NHS
Pan Mersey
Area Prescribing Committee

The Pan Mersey Area Prescribing Committee recommends the prescribing of Direct Oral Anticoagulants (DOACs) for the prevention of stroke and systemic emboli in non-valvular atrial fibrillation (AF)

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NICE TAs 249[1] (dabigatran), 256[2] (rivaroxaban), 275[3] (apixaban) and 355[4] (edoxaban) and NICE NG196 Atrial Fibrillation[5] recommend the use of DOACs as first line treatment options for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF).

NICE NG196 states to offer anticoagulation with a DOAC to people with AF and a CHA_2DS_2-VASc score of 2 or above for women and 1 or above for men, considering the risk of bleeding, who not currently anticoagulated.[5]

Apixaban, dabigatran, edoxaban and rivaroxaban are all recommended options when used in line with the relevant NICE TA. Where there is no clinical reason to use a specific DOAC, it is recommended to use the DOAC with the lowest acquisition cost. At the time of writing, this is edoxaban which clinicians should use first line where this is clinically appropriate (see Prescribing information and implementation notes).

If DOACs are contraindicated, not tolerated or not suitable in people with AF, offer a vitamin K antagonist.

For adults with AF who are already taking a vitamin K antagonist and are stable, continue with their current treatment and discuss the option of switching to a DOAC at their next review.

The ORBIT or HAS-BLED score should be used to assess bleeding risk in people who are starting or have started anticoagulants and identify modifiable risk factors. Aspirin monotherapy is no longer recommended for the sole purpose of stroke prevention in AF[5].

Clinicians are reminded to use the actual body weight for calculating CrCl when initiating DOACs and ensuring this is communicated effectively between specialists and primary care upon discharge.

The decision to start treatment with a DOAC should be made after an informed discussion between the clinician and the patient about the relative risks and benefits of each agent. A trial of warfarin is not needed prior to initiating a DOAC. Each anticoagulant has different risks and benefits that should be considered and fully discussed with the patient's clinical needs and preferences as part of informed shared decision making before prescribing. NICE NG197 on shared decision making is available to assist this process.

For people who are taking DOACs, NG196 recommends that the prescriber reviews the need for anticoagulation and the quality of anticoagulation (taking into account MHRA advice on direct-acting oral anticoagulants about bleeding risk and renal impairment) at least annually.

Prescribers should be aware that specific antidotes are available for apixaban, dabigatran, and rivaroxaban. There is currently no licensed antidote available for edoxaban, however the Pan Mersey APC recommends the use of andexanet as a reversal agent for edoxaban in line with NICE TA697. This should be taken into account when deciding whether or not to initiate therapy with a DOAC.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

Direct Oral Anticoagulants (DOACs) for the prevention of stroke and systemic emboli in non-valvular atrial fibrillation (AF)

Effectiveness

Apixaban , rivaroxaban and edoxaban are direct factor Xa inhibitors and dabigatran is a direct thrombin inhibitor. The NICE NG196 evidence review consisting of a network meta-analysis (NMA) of 26 randomised trials comparing the effectiveness of anticoagulants as prophylactic treatment for patients at risk of stroke due to non-valvular AF concluded that evidence pointed clearly to a superiority of the DOAC drugs over warfarin, both in terms of benefits and harms. The NMA concluded that the DOACs performed differently depending on the outcome. The NMA estimated a ranking of the efficacies of treatments per outcome, taking all data and uncertainties into account and showed that Rivaroxaban was likely to be the best DOAC for minimising MI and all-cause mortality, at a probability of around 60% for each outcome. In addition, Apixaban was likely to be the best DOAC for minimising major bleeding, intracranial bleeding and clinically relevant bleeding, at a probability of around 80% for each. Meanwhile, dabigatran was most likely to be the best DOAC for minimising Stroke or Systemic embolism, and Ischaemic Stroke, again at a probability of about 80% for each. Edoxaban was not ranked as the best treatment for any outcome but emerged as the second best for reducing major bleeding and intracranial bleeding[7].

An observational study (PROSPER[6]) of 11662 stroke survivors aged between 74 and 86 years showed that patients discharged with a DOAC (vs warfarin) had more days at home during the first-year post discharge and were less likely to experience major cardiovascular events and DOAC use at discharge was associated with better long-term outcomes relative to warfarin. In those taking DOACs there were also fewer deaths (0.88 [95% CI, 0.82-0.99] *P*=0.02) and all-cause readmissions (0.93 [95% CI, 0.88-0.97]; *P* = 0.003).

NICE recommends each individual DOAC as an option for the prevention of stroke in non-valvular AF[1-5] taking into account clinical and cost-effectiveness. It also notes that people taking a DOAC benefit by being able to have an oral treatment and avoid the frequent monitoring that is necessary with other types of anticoagulation treatment[5].

Safety

There is a specific antidote available for dabigatran (idarucizumab), and for apixaban and rivaroxaban (andexanet alfa). There is currently no specific, established antidote to edoxaban however data suggests reversibility with prothrombin complex[10].

The PROSPER observational study of 11662 stroke survivors concluded that in those taking DOACs there were fewer cardiovascular hospital readmissions (0.92 [95% CI, 0.86-0.99]; *P* = 0.02), haemorrhagic strokes (0.69 [95% CI, 0.50-0.95]; *P* = .02), and hospitalizations with bleeding (0.89 [95% CI, 0.81-0.97]; *P* = .009) but a higher risk of gastrointestinal bleeding (1.14 [95% CI, 1.01-1.30]; *P* = .03)[6].

Consult SPC for full list of side effects, contraindications and interactions [8-11].

Cost[12]

	Cost per patient per year (ex VAT)*
Apixaban 2.5mg - 5mg twice daily	£693.50
Dabigatran 110mg, 150mg twice daily	£620.50
Edoxaban 30mg, 60mg daily	£638.75
Rivaroxaban 10mg, 15mg, 20mg daily	£657.00
Dose adjusted warfarin (based on 6mg average daily dose and self-monitoring of INR)	£256.76

***NHS list price. Source: NHSBSA[12]**

NICE NG196 concluded that as there were no studies directly comparing DOACs head-to-head but indirect comparisons based on the clinical evidence showed that the different DOACs offered different benefits depending on the outcome considered. The committee had concerns over the lack of head-to-head comparisons, differences in the study populations and uncertainties in the economic model. NICE recommends each individual DOAC as an option for the prevention of stroke in non-valvular AF based on both clinical and cost effectiveness.[5]

Patient factors

All DOACS are contraindicated in patients taking any other anticoagulants except when switching, maintaining an open catheter or during catheter ablation. They are also contraindicated when there is active clinically significant bleeding and in conditions where there is a significant risk of bleeding.

Renal function should be assessed in all patients before starting a DOAC and at least once a year, and more frequently in those with a suspected decline in renal function.

Prior to initiating treatment, a liver function test should be performed for apixaban, edoxaban and dabigatran.

Where DOACs are initiated in secondary/tertiary care it is good practice to communicate patient weight to the GP to assist with dosing and calculation of CrCl.

Patients should be issued with a Patient Alert Card (available from manufacturer or can be downloaded from SPC).

See SPC for each DOAC for further warning, cautions and interactions.

Prescribing information and implementation notes

- For patients commencing treatment for AF: subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should use edoxaban where this is clinically appropriate. If edoxaban is contraindicated or not clinically appropriate for the specific patient then, subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should then consider rivaroxaban first, then apixaban or dabigatran[13].
- For patients already prescribed a DOAC for the treatment of AF: subject to the criteria specified in the relevant NICE technology appraisal guidance, commissioners may wish to consider developing local policy to review patients currently prescribed apixaban, rivaroxaban or dabigatran, where clinically appropriate[13].
- The recommended starting dose of apixaban for the prevention of stroke and systemic embolism in AF is 5mg twice daily. In patients with 2 or more of the following: age ≥80 years, body weight ≤60kg or serum creatinine ≥133 micromole/L, or if CrCl is 15-29ml/min, the dose should be reduced to 2.5mg twice daily. The effect of apixaban on clotting times is predictable therefore routine monitoring is not required.
- The recommended starting dose of dabigatran for the prevention of stroke and systemic embolism in AF in patients <80 years is 150mg twice daily. In patients ≥ 80 years, the dose should be reduced to 110mg twice daily. The effect of dabigatran on clotting times is predictable therefore routine monitoring is not required.
- The recommended starting dose of edoxaban for the prevention of stroke in AF is 60mg daily. Patients with 1 or more of: moderate-severe renal impairment (CrCl 15-50ml/min), body weight ≤60Kg or use of concomitant erythromycin, ciclosporin, dronedarone or ketoconazole should have the dose of edoxaban reduced to 30mg daily.
- The recommended dose of rivaroxaban for the prevention of stroke and systemic embolism in AF is 20mg daily **taken with food**. In patients with moderate to severe renal impairment (CrCl 15-49 ml/min) the dose should be reduced to 15mg daily **with food**. The effect of rivaroxaban on clotting times is predictable, therefore routine monitoring is not required.
- Apixaban is not recommended if creatinine clearance is <15ml/min or in patients with severe hepatic impairment and should be used in caution in those with mild to moderate hepatic impairment.
- Dabigatran is contraindicated in patients with severe renal impairment (CrCl < 30ml/min). For patients with gastritis, esophagitis, or gastroesophageal reflux, a dose reduction may be considered due to the elevated risk of major gastro-intestinal bleeding.
- Edoxaban is not recommended if creatinine clearance is <15ml/min and in severe hepatic impairment and is contraindicated in severe uncontrolled hypertension.
- Rivaroxaban is not recommended if creatinine clearance is <15ml/min.
- For further information on missed doses and switching to or from warfarin or a parenteral anticoagulant please see the full SPC for each drug.

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