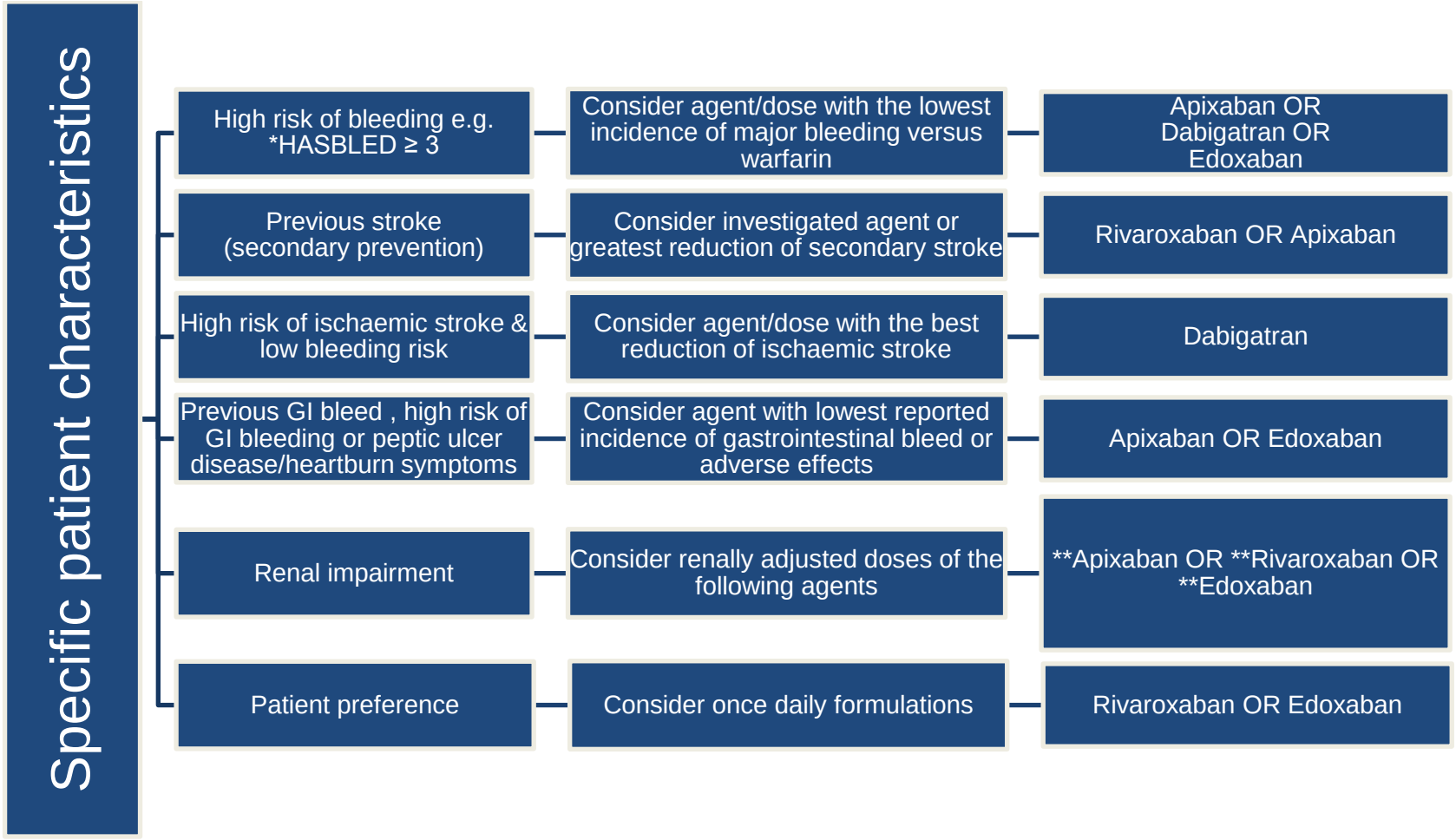
Figure 1: Pointers toward which NOAC/DOAC to choose for Non-Valvular Atrial Fibrillation



Important: *Doses may need to be adjusted for interactions, weight and co-morbidities.*

**These risk factors are modifiable.*

*** Check SPC on what stage of renal impairment to dose reduce*

Adapted from Savelieva I et al[2]

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Which NOAC/DOAC to choose for venous thromboembolism treatment

The choice of NOAC/DOAC to use for venous thromboembolism (VTE) treatment within the trust is also dependant on some of the patient specific characteristics outlined in figure 1). An important factor to consider is that dabigatran and edoxaban requires at least 5 days initial treatment with therapeutic doses of low molecular weight heparin (LMWH) before initiation of the NOAC/DOAC. In situations where apixaban and rivaroxaban is the choice of agent and LWMH has been administered prior to NOAC/DOAC being started, the initial days of higher doses can be subtracted from the day of treatment dose LMWH administered.

NOAC/DOAC selection and evidence

In the absence of direct comparisons between phase III trials for different NOACs/DOACs and difference in study populations, the following recommendations are based on study design and primary outcomes in comparison to warfarin. Figure 1 summaries patient factors that need to be considered to allow appropriate NOAC/DOAC selection.

Bleeding and gastrointestinal (GI) disorders

The RE-LY[3] trial demonstrated that dabigatran 110mg twice daily 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. In addition, dabigatran consists of a tartaric core,[4] which can contribute to dyspepsia, therefore it is best avoided in patients with GI disorders.

In the ROCKET-AF[5] trial with rivaroxaban there was no significant difference in major bleeding, fewer fatal bleeds but more GI bleeds than warfarin. Dyspepsia is an established side effect of rivaroxaban, therefore should be used with caution in patients with GI disease even without active ulceration.[6]

The ARISTOTLE[7] trial showed a comparable rate of GI bleeding in the apixaban 5mg twice daily compared to warfarin. The ENGAGE-AF TIMI 48[8] showed a non-significant increased risk of GI bleed with edoxaban 60mg vs warfarin. However, in those identified at high risk of bleeding and given a dose reduced of edoxaban 30mg, this was associated with a significant reduction in GI bleed compared to warfarin.

High risk of ischemic stroke

Compared with warfarin, all NOACs/DOACs have shown a favourable risk/benefit ratio with reductions in stroke and system embolism (SE) by 19%.[9] Both dabigatran 150mg twice daily and apixaban 5mg twice daily were found to be superior to warfarin,[3,7] with rivaroxaban and edoxaban being non-inferior.[5,8] However, dabigatran 150mg twice daily was shown to be superior to warfarin specifically in reducing ischaemic strokes.

Phase III trials for rivaroxaban and edoxaban enrolled patients with a higher risk of thromboembolic events; mean $CHADS_2$ of 3.5 and 2.8 respectively. A limitation of ROCKET-AF[5] was that the warfarin arm had the lowest TTR of 55% out of all the NOAC/DOAC phase III studies.

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Previous stroke
In a meta-analysis of 14,527 patients with prior stroke or TIA from RE-LY, ARISTOTLE and ROCKET-AF, NOACs/DOACs were associated with a significant reduction of stroke and SE compared with warfarin.[10]

Renal impairment
It is essential to calculate patients creatinine clearance (CrCl) using the Cockroft-Gault equation before NOAC/DOAC initiation. There is risk of NOAC/DOAC accumulation and subsequent bleeding therefore all should be avoided in severe renal impairment CrCl <15ml/min (with the exception of dabigatran which should be avoided in CrCl <30ml/min). Dose reductions are recommended in mild-moderate renal impairment, refer to SPC for individual agent for dosing advice.

Note: Dose reductions of specific NOACs/DOACs may vary depending on indication, such in AF and VTE.

Coronary artery disease
Concurrent antiplatelet treatment with all oral anticoagulants increases patients risk of bleeding, however concomitant therapy may be required in patients with a need for anticoagulation and ischaemic heart disease – notably acute coronary syndrome or those treated with angioplasty.

Ongoing trials are investigating NOACs/DOACs use alongside antiplatelets, therefore evidence is still limited until this data is published. When a NOAC/DOAC is combined with dual antiplatelet therapy and indicated for non-valvular AF, the lower dose tested for stroke prevention is recommended,[11] i.e. apixaban 2.5mg twice daily, dabigatran 110mg twice daily, edoxaban 30mg once daily and rivaroxaban 15mg once daily; without any other factors requiring further dose reduction.

Potential for drug-drug interactions
Strong inhibitors of CYP3A4 and P-glycoprotein or inducers of CYP3A4 can have significant interactions with NOACs/DOACs, which should either be avoided or a dose adjustment for the NOAC/DOAC maybe required. Refer to SPC for further information.

Patient preference
NOAC/DOAC therapy should be tailored to each patients lifestyle to allow for optimal adherence. Once daily preparations can be preferable for patients in whom polypharmacy maybe problematic.

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Table 2: Other considerations when initiating NOACs/DOACs

Reversal agent	Dabigatran is the only NOAC/DOAC currently with a licensed reversal agent; idarucizumab. Warfarin has a half-life of 40 hours[12] and is rapidly reversible, however it important to note that NOACs/DOACs have a much shorter half-life ranging from 5 hours[6] up to 18 hours in the elderly.[4]
Food restrictions	Rivaroxaban doses of 15mg and above must be taken with food; bioavailability can be reduced by approximately 40% when fasting.[6]
Compliance aids	Dabigatran is moisture sensitive and therefore not suitable for use in a medicine compliance aid.[4]

Table 3: Outcome data of phase III trials for all NOACs/DOACs indicated AF and VTE in comparison to warfarin

NOAC/DOAC	Stroke Prevention in Atrial Fibrillation		Treatment of DVT/PE	
	Prevention of Stroke/SE vs Warfarin	Major Bleeding vs Warfarin	Prevention of Recurrent DVT/PE vs Warfarin	Major Bleeding vs Warfarin in DVT/PE
Dabigatran	↓	↔	↔	↔
Rivaroxaban	↔	↔	↔	↓
Apixaban	↓	↓	↔	↓
Edoxaban	↔	↓	↔	↓

↓: reduced in comparison to warfarin; ↔: comparable to warfarin
Adapted from Wadhera RK et al[13]

Before initiating a NOAC/DOAC

Before initiating a NOAC/DOAC; the following should be carried out to ensure safe prescribing:

1. **Check baseline bloods**
   FBC, INR, APTT/PT, LFTs - to rule out any underlying coagulation conditions. Seek haematology advice if baseline abnormal or if LFTs are above twice the upper normal limit.
   U&Es – To assist in appropriate NOAC/DOAC dosing

2. **Review medication interactions** (see above)

3. **Rule out contraindications**
   Valvular atrial fibrillation, which is defined as moderate to severe mitral or aortic valve stenosis and mechanical heart valves, are contraindications to NOACs/DOACs. Avoid NOACs/DOACs in patients who may have suffered from rheumatic fever as they are at risk of developing valvular disease.

4. **Review need for concurrent antiplatelets**
   If patient has coronary artery disease - Seek advise from cardiologist.
   If patient has stent e.g. vascular, seek advise from appropriate specialist.

5. **Stop pharmacological and mechanical thromboprophylaxis (if in-patient)[14]**
   Refer to Standards for Managing Anticoagulation Therapy for full processes involving management of NOACs/DOACs from admission to discharge.

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