Direct Oral Anticoagulants ‘DOACs’ for Treatment and Secondary Prevention of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in Primary Care

Referral to Churchill DVT Clinic for suspected lower limb DVT

A Primary Care service specification is in place for GPs to perform a D-dimer test and Wells score for patients presenting with a suspected DVT. The Churchill Hospital DVT Service accepts adult patients suspected of having a lower limb DVT who are suitable for out-patient assessment and treatment. It operates seven days a week, 9am-5pm Monday-Friday, 9am-1pm Saturday/Sunday/Bank Holidays. On Christmas Day and New Year's Day the service is closed.

New patients are required to arrive at least one hour before the clinic closes.

Referrals are by telephone to the DVT nurse. The clinic will take details and also ask for a brief letter to either accompany the patient or to be faxed to 01865 857092 or be emailed to dvt.service@nhs.net. The DVT email account is checked twice a day, morning and afternoon, by a DVT nurse. If an appointment is delayed until the next day, the GP should take a D-dimer and the patient should be given therapeutic anticoagulation (see ‘Out of hours’ section below for dosing details).

Monday to Friday – telephone 01865 225629
Saturday and Sunday – telephone Churchill switchboard (01865 741841) and bleep 5165.

Please note that for suspected pulmonary embolism refer patient to medical team registrar on ext. 27591.

Exclusion criteria

- Pregnancy (patients ≥16 weeks pregnant go to the maternity assessment unit (MAU) (ext. 20221) and patients <16 weeks pregnant go to the ambulatory assessment unit (part of acute general medicine) (ext. 21812; consultant bleep 4658).
- Suspected upper limb DVT
- In-patients (unless investigation complete and being discharged)
- Unable to transfer from chair to chair by self.
- Suspected pulmonary embolism
- Weight >180 kg
- Active bleeding
- Known to be at increased risk of bleeding, e.g.
  - Active peptic ulceration
  - Liver disease (INR ≥ 1.5)
  - Renal insufficiency: creatinine > 200 µmol/L with unknown eGFR or eGFR <20 mL/min/1.73m² (eGFR calculator at http://egfrcalc.renal.org/).
  - Uncontrolled hypertension (>200/110 mmHg)
  - Recent (<1/12) eye or CNS surgery
  - Recent (<1/12) haemorrhagic stroke

Patients with inherited bleeding disorders or thrombocytopenia (platelets <100 x 109/L) or with a Hb < 100 g/L should be discussed with a doctor in the Haemophilia and Thrombosis Centre or with the on-call haematology registrar.
• At the weekend (and on bank holidays) the DVT clinic cannot accept patients who require hospital transport

Out of Hours referrals to Churchill DVT service for suspected lower limb DVT

‘Out of hours’ is between 4pm when the DVT clinic accepts the last patient (1pm on Saturday/Sunday/Bank Holidays {clinic is closed Christmas Day and New Year’s Day}) and 9am the following morning. A GP seeing a patient with suspected DVT out of hours should decide whether they are suitable for out-patient assessment and treatment (see exclusion list above). If they are not suitable the patient should be referred to the on-call medical team at the JR (01865 741166).

If they are suitable a dose of either a Low Molecular Weight Heparin (LMWH), apixaban or rivaroxaban should be given (dosing below) pending a DVT clinic appointment the following day.

If the GP cannot give LMWH, apixaban or rivaroxaban they should phone the medic on-call at the Churchill Hospital (01865 741841) to arrange a dose of LMWH to be given on John Warin Ward. If a patient attends the GP Out Of Hours Service they will receive a dose of dalteparin and arrangements made to attend the Churchill DVT clinic the next day.

A blood sample for D-dimer testing MUST be taken before anticoagulation is given. This should be given to the patient to bring in to their DVT appointment. Note: D-dimers cannot be used as part of the diagnostic algorithm once patients have received a dose of anticoagulant, and this sample is therefore critical for effective diagnosis and use of resources.

• Dose of dalteparin:

<table>
<thead>
<tr>
<th>Weight (Kg)</th>
<th>Dalteparin (Units)</th>
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</thead>
<tbody>
<tr>
<td>&lt;46</td>
<td>7,500</td>
</tr>
<tr>
<td>46-56</td>
<td>10,000</td>
</tr>
<tr>
<td>57-68</td>
<td>12,500</td>
</tr>
<tr>
<td>69-82</td>
<td>15,000</td>
</tr>
<tr>
<td>&gt;82</td>
<td>18,000</td>
</tr>
</tbody>
</table>

• Dose of apixaban: 10 mg bd (supply four to six 5 mg tablets in order to ensure a dose is not missed before review at DVT clinic).

• Dose of rivaroxaban: 15 mg bd (supply two to three 15 mg tablets in order to ensure a dose is not missed before review at DVT clinic).

Apixaban and rivaroxaban should not be used in pregnancy.

The patient should be given a referral letter and asked to phone the DVT Service between 9:00a.m. and 9:30a.m. the following day (they must be given the telephone number 01865 225629). The GP should either email (dvt.service@nhs.net) or both send a fax (01865 857092) and leave a message on the answerphone (01865 225629) to alert the clinic. If transport is needed for the first visit this must be arranged by the patient’s own GP the following morning (a return journey should be booked with the patient arriving at the clinic at 12.30pm and being collected at 3.30pm).

Copies of the leaflet ‘Information for patients attending the DVT Clinic’ giving information to patients on how to get to the clinic and what to expect, can be downloaded from http://www.ouh.nhs.uk/services/referrals/specialist-medicine/haemophilia.aspx.
**Treatment of DVT**

Once a positive diagnosis has been made at the clinic the patient is treated with either a low molecular weight heparin (LMWH) and /warfarin or a DOAC (formerly 'NOAC').

Dalteparin remains the gold standard treatment for cancer-related VTE. Evidence suggests that patients with cancer have lower VTE recurrence rates when treated with LMWH instead of warfarin (Lee, et al 2003). See Dalteparin guidelines for primary care.

Warfarin will be used if eGFR < 30 ml/min, or if there is liver dysfunction, or if the patient weighs more than 120 kg. Although the Summary of Product Characteristics (SPCs) does not have an upper limit for body weight OUHFT recommend that DOACs should not be used in patients with a weight of more than 120 kg. This is because there are limited clinical data available for patients at the extreme of weight, and the available pharmacokinetic/ pharmacodynamic evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under-dosing. See MIL Vol. 8, No. 1: Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) with rivaroxaban or apixaban in adults.

Choice of anticoagulant should be discussed with the patient, some may prefer to choose a drug with a longer history of use or have warfarin again if they have taken it previously. If there is no medical reason to favour warfarin and if there is no patient preference for warfarin the DVT clinic will use a DOAC.

The first **three weeks** of DOAC treatment will be provided by the DVT clinic. Further supplies must therefore be obtained from the patient's GP. OUHFT will provide clear written communication regarding diagnosis, medication commenced including dosing regime and likely duration of therapy (if known at that stage). Please ensure that patient’s therapy (DOAC) is reviewed and if indicated, stopped after completion of the intended course (as per OUHFT letter). Patients on warfarin will be monitored by the anticoagulant clinic at the Churchill Hospital using the RAID system and warfarin dose titrated accordingly. Warfarin tablets are supplied by the GP.

For women on the combined oral contraceptive pill (COC), the COCP should be stopped at least one month before anticoagulation is discontinued and an alternative form of contraception should be organised. The patient should be warned of the risks of pregnancy on warfarin or a DOAC.

**Interaction with other medicinal products**

Please consult the latest BNF and the SPC for details of potential interactions.

**DOACs**

DOACs are not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (such as ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase plasma concentrations of DOACs to a clinically relevant degree. Co-administration of DOACs with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John’s Wort, may lead to reduced plasma concentrations of DOACs. It is therefore recommended that strong CYP3A4 inducers should not be co-administered with DOACs when treating acute venous thromboembolism. Macrolide antibiotics, such as clarithromycin and erythromycin, may inhibit metabolism of DOACs and therefore caution should be applied if co-prescribed. Co-administration of dabigatran or rivaroxaban with...
dronedarone should be avoided. Care should also be taken if patients are treated concomitantly with medicinal products affecting haemostasis (e.g. NSAIDS, aspirin, platelet aggregation inhibitors or other antithrombotic agents). Further information for cardiac patients can be found in Primary Care Prescriber Decision Support for DOACs for stroke prevention in Atrial Fibrillation. Concomitant treatment with unfractionated heparin (UFH), dalteparin or fondaparinux is contraindicated (except when UFH is being used to maintain patency of a central venous or arterial catheter).

**Duration of treatment**

Patients who may require long-term anticoagulation will be reviewed at three months to decide whether to stop or whether to continue indefinitely.

Patients who are definitely stopping at three months do not have a routine follow-up.

<table>
<thead>
<tr>
<th>Patient groups requiring 3 months treatment</th>
<th>Patient groups requiring 3 months treatment then a review to consider for long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1st proximal DVT with transient risk factors (TRF)*</td>
<td></td>
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<tr>
<td>• 1st PE with TRF*</td>
<td></td>
</tr>
<tr>
<td>• 1st isolated calf vein DVT</td>
<td>• Recurrent thrombosis</td>
</tr>
<tr>
<td></td>
<td>• Proximal DVT or PE with on-going risk factors such as cancer</td>
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<tr>
<td></td>
<td>• 1st unprovoked proximal DVT</td>
</tr>
<tr>
<td></td>
<td>• 1st unprovoked PE</td>
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</tbody>
</table>

*Transient risk factors (TRF); Surgery, Significant trauma e.g. fracture, plaster cast, COC/HRT, Pregnancy/puerperium, Temporary immobility e.g. confined to bed ≥ 3 days or a flight >6 hours (please note that is a weaker TRF). If temporary immobility is the only TRF the patient should have a three months review.

**Ongoing monitoring by GP**

GPs will be responsible for the ongoing monitoring of patients who require long-term anticoagulation.

Patients who require long-term anticoagulation with a DOAC should be reviewed by their GP on a regular basis, but as a minimum annually.

**At each visit;**

- Assess compliance and reinforce advice regarding regular dosing schedule, consider compliance aids if appropriate.
- Enquire about adverse effects such as bleeding.
- Assess for the presence of thromboembolic events.
- Enquire about other medicines, including OTC medicines especially aspirin and NSAIDs.
- Consider other side effects and carefully assess relation with DOAC, decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug.

**Blood sampling:**

- Monitor haemoglobin, renal and liver function yearly.
- Renal function should be assessed more frequently (6 monthly) in compromised patients such as the elderly (≥ 75-80 years) or frail (defined as ≥ 3 of the following criteria/; unintentional weight loss,
self-reported exhaustion, weakness assessed by handgrip test, slow walking speed/gait apraxia, low physical activity).

- If CrCl ≤ 60 ml/min, recheck patient’s renal function at an interval of ‘CrCl/10’ monthly.
- Recheck renal or liver function if there is an inter-current condition that may impact renal or hepatic function.

For dosage in renal impairment see the summary table below.

**Missed dose**

For DOACs with a twice daily dosing regimen, the forgotten dose can be taken up until 6 hours prior to the next scheduled dose, and then continue with twice daily intake as before. If the next dose is due a double dose can be taken.

For DOACs with once daily dosing regimen, the forgotten dose can be taken up until 12 hours prior to the next scheduled dose, and then continued on the following day with once a day dosing. For once a day dosing regimens the dose should not be doubled within the same day to make up for a missed dose.

For rivaroxaban, if a dose is missed during the 15 mg twice daily treatment phase (day 1-21), the patient should take the missed dose immediately and take the next dose on time (if the next dose is due two 15 mg tablets can be taken together). The patient should then continue with 15 mg twice daily. If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take the missed dose immediately, and continue on the following day with the once daily intake as recommended. The dose should **not** be doubled within the same day to make up for a missed dose.

**Overdose**

Depending on the amount of suspected overdose, hospitalisation for monitoring or urgent measures is advised.

**Drug information booklets**

- Warfarin – NPSA “yellow book”
  - Booklets and patient alert cards can be ordered the Primary Care Support England (PCSE) supply system
- Apixaban (Eliquis®)
  - Booklets and patient alert cards can be ordered from Bristol-Myers Squibb Medical Information (Telephone: 0800 731 1736; E-mail: medical.information@bms.com)
- Dabigatran (Pradaxa®)
  - Booklets and patient alert cards can be ordered from Boehringer Ingelheim Medical Information (Telephone: 01344742579, E-mail: medinfo@bra.boehringer-ingelheim.com)
- Edoxaban (Lixiana®)
  - Booklets and patient alert cards can be ordered from Daiichi Sankyo Medical Information (Telephone: 01748828818, E-mail: medinfo@daiichi-sankyo.co.uk)
- Rivaroxaban (Xarelto®)
  - Booklets and patient alert cards can be ordered from Bayer plc Medical Information (Telephone: 01653563116, E-mail: Medical.information@bayer.co.uk)
Booklets and alert cards can be downloaded and printed from http://www.xarelto-info.co.uk/hcp/
### Summary table of DOACs for Treatment and Prevention of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>APIXABAN (ELIQUIS®)</th>
<th>DABIGATRAN (PRADAXA®)</th>
<th>EDOXABAN (LIXIANA®)</th>
<th>RIVAROXABAN (XARELTO®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct factor Xa inhibitor</strong></td>
<td>10mg twice daily</td>
<td>150mg twice daily following treatment with a parenteral anticoagulant for at least 5 days.</td>
<td>60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days</td>
<td>15mg twice daily for 21 days, then 20 mg daily with food to aid absorption.</td>
</tr>
<tr>
<td><strong>Dose for treatment of DVT/PE</strong></td>
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<tr>
<td><strong>Dose in secondary prevention of DVT/PE</strong></td>
<td>2.5 mg twice daily following completion of 6 months anticoagulant treatment.</td>
<td>150 mg twice daily</td>
<td>60 mg once daily</td>
<td>20 mg daily with food to aid absorption</td>
</tr>
<tr>
<td><strong>Dose in renal impairment</strong></td>
<td>Do not use if CrCl &lt;15ml/min* Use with caution if CrCl 15-29ml/min* Consider dose reduction 110mg BD if CrCl 30-50ml/min*</td>
<td>Do not use if CrCl less than 30ml/min* If CrCl 15-50 ml /min then consider 30 mg once daily</td>
<td>Do not use if CrCl less than 15ml/min* If CrCl 15-49 ml /min then consider 15mg OD with food if assessed bleeding risk outweighs risk of recurrent DVT and PE. Do not use if CrCl less than 15ml/min*</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic impairment</strong></td>
<td>Not recommended in severe hepatic impairment as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy</td>
<td>Not recommended in patients with elevated liver enzymes &gt;2 upper limit of normal. Contraindicated in patients with hepatic impairment or liver disease expected to impact on survival.</td>
<td>Not recommended in severe hepatic impairment as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy</td>
<td>Use with caution as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity A lesion or condition, if considered a significant risk factor for major bleeding Active bleeding Hepatic disease or impairment Anti-coagulant in use (except during switching - see below) Prosthetic heart valves Pregnancy and breastfeeding</td>
<td>Hypersensitivity A lesion or condition, if considered a significant risk factor for major bleeding Active bleeding Hepatic disease associated with coagulopathy and clinically relevant bleeding risk Anti-coagulant in use (except during switching - see below) Prosthetic heart valves Pregnancy and breastfeeding</td>
<td>Hypersensitivity A lesion or condition, if considered a significant risk factor for major bleeding Active clinically significant bleeding Hepatic disease associated with coagulopathy and clinically relevant bleeding risk Anti-coagulant in use (except during switching - see below) Prosthetic heart valves Pregnancy and breastfeeding</td>
<td>Hypersensitivity A lesion or condition, if considered a significant risk factor for major bleeding Active bleeding Hepatic disease associated with coagulopathy and clinically relevant bleeding risk Anti-coagulant in use (except during switching - see below) Uncontrolled severe hypertension Prosthetic heart valves Pregnancy and breastfeeding</td>
</tr>
<tr>
<td><strong>Extravasation BMI</strong></td>
<td>If &lt;50kg or &gt;100-120kg** then exposure of DVT/PE may be variable 20-30%. It is recommended that at these body weights the Cockcroft and Gault formula is used to calculate CrCl rather than eGFR</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Pharmacological issues</strong></td>
<td>May be dispersed in water Stable in dosette boxes</td>
<td>Capsules can only be stored in original packaging thus not suitable for dosette boxes</td>
<td>Stable in dosette boxes</td>
<td>May be dispersed in water Stable in dosette boxes</td>
</tr>
<tr>
<td><strong>Switching from warfarin</strong></td>
<td>Stop warfarin and start apixaban once INR is less than 2 Stop warfarin and start dabigatran once INR is less than 2 Stop warfarin and start edoxaban once INR is 2.5 or less</td>
<td></td>
<td></td>
<td>Stop warfarin and start rivaroxaban once INR 2.5 or less (not forgetting higher initial dosing when within three weeks of an acute event)</td>
</tr>
<tr>
<td><strong>Switching to warfarin</strong></td>
<td>Co-administer apixaban and warfarin for 2 days. After 2 days, check INR prior to next apixaban dose and continue until INR 2 or greater</td>
<td>Start warfarin 2 days (CrCl 30-49ml/min) or 3 days (CrCl 50ml/min or above) before stopping dabigatran</td>
<td>Co-administer edoxaban*** and warfarin until INR 2 or greater, for up to a maximum of 14 days. During this time, frequently check INR immediately prior to the edoxaban dose</td>
<td>Co-administer rivaroxaban and warfarin until INR 2 or greater</td>
</tr>
</tbody>
</table>

**NB:** Warfarin is the preferred option in those with a creatinine clearance below 30ml/min because of a lack of outcome data for DOACs in this setting. Seek specialist advice in severe renal impairment.

**Warfarin is the preferred option in patients with a weight of more than 120kg due to concerns about under-dosing.**

**For patients on 60mg daily reduce to 30mg daily and for patients on 30mg daily reduce to 15mg daily. Refer to SPC for further details.**

DOACs for Treatment and Secondary Prevention of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in Primary Care
References


16. Oxford University Hospitals NHS Trust Medicines Information Leaflet Volume 8, Number 1: Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) with rivaroxaban or apixaban in adults. February 2017.