PrescQIPP Community Interest Company

Anticoagulation in venous thromboembolism (VTE)

This bulletin discusses the choice of anticoagulation in venous thromboembolism (VTE) in line with National Institute for Heath and Care Excellence (NICE) guidance on the management of venous thromboembolic diseases [NG158].[1]

Recommendations

- DOACs demonstrate non inferiority for VTE acute treatment (compared with warfarin) and secondary prevention (compared with warfarin and aspirin). However in terms of safety, apixaban (5mg twice daily) and rivaroxaban (15mg twice daily, then 20mg daily) may reduce the risk of major and clinically relevant bleeding, compared with warfarin, for acute and secondary treatment and for secondary prevention of VTE.
- NG158 states to offer either apixaban or rivaroxaban to people with confirmed proximal deep vein thrombosis (DVT) or pulmonary embolism (PE). If neither apixaban nor rivaroxaban is suitable offer:
  - » Low Molecular Weight Heparin (LMWH) for at least five days followed by dabigatran or edoxaban or
  - » LMWH concurrently with a vitamin K antagonist (VKA), e.g. warfarin for at least five days, or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own.
- Prescribe DOACs generically to ensure that generic savings are made when generic versions become available.
- NG158 states to consider stopping anticoagulation treatment three months after a provoked DVT or PE, if the provoking factor is no longer present and the clinical course has been uncomplicated. Consider stopping anticoagulation three to six months after active cancer.
- Take into account information that may help predict risk of recurrence and risk of bleeding in the individual patient. Consider comorbidities, contraindications, and the patient's preferences. When starting treatment, carry out baseline blood tests (including full blood count, renal and hepatic function, prothrombin time and activated partial thromboplastin time). See attachment 8: Table of anticoagulant comparisons.
- Ensure that DOACs are stopped after the documented or licensed treatment period is reached for prevention of VTE after major elective orthopaedic surgery (i.e. knee or hip replacement). Refer to attachment 8: Table of anticoagulant comparisons.
- Review and, if appropriate, optimise prescribing and local policies relating to anticoagulants, including DOACs, to ensure these are in line with NG158.
- For people who decline continued anticoagulation treatment, NICE recommends to consider aspirin 75mg or 150mg daily (which is an off label use).

Background

In VTE, a blood clot forms in a vein. This can dislodge and travel in the blood, particularly to the pulmonary arteries, this is known as a pulmonary embolism (PE). A blood clot that forms in the deep veins, e.g. of the legs or pelvis, is known as a deep vein thrombosis (DVT). The term VTE includes both DVT and PE. A provoked DVT or PE is defined as a DVT or PE in a person with a recent (within three

months) and transient major clinical risk factor for VTE, such as surgery, trauma, significant immobility (e.g. bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy or puerperium; or in a person who is having hormonal therapy (combined oral contraceptive pill or hormone replacement therapy). An unprovoked DVT or PE is defined as a DVT or PE in a person with no recent major clinical risk factor for VTE who is not having hormonal therapy (combined oral contraceptive pill or hormone replacement therapy).[1]

A systematic review and meta-analysis demonstrated that patients demonstrated that patients who were treated with DOACs for acute VTE had non-inferior efficacy, but an overall superior safety profile compared to warfarin.[2]

An independent systematic review produced for the Department of Health and Social Care demonstrated that:

There was no strong evidence to support the use of DOACs for VTE for primary prevention (compared with LMWH; assessed for hip- and knee-surgery patients only), acute treatment (compared with warfarin) and secondary prevention (compared with warfarin and aspirin). However, apixaban (5mg twice daily) and rivaroxaban (15mg twice daily, then 20mg once daily) may reduce the risk of major bleeding and clinically relevant bleeding compared with warfarin for the acute treatment and secondary prevention of VTE. Apixaban (5mg twice daily) may reduce the risk of major bleeding, compared with some other DOACs (dabigatran 150mg once daily, edoxaban 60mg or 30mg (17.6%) once daily, and rivaroxaban 15mg twice daily then 20mg once daily) in patients receiving acute treatment of VTE.

Apixaban (5mg twice daily) was likely to be the most cost-effective alternative to warfarin for acute treatment of VTE, although more research into the relative efficacy and safety of apixaban compared with other DOACs is needed.[3]

NICE recommendation in confirmed proximal DVT or PE

The NICE guidance on the diagnosis, management and thrombophilia testing of venous thromboembolic diseases [NG158] recommends to offer either apixaban or rivaroxaban for at least three months to people with confirmed proximal DVT or PE.

If neither apixaban nor rivaroxaban is suitable, offer:[1]

- LMWH for at least five days followed by dabigatran or edoxaban **or**
- LMWH concurrently with a vitamin K antagonist (VKA; e.g. warfarin) for at least five days, or until the INR is at least 2.0 on two consecutive readings, followed by a VKA on its own.
- Consider anticoagulation treatment with regular monitoring of therapeutic levels for people with confirmed proximal DVT or PE who weigh less than 50kg or more than 120kg, to ensure effective anticoagulation. Follow protocols for dosage calculation – see attachments 8 and 9.
- In patients with renal impairment or established renal failure, offer people with confirmed proximal DVT or PE and renal impairment (estimated CrCl between 15ml/min and 50ml/min) one of:
  - Apixaban
    - If CrCl 30-49ml/min; no dosage adjustment is necessary
    - If CrCl 15-29ml/min; use with caution
    - If CrCl <15ml/min; not recommended[4]
  - Rivaroxaban
    - If CrCl 30-49ml/min; 15mg twice daily for the first three weeks. Thereafter, when the recommended dose is 20mg, a reduction in dose from 20mg to 15mg once daily should be considered if the patient's assessed risk of bleeding outweighs the recurrent DVT and PE
    - If CrCl 15-29ml/min; use with caution
    - If CrCl <15ml/min; not recommended[5]

- LMWH for at least five days followed by:
  - Edoxaban **or**
  - Dabigatran if estimated creatinine clearance is 30ml/min or above
- LMWH or unfractionated heparin (UFH), given concurrently with a VKA for at least five days or until the INR is at least 2.0 on two consecutive readings, followed by a VKA on its own.[1] See attachment 9.

Duration of treatment for provoked DVT or PE

NG158 states to consider stopping anticoagulation treatment three months after a provoked DVT or PE if the provoking factor is no longer present and the clinical course has been uncomplicated. However, after active cancer consider stopping after three to six months. Active cancer is defined as a person receiving active antimitotic treatment; or diagnosed within the past six months; or recurrent or metastatic; or inoperable cancer. Squamous skin cancer and basal cell carcinoma are excluded from these definitions.[1]

Consider continuing anticoagulation beyond three months (six months for people with active cancer) after an unprovoked DVT or PE. The decision is based on the balance between the person's risk of VTE recurrence and their risk of bleeding. Provide direct contact details of a healthcare professional or team with expertise in thrombosis who can discuss new signs or symptoms or other concerns. The risks and benefits of long-term anticoagulation must be discussed with people and their preferences taken into account.[1]

Evidence supporting extended anticoagulation exists after an unprovoked DVT or PE; however, for many patients, uncertainty regarding when to discontinue anticoagulation persists. A systematic review of three randomised controlled trials (RCTs) examined extended anticoagulation with DOACs as compared to non-extended therapy for the treatment of VTE. The study found that extended DOAC therapy for one year in patients with clinical uncertainty for ongoing anticoagulation can reduce VTE recurrence and mortality; however, it could increase clinically relevant non-major bleeding events.[6]

Dosage adjustment and monitoring

Note the cautions and requirements for dose adjustment and monitoring in each medicine's Summary of Product Characteristics (SPC) and follow locally agreed protocols or advice from a specialist or multidisciplinary team.[1] See also attachment 8. Table of anticoagulant comparisons.

Antiplatelet therapy

For people who decline continued anticoagulation treatment, consider aspirin 75 mg or 150 mg daily.[1] Special care should be taken when deciding to prescribe DOACs to patients with concomitant treatments which may increase the risk of major bleeding such as antiplatelets.[7] A systematic review of six RCTs (26,924 patients) of whom 3,550 (13.2%) received concomitant antiplatelet therapy, mainly aspirin (67.7%) demonstrated that concomitant antiplatelet therapy did not reduce the incidence of recurrent VTE and VTE-related death with any oral anticoagulant. Compared with no antiplatelet therapy, concomitant antiplatelet therapy was associated with a higher risk of major bleeding in patients with any oral anticoagulant. In patients receiving concomitant antiplatelet therapy, there were no statistically significant differences in efficacy or safety outcomes with DOACs or VKAs. The authors concluded that concomitant use of antiplatelet therapy with oral anticoagulants does not appear to affect the risk of recurrent VTE, but increases the risk of major bleeding.[8]

Cost and savings

In England, Wales and Scotland £845 million is spent annually on DOACs, warfarin and phenindione (excluding monitoring) (NHSBSA Dec21-Feb22, and Public Health Scotland Nov21-Jan22). **DOACs account for 99% of this spend and 77% of these items in England and Wales** (NHSBSA Dec21-Feb22).

In Scotland, DOACs account for 98% of this spend and 71% of these items (Public Health Scotland Nov21-Jan22).

The 28 day cost comparison for DOACs and warfarin are provided in table 1. This does not include any discounts such as the NHSE nationally commissioned discount or local rebates.

Table 1. DOAC cost per 28 days at dose stated[9,10] (This is the NHS List price and not the NHSE nationally commissioned discounted or local rebate price.)

Dabigatran (Pradaxa®) 150mg twice daily	Rivaroxaban (Xarelto®▼) 20mg once daily	Apixaban (Eliquis®) 5mg twice daily	Edoxaban (Lixiana®) 60mg once daily	Warfarin 3mg daily
£47.60	£50.40	£53.20	£49.00	£0.73 + monitoring

A further breakdown of individual drugs is in Table 2 (items and % of total items) and Table 3 (spend and % of total spend).

Table 2: Usage of DOACs and warfarin across England, Wales and Scotland (NHSBSA Dec21-Feb22 and Public Health Scotland Nov21-Jan22)

Total items (% of total items)	England	Scotland	Wales
Apixaban	2,018,819 **(41.32%)**	115,857 **(36%)**	127,135 **(37.68%)**
Rivaroxaban	1,157,123 **(23.68%)**	37,522 **(12%)**	66,151 **(19.60%)**
Edoxaban	507,362 **(10.38%)**	71,326 **(22%)**	33,403 **(9.90%)**
Dabigatran	92,585 **(1.90%)**	2,224 **(1%)**	5,017 **(1.49%)**
Warfarin	1,109,645 **(22.71%)**	93,325 **(29%)**	105,731 **(31.33%)**

Table 3: Spend of DOACs and warfarin across England, Wales and Scotland (NHSBSA Dec21-Feb22 and Public Health Scotland Nov21-Jan22)

Total spend (% of total spend)	England	Scotland	Wales
Apixaban	£96,341,216 **(52.69%)**	£8,868,874 **(51%)**	£5,944,752 **(55.37%)**
Rivaroxaban	£56,591,316 **(30.95%)**	£2,829,188 **(16%)**	£2,953,071 **(27.50%)**
Edoxaban	£23,424,215 **(12.81%)**	£5,181,937 **(30%)**	£1,441,557 **(13.43%)**
Dabigatran	£4,607,344 **(2.52%)**	£155,924 **(1%)**	£233,054 **(2.17%)**
Warfarin	£1,675,042 **(0.92%)**	£239,413 **(1%)**	£157,285 **(1.46%)**

An audit to ensure appropriate monitoring and duration of anticoagulation treatment is available in attachment 7.

Savings on DOACs may be achieved through a number of medicine optimisation initiatives such as:

- Deprescribing DOACs at the end of recommended treatment duration intervals.

- Prescribe DOACs generically to ensure that savings are made when less costly generic versions become available.
- Switching to a lower cost DOAC (as determined locally) that is appropriate for individual patients on longer term DOAC treatment.
- Using the least costly DOAC (as determined locally) that is appropriate for new patients requiring oral anticoagulation.
- Ensuring that any patients using multiple capsules or tablets are prescribed the appropriate strength of formulation. DOACs are flat dose priced, so doubling the number of capsules or tablets rather than moving to the higher strength capsules or tablets, will double the cost of treatment.

A 10% reduction in the spend on DOACs could release annual savings of £76.8million in England and Wales and £6.8million in Scotland (NHSBSA Dec21-Feb22, and Public Health Scotland Nov21-Jan22) **In England and Wales, this equates to £118,484 per 100,00 population. In Scotland, this equates to £116,529 per 100,000 population.**

If 50% of patient on phenindione were switched to warfarin, this could release annual savings of £199,793 in England and Wales and £36,370 in Scotland (NHSBSA Dec21-Feb22, and Public Health Scotland Nov21-Jan22). **This equates to £308 per 100,000 population in England and Wales. In Scotland, this equates to £622 per 100,000 population** (NHSBSA Dec21-Feb22, and Public Health Scotland Nov21-Jan22).

Generic versions of apixaban have received UK marketing authorisations, although the decision to invalidate the UK supplementary protection certificate for apixaban is currently subject to potential appeal.[11,12] The apixaban Accord 2.5mg and 5mg tablets are currently the same cost as the brand Eliquis®.[13] However, competition arising from the launch of other generic versions are likely to reduce prices. Prescribing by generic name will ensure that savings are made when less costly generics are available. The PrescQIPP generic savings report will be updated when less costly generics are available.

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-282-anticoagulation/
Implementation tools	
Data pack	https://data.prescqipp.info/views/B282_Anticoagulation/FrontPage?%3Aembed=y&%3Aiid=1&%3AisGuestRedirectFromVizportal=y

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