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

Referral to Churchill/Horton DVT Clinic for suspected lower limb DVT

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

Referrals for both the Churchill and Horton DVT clinic are by **telephone to the DVT nurse in hours (see below for contact details)**. The nurse will take details and also ask for a brief letter to either accompany the patient or be emailed. Out of hours referrals can be made by email. The DVT email account is checked regularly. If an appointment is not available until the next day, the GP should take a venous blood sample for a D-dimer test (for patient to take to clinic appointment) and the patient should be given therapeutic anticoagulation (see 'Out of hours' section below for dosing details).

Please note that for suspected pulmonary embolism refer patient to medical referral line on 01865 227591.

Monday to Friday – telephone 01865 225629 (Churchill) or 01295 229282 (Horton)
Saturday and Sunday – telephone switchboard (0300 304 7777) and bleep 5165.
Out of hours –email: dvt.service@nhs.net (Churchill) or ouh-tr.hortondvtservice@nhs.net (Horton)

Exclusion criteria for DVT clinic

- 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.

- If patients require hospital transport for their first DVT clinic appointment this should be booked by the GP practice. In order to guarantee a booking both in to and out of the hospital bookings should be made before 3pm the day prior to the appointment.

- 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 after 5pm Monday-Friday, after 1pm Saturdays, Sundays and bank holidays, or on Christmas day or New Year's day. 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 medical referral line at the JR on 01865 227591.

If they are suitable for outpatient assessment, a venous blood sample for a D-dimer should be taken before a dose of either a low molecular weight heparin (LMWH), apixaban or rivaroxaban is administered(dosing below) pending a DVT clinic appointment the following day. NICE Quality Standard (QS29) states that people with suspected deep vein thrombosis are offered an interim therapeutic dose of anticoagulation therapy if diagnostic investigations are expected to take longer than 4 hours from the time of first clinical suspicion.

Patients should be asked to telephone the DVT clinic the following morning (01865 225629), and the GP should email or leave a message on the above answerphone to alert them of the patient. If the patient requires hospital transport for their first DVT clinic appointment this must be booked by their GP practice the following morning. GP practices should liaise with the DVT nurse with regards to the timings for this if possible.

If a patient attends the GP Out Of Hours Service they will receive a dose of dalteparin, apixaban or rivaroxaban, and arrangements made to attend the 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. Patients will commonly need to return for a second scan one week after their original review if a D-dimer is not taken and this will limit the DVT clinic's ability to see new patients. Please give the patient the D dimer sample to bring to their appointment the next morning. It is stable for 24 hours at room temperature.

- Dose of dalteparin

Body weight (kg)	**Dose of dalteparin by subcutaneous injection using a pre-filled syringe (units)**
Less than 46 Consider discussing with haem SpR if less than 40kg	7,500 once daily
46-56	10,000 once daily
57-68	12,500 once daily
69-82	15,000 once daily
83-98	18,000 once daily
99-112	10,000 **twice daily**
113-137	12,500 **twice daily**
138-165	15,000 **twice daily**
More than 166 Consider discussing with haem SpR if greater than 180kg	18,000 **twice daily**

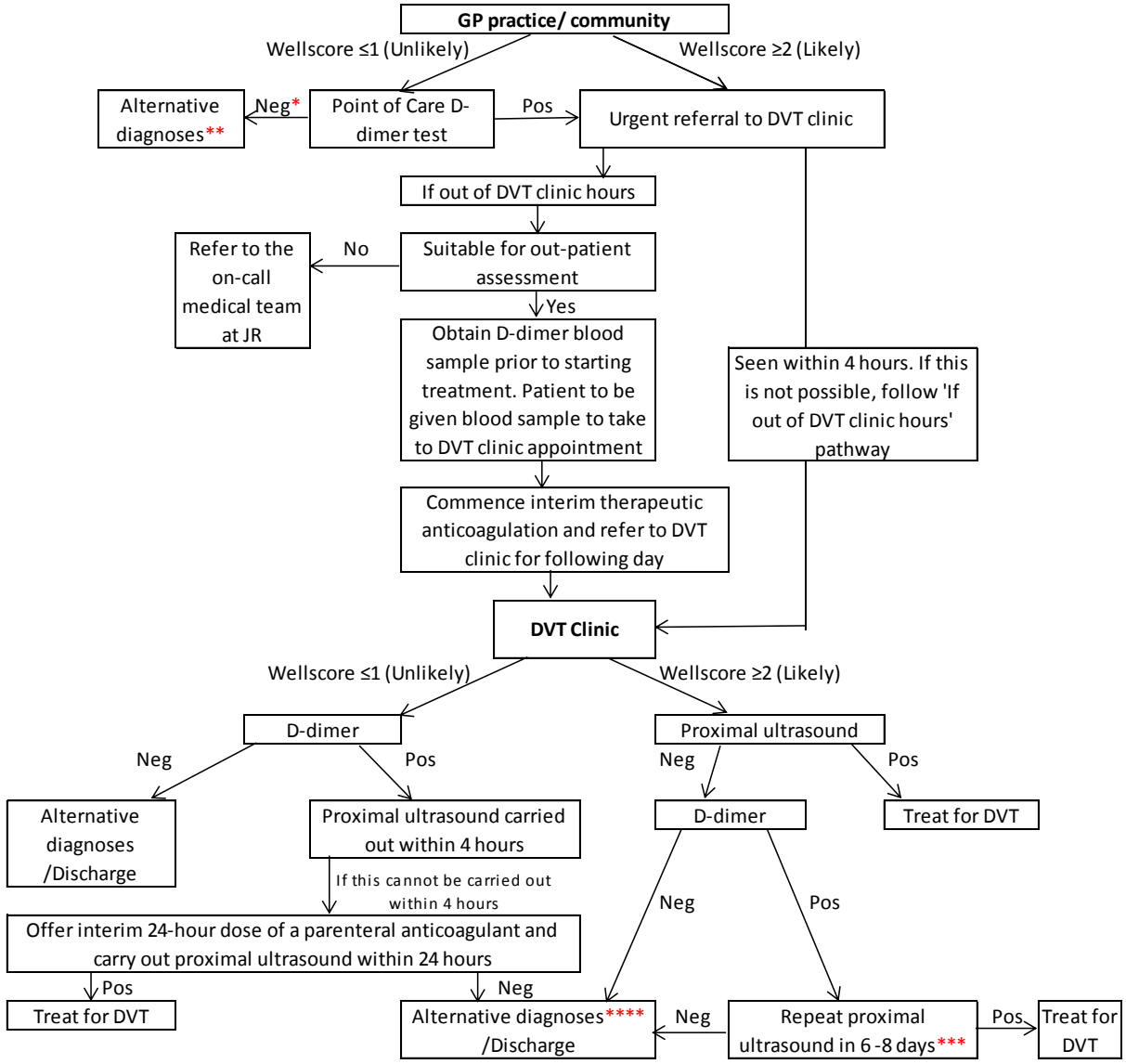
In patients weighing more than 98 kg therapeutic dalteparin doses are to be given twice daily and the GP should arrange for the appropriate dosing regimen. Please discuss with the clinical team if this is practically difficult. Doses of dalteparin differ from the BNF in patients over 98kg in line with OUH DVT protocols and ASH guidance

- 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 are contraindicated in pregnancy and breastfeeding, and are not recommended in patients who weigh more than 120kg.

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.

Primary Care overview of DVT diagnosis, referral and follow-up



* A negative D-dimer results is defined as < 500µg/l FEU.
* Alternative diagnoses should be considered and patients should be advised that they are not likely to have DVT. Discuss and symptoms of DVT and when and where to seek medical help.
*** "Likely" patients who have a positive D-dimer need a repeat scan of the proximal veins in 6 to 8 days time. They remain off anticoagulation whilst awaiting this. An alternative strategy for these patients would be to extend the initial scan to the whole leg i.e. to also scan the calf veins. However please note this is not that this is generally not standard practice at OUH, but can be performed in exceptional circumstances to prevent a patient having to return at 6-8 days.
**** If a patient has a negative scan but has whole leg swelling a pelvic DVT should be considered and a CT venogram can be requested.

Treatment of DVT

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

Dalteparin remains the gold standard treatment for cancer associated 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. Data are emerging from clinical trials around the use of DOACs (in particular for Rivaroxaban and Edoxaban) as treatment for cancer associated VTE. At

present LMWH remains the standard of care although there are advantages of using oral medications. DOACs in this setting should only be prescribed with consultation from haematology.

Warfarin will be used if creatinine clearance (using Cockcroft and Gault equation) is less than 30 ml/min, or if there is liver dysfunction. It can also be an advantage to have a monitored treatment in the poorly compliant. 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 who weigh 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. Apixaban and rivaroxaban are convenient for initiation of treatment as the quick onset of action negates the need for parenteral therapy. Whilst it is recognised that dabigatran (an oral thrombin inhibitor) and edoxaban (a factor Xa inhibitor) are also licensed for VTE they are not considered within these guidelines because they are deemed a less practical option for acute management; parenteral anticoagulation for at least five days is required before dabigatran or edoxaban can be initiated.

The first **three weeks** of DOAC treatment will be provided by the DVT clinic. Further supplies must therefore be supplied by 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 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. An initial supply of warfarin and LMWH will be made from the DVT clinic; ongoing supply of warfarin will be from the GP.

For women on the combined oral contraceptive pill (COCP), the COCP should be stopped at least one month before anticoagulation is discontinued and an alternative form of contraception should be organised. Female patients of childbearing potential should be warned of the risk to the foetus if taking warfarin or a DOAC during pregnancy.

Management of patients with antiphospholipid syndrome (APS) and the use of DOACs in thromboembolism

Following the results of a randomised clinical trial of patients with triple positive APS, the European and UK medicines regulatory bodies have recently issued a warning about the DOACs in patients who are known to have APS. 'Triple positive APS' refers to a patient who fulfils the clinical criteria for APS, and who is also positive for all three of the laboratory tests used to diagnose APS (lupus anticoagulant, anti-cardiolipin antibodies, and anti-beta2-glycoprotein 1 antibodies).

In the following instances, the haematology specialists from the Oxford Haemophilia and Thrombosis Centre recommend the following:

Anticoagulation management in known APS:

APS and venous thrombosis:

1. Triple positive APS patients should be offered warfarin as first line therapy.

2. Non-triple positive patients - there is no evidence to support the choice of anticoagulant for this patient group. A discussion should be had with the patient about the clinical uncertainty around whether a DOAC is as effective at preventing thrombotic events as warfarin. A shared decision, taking the patient's wishes into consideration, should be made and documented. It is recognised that if a patient has been stable and has not developed a further thrombotic event whilst on a DOAC, that it is reasonable to continue that medication.

New patients with an unprovoked VTE:
It is recommended that new patients with an unprovoked VTE should be tested for APS in the following situations:

- history of SLE or other autoimmune disease
- presence of livedo reticularis
- prolonged APTT prior to starting anticoagulation
- recurrent thrombosis
- VTE at an unusual site
- history of arterial disease without a clear risk
- thrombocytopenia
- recurrent miscarriage/still birth/severe pre-eclampsia
- cardiac valve abnormalities in the absence of another cause

This test will be conducted at the 3 month thrombosis review clinic.

Switching from warfarin to a DOAC in patients on long-term anticoagulation for VTE prevention:
For patients already taking long-term anticoagulation for unprovoked VTE, who are being considered by their doctor for a medication switch from warfarin to a DOAC, the doctor should test the patient for APS prior to switching only in the settings above, where there is deemed to be an increased risk of APS.

The tests are:

1. **lupus anticoagulant,**
2. **anticardiolipin antibody**
3. **anti-beta2-glycoprotein 1 antibody.**

If the initial tests are positive, a repeat test should be conducted after 3 months (12 weeks) and reviewed before switching. If the results are still positive then follow the advice in the paragraph above on "anticoagulation management in known APS". If the results are negative on repeat testing then switching from warfarin to a DOAC can be considered.

DOACs interactions with other medicinal products

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

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, primidone 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.

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

*Transient risk factors (TRF); Surgery, Significant trauma e.g. fracture or plaster cast, COC/HRT, Pregnancy/puerperium, Temporary immobility e.g. confined to bed ≥ 3 days or a flight > 8 hours (please note this is a weaker TRF). If temporary immobility is the only TRF the patient should have a three months review.

Ongoing monitoring by GP

GPs are responsible for the ongoing monitoring of patients who require long-term anticoagulation. Patients should be reviewed by their GP on a regular basis, but as a minimum annually.

At each review;

- Assess adherence 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 the need for continuation, 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).

- An estimated creatinine clearance (using Cockcroft and Gault equation) must be used when monitoring a patient on anticoagulation. 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

If a dose of apixaban is missed, the patient should take the apixaban immediately and then continue with twice daily intake as before.

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.

Medicine information booklets

- Warfarin – NPSA "yellow book"
  - Booklets and patient alert cards can be ordered the Primary Care Support England (PCSE) supply system. Patients will be supplied a copy if under the Oxfordshire Anticoagulation Service
- 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)
  - Booklets can be downloaded and printed from https://www.eliquis.co.uk/patient/dvt-or-pe/patient-information-booklet
- 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)

	APIXABAN (ELIQUIS®)	DABIGATRAN (PRADAXA®)	EDOXABAN (LIXIANA®)	RIVAROXABAN (XARELTO®)
Mechanism of action	Direct factor Xa inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Dose for treatment of DVT/PE	10mg twice daily for 7 days, then 5 mg twice daily	150mg twice daily following treatment with a parenteral anticoagulant for at least 5 days.	60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days	15mg twice daily for 21 days, then 20 mg daily with food to aid absorption.
Dose in secondary prevention of DVT/PE	2.5 mg twice daily following completion of 6 months anticoagulant treatment*	150 mg twice daily	60 mg once daily	10 mg daily with food to aid absorption following completion of 6 months anticoagulant treatment*
Dose in renal impairment	Do not use if CrCl <15ml/min** Use with caution if CrCl 15-29ml/min**	Do not use if CrCl less than 30ml/min** Consider dose reduction 110mg BD if CrCl 30-50ml/min**	30mg od if CrCl 15-50ml/min** Use with caution if CrCl 15-29ml/min** 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**
Hepatic impairment	Not recommended in severe hepatic impairment as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy	Not recommended in patients with elevated liver enzymes >2 upper limit of normal. Contraindicated in patients with hepatic impairment or liver disease expected to impact on survival.	Not recommended in severe hepatic impairment as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy	Use with caution as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy
Contraindications (List not exhaustive–refer to current SPC www.medicines.org.uk)	• 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 • Anticoagulant in use (except during switching -see below) • Prosthetic heart valves • Mod-severe mitral stenosis • Pregnancy and breastfeeding	• 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 • Anticoagulant in use (except during switching -see below) • Prosthetic heart valves • Mod-severe mitral stenosis • Pregnancy and breastfeeding	• 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 • Anticoagulant in use (except during switching - see below) • Prosthetic heart valves • Mod-severe mitral stenosis • Pregnancy and breastfeeding	• 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 • Anticoagulant in use (except during switching - see below) • Uncontrolled severe hypertension • Prosthetic heart valves • Mod-severe mitral stenosis • Pregnancy and breastfeeding
Extremes of BMI	If <50kg or >100-120kg*** then exposure of DOAC is variable by 20-30%. It is recommended that at these body weights the Cockcroft and Gault formula is used to calculate CrCl rather than eGFR			
Pharmaceutical issues	May be dispersed in water Stable in dosette boxes	Capsules can only be stored in original packaging thus not suitable for dosette boxes	Stable in dosette boxes	May be dispersed in water Stable in dosette boxes
Switching from warfarin	Stop warfarin and start apixaban once INR is less than 2	Stop warfarin and start dabigatran once INR less than 2	Stop warfarin and start edoxaban once the INR is 2.5 or less	Stop warfarin and start rivaroxaban once INR 2.5 or less (not forgetting higher initial dosing when within three weeks of an acute event)
Switching to warfarin	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	Start warfarin 2 days (CrCl 30-49ml/min) or 3 days (CrCl 50ml/min or above) before stopping dabigatran	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 edoxaban dose.	Co-administer rivaroxaban and warfarin until INR 2 or greater

NB: *For patients taking long-term apixaban or rivaroxaban as secondary prevention a risk-benefit assessment should be made to decide on the appropriate long-term dose. This assessment may take place between 3 and 6 months from the initial diagnosis of VTE. For patients deemed to be at higher risk of recurrent VTE, continuation of apixaban at 5mg bd or rivaroxaban 20mg od, should be considered.

****** 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.

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