NHS
Pan Mersey
Area Prescribing Committee

The Pan Mersey Area Prescribing Committee recommends the prescribing of Direct Oral Anticoagulants (DOACs) for the treatment and prevention of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

AMBER following specialist initiation

GREEN for NHS Wirral CCG

GREEN where there is an agreed local pathway whereby GPs may start a DOAC for suspected VTE

NICE TA261[1] and TA287[2] (rivaroxaban), TA327[3] (dabigatran), TA341[4] (apixaban) and TA354[5] (edoxaban) recommend DOACs as an option for treating and/or preventing recurrent DVT and/or PE in adults. **Treatment with dabigatran and edoxaban should be preceded with at least 5 days of low molecular weight heparin (LMWH).** LMWH pre-treatment is not required with rivaroxaban or apixaban. Determining treatment duration is the responsibility of the consultant/specialist initiating treatment and should be clearly communicated to the patient's GP.

NICE NG158[6] states:

- Offer either apixaban or rivaroxaban to people with suspected or confirmed proximal DVT or PE. If neither apixaban nor rivaroxaban is suitable offer:
- LMWH for at least 5 days followed by dabigatran or edoxaban or
- LMWH concurrently with warfarin or another vitamin K antagonist (VKA) for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by the VKA on its own.
- Offer anticoagulation treatment for at least 3 months to people with confirmed proximal DVT or PE.

For the following groups of patients:

- Offer apixaban, rivaroxaban, or edoxaban for people with confirmed proximal DVT or PE and renal impairment (estimated creatinine clearance between 15 ml/min and 50 ml/min). Only offer dabigatran if estimated creatinine clearance is 30 ml/min or above. People with established renal failure (estimated creatinine clearance less than 15ml/min) should not be offered a DOAC.
- Consider a DOAC for people with active cancer and confirmed proximal DVT or PE (off-label use for this indication). When choosing anticoagulation treatment for people with active cancer and confirmed proximal DVT or PE, take into account the tumour site, interactions with other drugs including those used to treat cancer, and the person's bleeding risk. Review at 3 to 6 months according to clinical need.

People with confirmed proximal DVT or PE and an established diagnosis of triple positive antiphospholipid syndrome should not be offered treatment with a DOAC.

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.

The 2020 NICE recommendations are expected to lead to increased use of DOACs, particularly apixaban and rivaroxaban, to treat suspected and confirmed VTE. This should reduce the need for resources to monitor INR, manage bleeding complications and administer parenteral anticoagulation. The recommendation to start anticoagulation treatment before blood test results are available may increase prescribing of anticoagulation treatment. Additionally, more use of DOACs may also increase the need for expensive reversal agents.

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.

APC board date: 22 Sep 2021 Prescribing policy statement
Review date: May 2024 (or earlier if there is significant new evidence relating to this recommendation) Version: 3.2
APC administration provided by Midlands and Lancashire Commissioning Support Unit

Direct Oral Anticoagulants (DOACs) for the treatment and prevention of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

Effectiveness

Apixaban , rivaroxaban and edoxaban are direct factor Xa inhibitors and dabigatran is a direct thrombin inhibitor. A systematic review of 3,665 patients aged 75 years and older concluded that in older adults with VTE, DOACs appear to improve rates of recurrent VTE and VTE-related deaths compared with VKAs with similar bleeding outcomes[7].

A Cochrane review compared the efficacy and safety of LMWH, DOACs and VKAs for the long-term treatment of VTE in people with cancer. It concluded that LMWHs compared to VKAs probably produce an important reduction in VTE and that, while DOACs compared to LMWHs may show a likely reduction in VTE recurrence, they may show an increase in major bleeding[8].

NICE recommends each individual DOAC as an option for treating and/or preventing recurrent DVT and/or PE in adults[1-5]. 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[6].

Safety

NICE states that treatment with a DOAC is less likely to result in bleeding complications than treatment with LMWH and a VKA[6]. A choice of apixaban and rivaroxaban have been recommended first line as they have been shown to result in fewer bleeds.

Although NICE has recommended that DOACs can be considered for people with active cancer, DOACs are contraindicated in the presence of malignant neoplasms at high risk of bleeding. This will include the majority of gastric cancers and NICE states: *'The committee agreed that DOACs may be unsuitable for people with tumours that are associated with an increased risk of these types of bleeds (such as people with gastrointestinal malignancies). However, they agreed that treatment decisions for people with active cancer need to be made on a case-by-case basis.'*[6]

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.

An observational study with 59,525 participants looked at the safety of DOAC use compared with warfarin use for the treatment of VTE[9]. It concluded that treatment with DOACs, compared with warfarin, was not associated with an increased risk of major bleeding or all-cause mortality in the first 90 days of treatment.

Consult SPC for full list of side effects and interactions[10-13].

Cost[14-15]

	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
LMWH	£1,015 -£1,928 (6 months)

NICE estimates 100-200 people per 100,000 population per year require treatment.

NICE NG 158 states that although the use of DOACs will increase, implementing NG158 will result in savings for the NHS.

Patient factors

Prior to initiating treatment, and at least annually, a liver function test should be performed. See SPC for cautions and contraindications in hepatic impairment.

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

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 considered to be a significant risk of bleeding.
Edoxaban is contraindicated in uncontrolled, severe hypertension.
Consult SPC for other significant warnings, contraindications, and cautions.

Prescribing and implementation information

- Treatment should be started by a specialist in the management of VTE. Following initiation, prescribing can be continued in primary care by the GP. **Initial supply of the DOAC should be made by specialists care and, for apixaban or rivaroxaban, include the loading dose, and start of maintenance dose.**
- For suspected VTE, initial supply of a DOAC may be made in primary care or another specialist setting where there is an agreed local pathway in place. (See statement at the top of first page).
- Use of a DOAC for VTE in cancer is off-label and should NOT be started in primary care.
- **Duration of treatment must be communicated to the GP on initiation of treatment.** It is good practice to also communicate patient weight, to assist with dosing and calculation of creatinine clearance.
- DOACs have not been studied in patients at extremes of body weight >120kg or <50kg, consider use of a VKA in these patients or discuss with a consultant haematologist.
- Patients should receive at least 5 days treatment with LMWH before starting dabigatran or edoxaban.
- Renal function should be assessed in all patients before starting the DOAC and at least once a year, and more frequently in those with a suspected decline in renal function.
- **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.** Apixaban, edoxaban and rivaroxaban are not recommended if creatinine clearance is <15ml/min. Dabigatran is contraindicated in patients with severe renal impairment (CrCl < 30ml/min).
- For people who do not have renal impairment, active cancer, established triple positive antiphospholipid syndrome or extreme body weight (>120kg or <50kg): • offer continued treatment with the current anticoagulant if it is well tolerated or • if the current treatment is not well tolerated, or the clinical situation or person's preferences have changed, consider switching to apixaban if the current treatment is a direct-acting anticoagulant other than apixaban.
- Switching information is detailed in each Summary of Product Characteristics. When the required information is not available, the specialist should be contacted.
- A missed dose of apixaban should be taken immediately and then twice daily intake continued as before.
- 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.
- A missed dose of edoxaban should be taken immediately, then continued once daily on the following day.
- If a rivaroxaban dose is missed during the 15mg twice daily treatment phase (days 1-21), the patient should take it immediately to ensure intake of 30mg per day. In this case, two 15mg tablets may be taken at once. The patient should continue with the regular 15mg twice daily on the following day. If a dose is missed during the once daily treatment phase the patient should take the tablet immediately when they realise a dose has been missed and continue on the following day with the usual daily dose.
- For patients unable to swallow tablets or with a NG tube in situ, apixaban tablets may be crushed and suspended in water, dextrose 5% in water, or apple juice (stable for up to 4 hours).
- For patients who are unable to swallow whole tablets, edoxaban tablets may be crushed and mixed with water or apple puree and immediately administered orally. Alternatively, the tablets may be crushed and suspended in a small amount of water and immediately delivered through a gastric tube after which it should be flushed with water. (Stable in water and apple puree for up to 4 hours).
- For patients who are unable to swallow whole tablets, rivaroxaban tablets may be crushed and mixed with water or apple puree immediately prior to use and administered orally. The crushed tablets may also be given through gastric tubes.
- Dabigatran is not suitable for use in monitored dosage systems.
- Patients should be issued with a Patient Alert Card (available from manufacturer or can be downloaded from SPC).

References

1. National Institute for Health and Care Excellence. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism Technology appraisal 261; July 2012, reviewed November 2019. Accessed 09 February 2021.
2. National Institute for Health and care Excellence. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism Technology appraisal 287; June 2013, reviewed November 2019. Accessed 09 February 2021.
3. National Institute for Health and Care Excellence. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism Technology appraisal 327; December 2014, reviewed November 2019. Accessed 09 February 2021.
4. National Institute for Health and Care Excellence. Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism Technology appraisal 341; June 2015, reviewed November 2019. Accessed 09 February 2021.
5. National Institute for Health and care Excellence. Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism Technology appraisal 354; August 2015, reviewed November 2019. Accessed 09 February 2021.
6. National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing NICE Guideline 158; March 2020. Accessed 09 February 2021.
7. Chaudhary R et al. DOACs Versus VKAs in Older Adults Treated for Acute Venous Thromboembolism: Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2020 Sep;68(9):2021-2026
8. Kahale L et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. Cochrane Database of Systematic Reviews 19 June 2018. Accessed 18 February 2021
9. Min Jun et al. Comparative safety of direct oral anticoagulants and warfarin in venous thromboembolism: multicentre, population based, observational study BMJ 2017;359:j4323. Accessed 18 February 2021
10. Bristol-Myers Squibb-Pfizer. Summary of Product Characteristics Eliquis film-coated tablets, last updated 11/01/2021. Accessed 18 February 2021
11. Boehringer Ingelheim Limited. Summary of Product Characteristics Pradaxa hard capsules, last updated 14/05/2020. Accessed 18 February 2021
12. Daiichi Sankyo UK Limited. Summary of Product Characteristics Lixiana film-coated tablets, last updated 26/11.2020. Accessed 18 February 2021
13. Bayer plc. Summary of Product Characteristics Xarelto film-coated tablets, last updated 14/12/17. Accessed 18 February 2021
14. NHS Electronic Drug Tariff, February 2021. Accessed 09 February 2021 at: Drug Tariff
15. National Institute for Health and Care Excellence. Diagnostics Guidance DG 14; September 2014 Costing statement: Atrial fibrillation Accessed 18 February 2021.