MTRAC
Midlands Therapeutics Review and Advisory Committee

# Commissioning Support
# Non-vitamin K antagonist oral anticoagulants (NOACs)

*Apixaban (Eliquis®), Edoxaban (Lixiana®▼), Rivaroxaban (Xarelto®▼), Dabigatran (Pradaxa®)*

**For the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation**

**Considerations for Commissioners:**

It was the opinion of the committee that Commissioners should ensure that robust processes or local initiatives are in place to identify patients with atrial fibrillation (AF) at increased risk of stroke, and a record made of the decision whether or not to proceed with treatment. The following points are relevant to these processes:

- If a person decides to proceed with anticoagulant treatment, the NICE clinical guideline on the Management of atrial fibrillation (CG180; 2014) does not specify which anticoagulant to use. The choice of agent depends on the individual person's stroke risk, risk of bleeding, other co-morbidities and personal preferences.
- There are a range of decision tools available to support discussions with the patient about the choice of anticoagulant treatment including:
  - NICE patient decision aid (paper based) Atrial fibrillation: medicines to help reduce your risk of a stroke – what are the options?
  - Keele University Prescribing Decision support tool: Anticoagulation therapy for the prevention of stroke and systemic embolism in atrial fibrillation.
- Additional decision support tools are included in a Lancet review of atrial fibrillation, which provides two decision-making algorithms - establishing if there is a need for antithrombotic treatment, and whether to recommend warfarin or NOACs (below). Figure 2 relates to the choice between NOACs according to factors such as bleeding risk (using the HAS-BLED score) or type of bleed, renal impairment, or ethnicity (overleaf).[1]

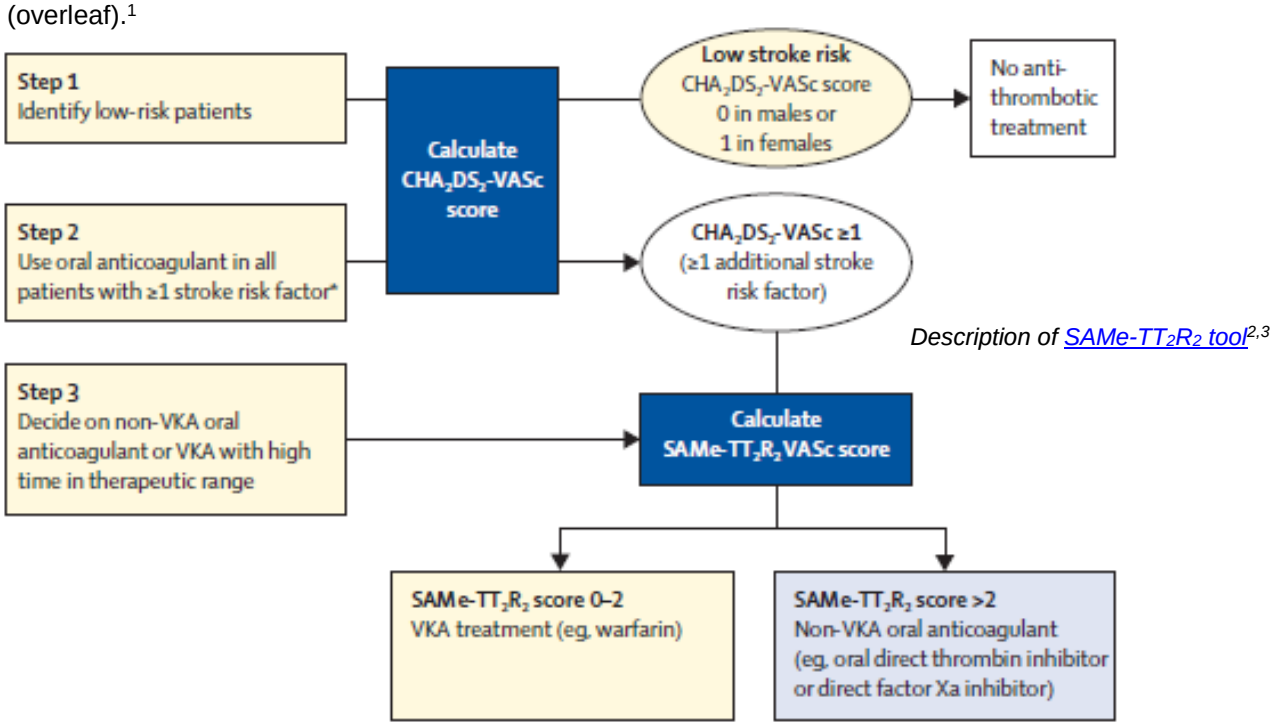


***Figure 1*** *reproduced with permission from: Atrial fibrillation 1: Stroke prevention in atrial fibrillation. Ben Freedman, Tatjana S Potpara, Gregory Y H Lip. Lancet 2016; 388: 806–17.*

## Description of the technology

Factor Xa inhibitors and direct thrombin inhibitors have different pharmacodynamic and pharmacokinetic properties, but all act on the final phase of the blood clotting process and represent as a whole the current alternative to vitamin K antagonists (VKAs). Rivaroxaban[4], apixaban[5] and edoxaban[6] directly inhibit activated factor X (factor Xa), a key component of the blood coagulation cascade, inhibiting both the formation and development of blood clots. No effects on platelets have been found. Dabigatran[7] is a direct inhibitor of thrombin, an enzyme involved in the formation of blood clots. Further details are shown in Table 1 overleaf.

## Clinical evidence for efficacy and safety

Five meta-analyses were identified that met the minimum requirements to include the four major RCTs

evaluating the NOACS for the prevention of stroke and SE in people with AF: dabigatran (RE-LY[8,9]), rivaroxaban (ROCKET-AF[10]), apixaban (ARISTOTLE[11]) and edoxaban (ENGAGE AF-TIMI[12]). The included analyses evaluated the efficacy and safety of NOACs, compared with warfarin only (2 studies[13,14]) or with warfarin, aspirin ± clopidogrel, or placebo (3 studies[15-17]). Results for direct comparisons of the NOACs with warfarin found:

- ***Incidence of stroke or SE***: with the exception of edoxaban 30 mg, all the NOACs showed numerically lower hazards of stroke or SE, and any stroke than warfarin. The result was statistically significant for apixaban and dabigatran 150 mg (4 studies[13-15,17]).
- ***All-cause mortality:*** Compared with warfarin, all-cause mortality was numerically reduced by all the NOACs, the differences for apixaban and edoxaban 30 mg *vs* warfarin were statistically significant in 3 studies[13-15]; a fourth study reported no significant differences between all NOACs and warfarin.[16]
- ***Ischaemic stroke:*** three studies reported that dabigatran 150mg alone showed a significantly lower risk of ischaemic stroke *vs.* warfarin.[13-15]
- ***Major bleeding:*** Pooled data from 50 trials found significantly less major bleeding with NOACs *vs*. warfarin for all anticoagulation indications; overall incidence of 3.3% *vs*. 3.9% (OR 0.77, 95%CI 0.64 to 0.91, p= 0.003).[18] For individual NOACs, apixaban, dabigatran 110mg, and edoxaban 30 mg or 60 mg all showed a significantly lower incidence of major bleeding than warfarin (results from 5 studies[13-17]).
- ***Gastrointestinal (GI) bleeding:*** significantly greater GI bleeding was reported with NOACs *vs*. warfarin (RR: 1.23; 95%CI 1.03 to 1.46; p = 0.01) in one study.[19] There was no effect on GI bleeding observed with apixaban, or with dabigatran 110 mg compared with warfarin. NOACs with a higher incidence of GI bleeding *vs*. warfarin were rivaroxaban (RR: 1.46; 95%CI 1.2 to 1.8; p < 0.001), edoxaban 60 mg (RR: 1.22; 95%CI 1.01 to 1.47; p = 0.038) and dabigatran 150 mg (RR: 1.50; 95%CI 1.20 to 1.88; p < 0.001).

## Patient factors

- Patient's preference for contact time and reassurance associated with INR monitoring, or convenience of a NOAC.
- Once-daily *vs*. twice-daily dosing.
- The availability of a reversal agent in the event that a patient has a major bleed or need for emergency surgery.
  - Idarucizumab is licensed for use in patients treated with dabigatran when reversal of its anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding.[20,21]
  - For apixaban, rivaroxaban and edoxaban there are two agents currently in clinical development: andexanet alfa (filed in EU for marketing authorisation) and ciraparantag (phase 2 trials; may also work for dabigatran).[22,23]

## Annual Costs

- Warfarin (generic; 7.5mg daily) £12.12 (not including INR monitoring)
- Apixaban (Eliquis®; 5mg twice daily) £693.50
- Dabigatran (Pradaxa®; 150mg twice daily) £620.50
- Edoxaban (Lixiana®▼; 60mg once daily) £675.25
- Rivaroxaban (Xarelto®▼; 20mg once daily) £657.00

**Table 1:** Selected information on NOACs, focussing on dose adjustments for renal and hepatic impairment. The Figure below uses these and other patient characteristics to suggest treatment options for different patient groups.

| **Product (Trade name, manufacturer)** Formulation(s) and recommended daily dose for prevention of stroke and SE Hyperlinks to SPCs | **Renal impairment** *(Renal function tests advised in SPCs for dabigatran and edoxaban)* | | | **Hepatic impairment** All NOACs contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk *Liver function tests advised in SPCs for apixaban and edoxaban* | |
|---|---|---|---|---|---|
| | **Mild**[c] (CrCl 50 - 80 ml/min) | **Moderate**[c] (CrCl 30 - 49 ml/min) | **Severe**[c] (CrCl 15 - 29 ml/min) | | |
| **Apixaban** (Eliquis®; Bristol-Myers Squibb-Pfizer) 2.5 mg tablet; 5 mg tablet Dose: 5 mg bd[b] | Dose reduction to 2.5 mg bd advised where serum creatinine ≥1.5 mg/dL (133 micromol/L) is associated with age ≥80 years or body weight ≤60 kg | | 2.5 mg bd Not recommended where creatinine clearance < 15 mL/min, or in patients on dialysis | **Mild or moderate impairment:** Use with caution in Child Pugh A or B impairment, no dose adjustment required | **Severe impairment:** not recommended |
| **Dabigatran** etexilate mesilate (Pradaxa®; Boehringer Ingelheim Ltd) 110 mg capsule, 150 mg capsule Dose: 150 mg bd[b] | No dose adjustment necessary | 150 mg bd unless high risk of bleeding, then 110 mg bd | Contraindicated where CrCl < 30 mL/min | Not recommended in this population | |
| **Edoxaban** tosilate (Lixiana®▼;Daiichi Sankyo UK Ltd) 15mg tablet; 30mg tablet; 60 mg tablet Dose: 60 mg od[b] | 60 mg od | 30 mg od Not recommended where creatinine clearance < 15 mL/min (end-stage renal disease), or in patients on dialysis | | **Mild or moderate impairment:** Use with caution, no dose adjustment | **Severe impairment:** not recommended |
| **Rivaroxaban** (Xarelto®▼; Bayer plc) 20 mg tablet Dose: 20 mg od[b] | No dose adjustment necessary | 15 mg od | Use with caution; Not recommended where creatinine clearance < 15 ml/min | Contraindicated: cirrhotic patients with Child Pugh B and C | |

*[a]doses shown do not imply equivalence; [b]Or lower doses as advised in the SPC; bd, twice daily; od, once daily; CrCl, creatinine clearance (Cockcroft-Gault formula; ideal weight adjustment advised if patient significantly overweight)*

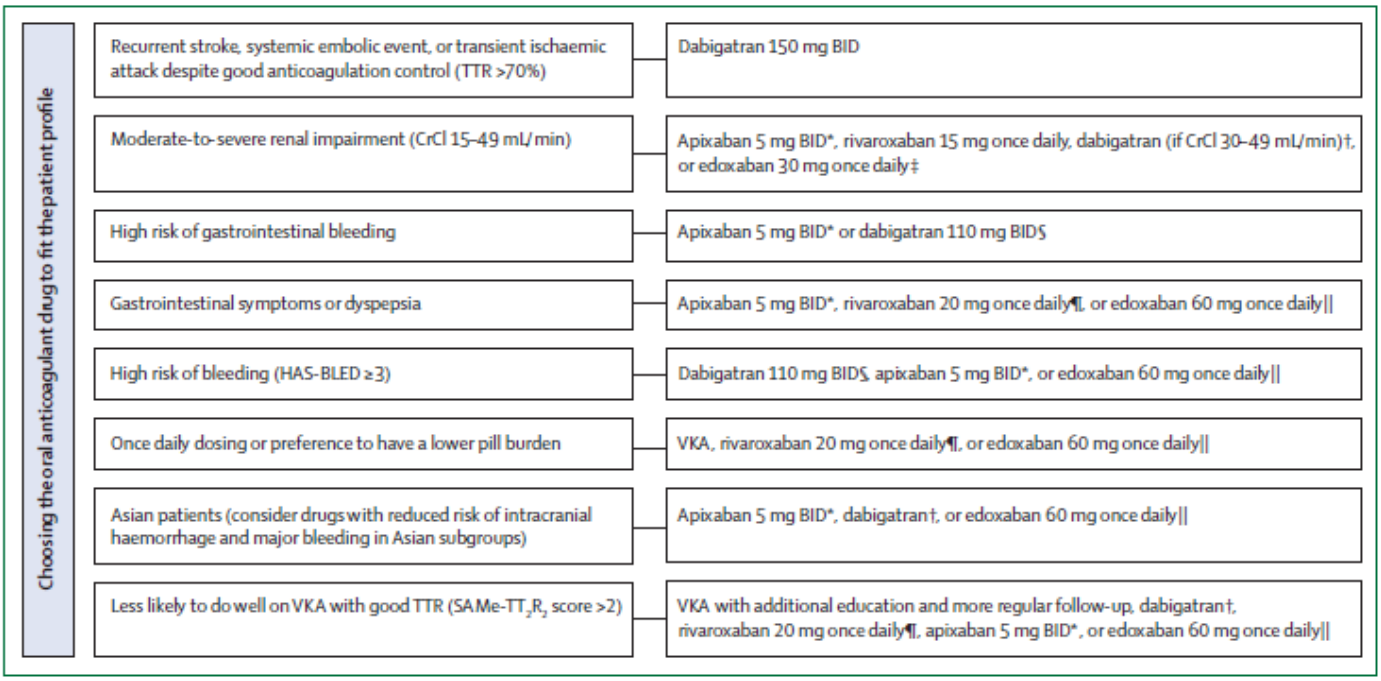


Figure 2: A simplified schema to assist physician choice of anticoagulant (VKA or individual NOAC) according to patient characteristics. BID = twice daily. CrCl=creatinine clearance. NOAC=non-vitamin K antagonist oral anticoagulant. TTR=time in therapeutic range. VKA=vitamin K antagonist. *Reduced to 2.5 mg BID with two of three criteria from age ³ 80 years, bodyweight ≤ 60 kg, or serum creatinine concentration ³ 133µmol/L. †110mg BID for patients with a CrCl 30-49 mL/min. ‡ 30mg with CrCl 15-49 mL/min, P-glycoprotein inhibitors, or weight < 60kg. ¶ Reduced to 15mg if CrCl 15-49 ml/min. ‖ Dose to be halved if the patient has any of the following: CrCl 15-49 mL/min, bodyweight ≤ 60 kg, or concomitant use of P-glycoprotein inhibitors. *Figure reproduced with permission from: Atrial fibrillation 1: Stroke prevention in atrial fibrillation. Ben Freedman, Tatjana S Potpara, Gregory Y H Lip. Lancet 2016; 388: 806–17.(Legend amended to remove references to US circumstances).*

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