This policy statement is approved by Halton, Knowsley, Liverpool, South Sefton, Southport and Formby, St Helens, Warrington, West Lancashire, and Wirral CCGs

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PAN MERSEY APC

PAN MERSEY AREA PRESCRIBING COMMITTEE
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NHS Pan Mersey Area Prescribing Committee

Direct Oral Anticoagulants (DOACs) (previously known as NOACs) in Non-Valvular Atrial Fibrillation: a multiple prescribing statement for Apixaban, Dabigatran, Edoxaban and Rivaroxaban

GREEN

DOACs are recommended as treatment options for the prevention of stroke and systemic emboli in non-valvular atrial fibrillation where an oral anticoagulant is indicated.

NICE TAs 249[1] (dabigatran), 256[2] (rivaroxaban), 275[3] (apixaban) and 355[4] (edoxaban) and NICE CG180 Atrial Fibrillation[5] recommend the use of DOACs as treatment options for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF).

The focus of stroke prevention in AF should be on identifying and reviewing patients with a CHA_2DS_2-VASc score ≥ 2 for women and ≥ 1 for men who are not currently anticoagulated, and initiating oral anticoagulants where appropriate. The 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].

The decision about whether to start treatment with warfarin or 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. A NICE patient decision aid is available to assist this process. Additional information is also available on the North West Coast Strategic Clinical Network website.

Key Groups in whom DOACs should especially (but not exclusively) be considered as an alternative to warfarin for stroke prevention in non-valvular AF include those who:

- have a warfarin allergy, warfarin specific contraindications, or are unable to tolerate warfarin therapy due to adverse effects
- are unable to comply with variable dosing and the specific monitoring requirements for warfarin (consider self-monitoring where appropriate)
- have poor INR control with warfarin **(excluding the first 3 months of treatment), despite adequate investigation of the cause,** defined as[5]:
    - 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months
    - 2 INR values less than 1.5 within the past 6 months
    - Time in therapeutic range (TTR) less than 65%
- have had an ischaemic stroke whilst stable on warfarin therapy
- at initiation, following informed discussion, state a preference to take a DOAC
- have a confirmed eGFR of 30-50ml/min/1.73m^2 (consider apixaban in preference to warfarin)[6]

Patients currently stable on warfarin therapy should not usually be considered for a switch to a DOAC. DOACs may not be a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin due to a high bleeding risk or poor compliance with warfarin therapy.

Prescribers should be aware that specific antidotes are available for apixaban, dabigatran, and rivaroxaban. There is currently no specific antidote available for any other DOACs. 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 policy 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. If appropriate an exceptional funding request will be required following the usual locally defined process.

APIXABAN tablets (Eliquis®) in Atrial Fibrillation

EFFECTIVENESS

Apixaban is an anticoagulant that directly inhibits factor Xa. 18201 patients with AF who were at increased risk of stroke were randomised to either apixaban 5mg twice daily (reduced to 2.5mg twice daily in patients with 2 or more of the following: age≥ 80years, body weight <60kg or serum creatinine above 133 micromole/l) or warfarin (ARISTOTLE)[7]. 43% of patients were warfarin naïve. Median follow up was 1.8 years and the time in therapeutic range (TTR) with warfarin was 62%. The primary end point (stroke [ischaemic or haemorrhagic] or systemic embolism) occurred at a rate of 1.27% per year in the apixaban group and 1.6% per year in the warfarin group (HR with apixaban 0.79; 95% CI 0.66-0.95; p<0.001 for non-inferiority and p=0.01 for superiority). The rate of death from any cause was lower in the apixaban group (3.52% per year vs. 3.94% per year; HR with apixaban 0.89; 95% CI 0.80-0.99; p=0.047).

5599 patients with AF at increased risk of stroke and for whom vitamin k antagonist therapy was unsuitable were randomised to either apixaban 5mg twice daily or aspirin 81-324mg daily (AVERROES)[8]. The mean follow up was 1.1 years. The primary outcome of stroke or systemic embolism occurred at a rate of 1.6% per year with apixaban and 3.7% per year with aspirin, HR with apixaban 0.45; 95% CI 0.32-0.62; p<0.001 for superiority.

SAFETY

In the ARISTOTLE[7] study, the rate of major bleeding was lower in the apixaban group (2.13% per year vs. 3.09% per year HR 0.69 95% CI 0.6-0.8; p<0.001). There was no difference in the incidence of GI bleeding between apixaban and warfarin (0.76% per year vs. 0.86% per year; p=0.37). Intracranial haemorrhage was lower in the apixaban group (0.33% per year vs. 0.80% per year; HR 0.42 ; 95% CI 0.3-0.58; p<0.001).

In the AVERROES[8] study, there was no difference in the rates of major bleeding between apixaban and aspirin (1.4% per year with apixaban vs. 1.2% per year with aspirin; p=0.57). There was no difference in the rate of intracranial haemorrhage.

There is a specific antidote available for apixaban (andexanet alfa).

Consult the SPC for more details at www.medicines.org.uk

COST PER PATIENT PER YEAR[9,10]

Apixaban (2.5mg or 5mg twice daily)	£694
Warfarin	£23
Estimated annual warfarin monitoring costs (NICE)	£250

Predicted use will be dependent upon uptake and selection criteria. Once established, it is likely to be between 500-1000 per 100,000 of the population. New incidence of AF is around 87 per 100,000 per year[11].

PATIENT FACTORS[12]

Patients with 2 or more of the following: age ≥80 years, body weight ≤60kg, or serum creatinine ≥133 micromole/l, should have a dose reduction to 2.5mg twice daily. Patients with a creatinine clearance (CrCl) of 15-29ml/min should also have a dose reduction to 2.5mg twice daily. Apixaban is not recommended in patients with creatinine clearance <15ml/min or in those undergoing dialysis.

Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and a clinically relevant bleeding risk. Prior to initiating treatment, a liver function test should be performed.

Apixaban is contraindicated in patients taking any other anticoagulants (except as detailed below) or ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors (e.g. ritonavir), rifampicin, phenytoin, carbamazepine or phenobarbitone.

PRESCRIBING INFORMATION

- 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.
- Renal function should be assessed in all patients before starting apixaban and at least once a year and more frequently in those with a suspected decline in renal function. Apixaban is not recommended if creatinine clearance is <15ml/min.
- Where apixaban is initiated in secondary/tertiary care, it is good practice to communicate patient weight to the GP to assist with dosing and calculation of creatinine clearance.
- Currently there is no specific, established antidote available for apixaban.
- When switching from warfarin to apixaban, stop the warfarin and start apixaban when INR <2.0.
- When switching from apixaban to warfarin, continue apixaban for at least 2 days after starting warfarin. After 2 days of co-administration, obtain an INR before the next scheduled dose of apixaban. Continue co-administration until INR ≥2.0.
- Switching from parenteral anticoagulation to apixaban (and vice versa) can be done at the next scheduled dose.
- A missed dose of apixaban should be taken immediately and then continue with twice daily intake as before.
- For patients unable to swallow tablets or with a NG tube *in situ,* the tablets may be crushed and suspended in water, dextrose 5% in water or apple juice (stable for up to 4 hours).
- Patients should be issued with a Patient Alert Card (available from manufacturer or can be downloaded from SPC).

DABIGATRAN ETEXILATE capsules (Pradaxa®) in Atrial Fibrillation

EFFECTIVENESS

Dabigatran is an anticoagulant that directly inhibits thrombin.

18113 patients with AF who were at increased risk of stroke were randomised to either warfarin, dabigatran 110mg bd or dabigatran 150mg bd (RE-LY)[13]. 50% of patients were warfarin naïve. Median treatment duration was 2 years and the overall time in therapeutic range (TTR) with warfarin was 64.4%. The primary end point (all stroke [ischaemic and haemorrhagic] and systemic embolism) occurred at a rate of 1.69% per year in those taking warfarin, 1.53% per year in those taking dabigatran 110mg bd (RR 0.91 95% CI 0.74-1.11 p=0.34) and 1.11% per year in those taking dabigatran 150mg bd (RR 0.66 95% CI 0.53-0.82 P<0.001). Dabigatran 110mg bd was non-inferior to warfarin and dabigatran 150mg bd was superior to warfarin. The rates of death from any cause were not different between the treatment groups. The benefits of dabigatran 150mg were seen in patients previously treated with warfarin and in warfarin naïve patients.

SAFETY

In the RE-LY study[13], major bleeding rates were similar for warfarin and dabigatran 150mg bd (3.36%per year vs 3.11% per year, RR 0.93 95% CI 0.81-1.07 p=0.3). Major bleeding was lower with dabigatran 110mg bd compared to warfarin (2.71% per year vs 3.36% per year RR 0.8 95% CI 0.69-0.93 p=0.003). The incidence of GI bleeding was higher with dabigatran 150mg bd (1.51% per year vs 1.02% per year RR 1.5 95% CI 1.19-1.89 P<0.001) compared to warfarin but not with dabigatran 110mg bd. Intracranial bleeding was uncommon but dabigatran 150mg bd and 110mg bd reduced the absolute risk compared with warfarin (0.32% per year, 0.23% per year vs 0.76% per year respectively P<0.001).

Dyspepsia occurred at a higher rate with both doses of dabigatran compared with warfarin.

There is a specific antidote available for dabigatran (idarucizumab).

Consult SPC for more details at: www.medicines.org.uk

COST PER PATIENT PER YEAR[9,10]

Dabigatran (110mg or 150mg twice daily)	£621
Warfarin	£23
Estimated annual warfarin monitoring costs (NICE)	£250

Predicted use will be dependent upon uptake and selection criteria. Once established, it is likely to be between 500-1000 per 100,000 of the population. New incidence of AF is around 87 per 100,000 per year[11].

PATIENT FACTORS[14]

Patients aged ≥80 years should have a dose reduction to 110mg bd due to an increased risk of bleeding. The dose should also be reduced to 110mg bd in patients taking verapamil. Consider 110mg bd when the thromboembolic risk is low and bleeding risk high. In gastritis, oesophagitis or gastroesophageal reflux consider 110mg bd.

Dabigatran is contraindicated in patients with hepatic impairment or with severe renal impairment (Creatinine clearance [CrCl] <30ml/min). Prior to initiating treatment, renal and liver function tests should be performed.

It is contraindicated in people who are taking other anticoagulants (except as detailed below), ketoconazole, itraconazole, dronedarone, tacrolimus, ciclosporin, rifampicin, carbamazepine or phenytoin.

PRESCRIBING INFORMATION

- The recommended starting dose of dabigatran for the prevention of stroke and systemic embolism in AF in patients <80 years is 150mg bd. In patients ≥ 80 years, the dose should be reduced to 110mg bd. The effect of dabigatran on clotting times is predictable therefore routine monitoring is not required.
- Renal function should be assessed in all patients before starting dabigatran and at least once a year, and more frequently in those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (CrCl < 30ml/min).
- Where dabigatran is initiated in secondary/tertiary care, it is good practice to communicate patient weight to the GP to assist with dosing and calculation of creatinine clearance.
- When switching from warfarin to dabigatran, stop warfarin and start dabigatran when the INR is below 2.0
- When switching from dabigatran to warfarin, start warfarin 3 days before dabigatran is discontinued if CrCl≥50ml/min and 2 days before dabigatran is discontinued if CrCl is 30-50ml/min
- When switching from parenteral anticoagulant to dabigatran, start dabigatran 0-2 hours before next dose of LMWH is due or at the same time as the continuous intravenous infusion of unfractionated heparin is stopped.
- When switching from dabigatran to parenteral anticoagulation, wait 12 hours after the last dose of dabigatran before starting the parenteral anticoagulant.
- A missed dose of dabigatran can be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted.
- Dabigatran is not suitable for use in monitored dosage systems.
- Patients should be issued with a Patient Alert Card (available from manufacturer).

EDOXABAN Tablets (Lixiana®▼) in Atrial Fibrillation

EFFECTIVENESS

Edoxaban is an anticoagulant that directly inhibits factor Xa. 21105 patients with AF who were at moderate-high risk of stroke (CHADS2 ≥2) were randomised to either edoxaban 60mg, edoxaban 30mg (doses in both arms were halved if estimated CrCl was between 30-50ml/min, body weight ≤60Kg or receiving concomitant verapamil or quinidine) or warfarin (ENGAGE-AF 48).[15] The median duration of treatment exposure was 907 days and the time in therapeutic range with warfarin was 64.9%. The primary endpoint (all stroke [ischaemic or haemorrhagic] and systemic embolus) occurred at a rate of 1.5% per year in those taking warfarin, 1.61% per year in those taking low dose edoxaban (HR vs warfarin 1.07 97.5% CI 0.87-1.31 p=0.005 for non-inferiority) and 1.18% per year in those taking high dose edoxaban (HR vs warfarin 0.79 97.5% CI 0.63-0.99 p<0.001 for non-inferiority).
In the pre-specified superiority analysis for efficacy, neither high dose or low dose edoxaban were superior to warfarin for preventing the primary endpoint.
The rates of death from any cause were lower in the low dose edoxaban group but not the high dose group compared to warfarin.

SAFETY

In the ENGAGE-AF 48 trial[15] the annualised rate of major bleeding was lower in both edoxaban groups compared with warfarin (3.43% with warfarin vs 2.75% with high dose edoxaban (HR 0.80 95% CI 0.71-0.91 p<0.001) and 1.61% with low dose edoxaban (HR 0.47 95% CI 0.41-0.55 p<0.001)). The incidence of major GI bleeding was higher in the high dose edoxaban group than with warfarin (1.51% vs 1.23%) but the rate was lowest with low dose edoxaban (0.82%).
The rates of life-threatening bleeding, intracerebral bleeding and major bleeding plus clinically relevant non-major bleeding were all significantly lower with both doses of edoxaban compared with warfarin.

There is currently no specific, established antidote to edoxaban. However, data suggest reversibility with prothrombin complex concentrate (PCC)[16]

Consult SPC for more details at: www.medicines.org.uk

COST PER PATIENT PER YEAR[9,10]

Edoxaban (60mg or 30mg daily)	£639
Warfarin	£23
Estimated annual warfarin monitoring costs (NICE)	£250

Predicted use will be dependent upon uptake and selection criteria. Once established, it is likely to be between 500-1000 per 100,000 of the population. New incidence of AF is around 87 per 100,000 per year[11].

PATIENT FACTORS[16]

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. Edoxaban is not recommended in patients with a CrCl <15ml/min or in those undergoing dialysis

In patients with elevated liver enzymes (ALT/AST>2 x upper limit normal [ULN]) or total bilirubin ≥1.5 x ULN) edoxaban should be used with caution. Prior to initiating treatment, a liver function test should be performed. Edoxaban is contraindicated in patients with hepatic disease associated with coagulopathy and a clinically relevant bleeding risk. It is contraindicated in people who are taking other anticoagulants (except as detailed below).

Edoxaban should be used with caution in patients taking rifampicin, phenytoin, carbamazepine or phenobarbitone.

In patients with concomitant conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risk should be made before combining this therapy.

PRESCRIBING INFORMATION

- 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. Edoxaban is not recommended if creatinine clearance is <15ml/min. Renal function should be assessed (using the Cockcroft-Gault method) in all patients before starting edoxaban and at least once a year, and more frequently in those with a suspected decline in renal function.
- Where edoxaban is initiated in secondary/tertiary care, it is good practice to communicate patient weight to the GP to assist with dosing and calculation of creatinine clearance.
- When switching from warfarin to edoxaban, stop warfarin (or other vitamin K antagonist [VKA]) and start edoxaban when the INR is ≤ 2.5.
- When switching from edoxaban to warfarin, start warfarin, reduce edoxaban to 30mg daily and continue until INR ≥ 2.0. (In patients already on edoxaban 30mg daily, reduce the dose to 15mg daily and continue until the INR ≥ 2.0).
- When switching from parenteral anticoagulant to edoxaban, start edoxaban at the time next scheduled dose of LMWH would be administered or 4 hours after ceasing intravenous heparin. These agents should not be given simultaneously.
- When switching from edoxaban to parenteral anticoagulation, start parental therapy at the time next scheduled dose of edoxaban would be administered. These agents should not be given simultaneously.
- A missed dose of edoxaban should be taken immediately and then continued once daily on the following day.
- Patients should be issued with a Patient Alert Card (available from manufacturer or can be downloaded from SPC).

RIVAROXABAN tablets (Xarelto®▼) in Atrial Fibrillation

EFFECTIVENESS Rivaroxaban is an anticoagulant that directly inhibits factor Xa. 14264 patients with atrial fibrillation who were at moderate to high risk of stroke (CHADS2 ≥2) were randomised to either rivaroxaban 20mg daily (reduced to 15mg daily if creatinine clearance (CrCl) was 30-49ml/min) or warfarin (ROCKET AF)[17]. 37.6% of patients were warfarin naïve. The median duration of treatment exposure was 590 days and the mean time in therapeutic range (TTR) with warfarin was 55%. In the intention to treat analysis, the primary end point (composite of stroke [ischaemic or haemorrhagic)] and systemic embolism) occurred at a rate of 2.1% per year in those taking rivaroxaban and 2.4% per year in those taking warfarin (HR with rivaroxaban 0.88; 95% CI 0.74-1.03; p<0.001 for non-inferiority and p=0.12 for superiority). Rivaroxaban was non-inferior (but not superior) to warfarin in relation to the primary end point. The rates of death were not different between the treatment groups.	**SAFETY** In the ROCKET AF[17] study, there was no difference in the primary safety end point of major and non major clinically relevant bleeding between rivaroxaban and warfarin (14.9% per year vs. 14.5% per year (HR in rivaroxaban group 1.03; 95% CI 0.96-1.11; p=0.44). The rates of major bleeding were similar for rivaroxaban and warfarin (3.6% per year vs. 3.4% per year; p=0.58). The incidence of GI bleeding was higher with rivaroxaban (3.2% per year vs. 2.2% per year; p<0.001). Intracranial bleeding was lower with rivaroxaban than with warfarin (0.5% per year vs. 0.7% per year; p=0.02). Rivaroxaban is contraindicated in patients with a creatinine clearance < 15ml/min. It is not removable by dialysis. There is a specific antidote available for rivaroxaban (andexanet alfa). Patients should be advised to take rivaroxaban with food as there have been a small number of reports suggesting lack of efficacy (thrombotic events) where rivaroxaban has been taken on an empty stomach. See MHRA Drug Safety Update (July 2019) for full details. Consult SPC for more details at: www.medicines.org.uk
COST PER PATIENT PER YEAR[9,10] Rivaroxaban (20mg daily) £657 Warfarin £23 Estimated annual warfarin monitoring costs (NICE) £250 Predicted use will be dependent upon uptake and selection criteria. Once established, it is likely to be between 500-1000 per 100,000 of the population. New incidence of AF is around 87 per 100,000 per year[11].	**PATIENT FACTORS[18]** Patients with moderate to severe renal impairment (CrCl 15-49 ml/min) should have a dose reduction to 15mg daily. Rivaroxaban should be used with caution in patients with severe renal impairment (CrCl 15-29 ml/min) due to an increase in plasma concentration of rivaroxaban. Rivaroxaban is contraindicated in hepatic disease associated with a clinical bleeding risk and in patients taking any other anticoagulant (except as detailed below), azole antimycotics (except fluconazole), dronedarone, HIV protease inhibitors, rifampicin, phenytoin, carbamazepine or phenobarbitone. Prior to initiating treatment (and at least annually) a liver function test should be performed.

PRESCRIBING INFORMATION

- 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.
- Renal function should be assessed in all patients before starting rivaroxaban and at least once a year, and more frequently in those with a suspected decline in renal function. Rivaroxaban is not recommended if creatinine clearance is <15ml/min.
- Where rivaroxaban is initiated in secondary/tertiary care, it is good practice to communicate patient weight to the GP to assist with dosing and calculation of creatinine clearance.
- When switching from warfarin to rivaroxaban, stop warfarin and start rivaroxaban when INR ≤3.0.
- When switching from rivaroxaban to warfarin, give both agents concurrently until INR ≥ 2.0 (check INR just before rivaroxaban dose is due).
- When switching from parenteral anticoagulant to rivaroxaban, start rivaroxaban 0-2 hours before next dose of LMWH is due or at the same time as the continuous intravenous infusion of unfractionated heparin is stopped.
- When switching from rivaroxaban to parenteral anticoagulant, give the first parenteral dose when next dose of rivaroxaban is due.
- A missed dose should be taken when realised then continue on the following day with the usual daily dose. The dose should not be doubled within the same day to make up for the missed dose.
- Patients should be issued with a Patient Alert Card (available from manufacturer).

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