1. Introduction and Who Guideline applies to

The introduction of the Direct Oral Anti-Coagulants (DOACs) represents a major change in anticoagulation management. Currently, there are four available DOACs: apixaban, dabigatran, edoxaban and rivaroxaban. The respective NICE Technology Appraisals state that these four agents should be offered to patients as an alternative to warfarin in accordance with their licensing for management of venous thromboembolism (VTE) and for stroke prevention in atrial fibrillation. The decision about whether to start treatment should be made after an informed discussion between the clinician and the patient about the risks and benefits of a DOAC compared with warfarin.

This document sets out the recommendations for use of DOACs in the acute treatment and secondary prevention of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).

This applies to:

- *Management of VTE in adults*
- *In all locations within the Trust*
- *Excluding any special circumstances (e.g. pregnancy, children, antiphospholipid syndrome)*
- *Physicians or appropriately trained non-medical prescribers, managing VTE.*

2. Guideline Standards and Procedures

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GLOSSARY

ACTFG	Anticoagulation Task and Finish Group
BNF	British National Formulary
CrCl	Creatinine Clearance (Cockroft-Gault calculation)
CRNM	Clinically Relevant Non-Major bleeding
CYP3A4	Cytochrome P3A4
DOACs	Direct Oral Anticoagulants
DVT	Deep Vein Thrombosis
H2RA	Histamine-2 Receptor Antagonist
ICE	Integrated Clinical Environment (Sunquest ICE system for discharge letters in UHL)
INR	International Normalised Ratio
NICE	National Institute of Health & Clinical Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PCC	Prothrombin Complex Concentrate
PE	Pulmonary Embolism
PPI	Proton Pump Inhibitor
SCA	Shared Care Agreement
VTE	Venous Thrombo-Embolism

Specialist investigations are required for the diagnosis of VTE (DVT and PE) usually available within secondary care, and consequently initiation of anticoagulation treatment for both these conditions remains in the secondary care domain. Ongoing treatment is usually managed in primary care in accordance with specialist advice.

Choice of anticoagulant drug

Treatment of VTE can be with one of the following options:

1. WARFARIN

Warfarin may be preferred

a) in patients with significant renal impairment (Cockcroft-Gault Creatinine Clearance (CrCl)<15 ml/min; or, on renal replacement therapy), *where DOACs are contraindicated*
b) where the compliance is or anticipated to be poor as compliance can be assessed with INR monitoring
c) in the context of a known prothrombotic condition (e.g. antiphospholipid syndrome or recurrent VTE)
d) in the context of mechanical heart valves, *where DOACs are contraindicated*
e) by some patients, on the basis that there are decades of experience.

Limitations include: practical issues (need for regular INR monitoring, and repeating INR e.g. with bleeds or drug changes), interactions (Vitamin K containing foods, alcohol and many medications) and the need for heparin cover at start-up.

2. ENOXAPARIN is preferred:

1. As the gold standard for treatment and prevention of cancer-related VTE. There remains lack of clarity as to when a cancer is deemed "active" or "inactive" for purposes of use of a DOAC, and such decisions should be made at Consultant level, in consultation with a Haematologist, where needed.
2. As a bridge to oral anticoagulation, in the context of acute medical illness.
3. In high risk perioperative situations – see Perioperative Bridging Guidance for details.

3. DOACs

There are four DOACs licensed for treatment of VTE and approved by NICE with a Technology Assessment (key characteristics in table below):

DOAC	Inhibits	Heparin at initiation	Reversal agent
Apixaban	Factor (F) Xa	**No**	No
Dabigatran	F II (thrombin)	Yes	**Yes**
Edoxaban	F Xa	Yes	No
Rivaroxaban	F Xa	**No**	No

The advantages are: quick onset of action, no need for heparin therapy at start-up (Apixaban & Rivaroxaban only); availability of specific antidote (Dabigatran only); and no need for frequent monitoring.

The efficacy and safety of DOACs compared to standard treatment with warfarin is summarised below:

Outcomes in DOAC trials for initial/short-term treatment, in comparison with standard warfarin therapy				
DOAC (vs Warfarin)	**Efficacy**	**Major Bleeding**	**CRNM* Bleeding**	**GI bleeding**
Apixaban	→	↓	↓	↓
Dabigatran	→	↓		--
Edoxaban	→	→	↓	--
Rivaroxaban	→	↓	→	↑
Because of differing characteristics & study design, cross DOAC comparisons cannot be made. Data shown only for illustration of trial outcomes in comparison with warfarin (in the respective trials).				
*CRNM clinically relevant non-major; GI gastro-intestinal; → similar; ↓ lower rate; ↑ higher rate; -- not reported				

Overall, the DOAC are similar to warfarin in efficacy, and have advantage in reducing bleeding complications. Rivaroxaban (but not apixaban) had an increased risk of GI bleeding compared with warfarin.

For long-term secondary prevention (vs placebo), with respect to rate of bleeding (major or CRNM): Apixaban had similar rates to placebo (3.2%, vs placebo 2.7%), while Rivaroxaban was associated with higher rates (20mg-6%, vs 1.2%). When different regimes were explored for Rivaroxaban, the bleed rates were 20mg-3.3%, 10mg-2.4%, vs aspirin 2.0%.

General caution is advised in the following circumstances:
a) extremes of body weight (<50kg or >120kg).
b) Creatinine clearance less than 30ml/min.
Please consult a Haematologist if intending to use a DOAC in either scenario. An individualised decision is required due to limited clinical data for patients at the extremes of weight and with severe kidney disease; and factor levels may be required to inform appropriate dosing.

Presumptive treatment of suspected DVT

Presumptive treatment for suspected DVT with a DOAC may be offered where it is cost-effective. Ideally, 3-day packs should be used to minimise drug wastage. These should be available in hospital front-door areas (e.g. Emergency Department; GP Assessment Unit; DVT clinic) to enable diversion of suitable patients to the specialist DVT clinic, and to avoid unnecessary hospitalisation.

LMSG RECOMMENDATION FOR DOAC USE IN VTE

No anticoagulant of choice is currently advised.

Apixaban and Rivaroxaban 'SIMPLE AMBER' status
i.e. hospital initiation and transfer of monitoring to primary care (no SCA needed).

Apixaban and Rivaroxaban are recommended in preference to the other two DOACs, and approved for use without the need for a Shared Care Agreement. The key practical advantage of these two drugs is that they do not need heparin therapy at start-up.

Dabigatran and Edoxaban 'AMBER' (Shared Care Agreement needed)
i.e. hospital initiation and transfer of monitoring to primary care (**with** shared care agreement).

Dabigatran and Edoxaban are **not** recommended as first line, and require an SCA for use. This is because heparin therapy for 5 days is required at treatment initiation, which has practical and cost implications. Specific situations where these may be used:

- lactose intolerance (Apixaban and Rivaroxaban have lactose as a constituent)
- where the bleed risk is high and an agent with an antidote (Dabigatran) is felt to be more appropriate

DOSING REGIMENS FOR DOACs in VTE management

	Initial*	Short term **(up to 3-6m)**		Long term **(after 6m)**
		Standard dose	Low dose option	
Apixaban	10mg bd x7d	5mg bd	---	2.5mg bd
Dabigatran	Heparin x5d	150mg bd **(start after 5d of heparin)**	110mg bd	---
Edoxaban	Heparin x5d	60mg od **(start after 5d of heparin)**	30mg od	---
Rivaroxaban	15mg bd x21d	20mg od	15mg od	10mg od (20mg od high VTE risk)
*Please note differing initial dose periods and dosing regimes; dose adjustment may be needed – please refer to BNF.				
m months; d days; bd twice daily; od once daily; VTE venous thromboembolism				

PRACTICAL ASPECTS OF PRESCRIBING

General contraindications to anticoagulation

The following substantially increase the risk of major bleeding and appropriate specialist(s) should be consulted in the decision to anticoagulate or not, and to consider other options for management (e.g. inferior vena cava filter):

- Current or recent gastrointestinal ulceration
- Presence of malignant neoplasm at high risk of bleeding
- Recent brain or spinal injury
- Recent brain, spinal or ophthalmic surgery
- Recent intracranial haemorrhage
- Known or suspected oesophageal varices
- Arteriovenous malformation
- Vascular aneurysms, major intraspinal or intracerebral vascular abnormalities

Starting DOAC therapy

Prior to starting treatment, baseline blood tests (coagulation screen, full blood count, renal function (including CrCl calculation) and liver function) and weight must be performed. Dose adjustment may be needed. Caution is advised in extreme body weights (<50 or >120 kilograms), where Haematology consultation should be considered.

Patients should be offered an interim therapeutic dose of anticoagulation if diagnostic investigations are suspected to take longer than 1 hour (PE) or 4 hours (DVT). The options are:

(i) Single therapeutic dose of Enoxaparin - will provide 24 hours of cover
(ii) DOAC pre-pack, if available.
(iii) No anticoagulant: if the risk of such interim therapy is felt to outweigh the benefit. This decision should be documented in the medical notes.

Missed doses

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 15mg doses are recommended i.e. 30mg). After 21 days, the dose should not be doubled within the same day to make up for a missed dose.
Apixaban: If a dose is missed, the patient should take the dose immediately and then continue with twice daily intake as before.

Drug interactions

Antiplatelet statement

In the context of anticoagulation, antiplatelets significantly increase the rate of bleeding complications. Standard advice is to discontinue antiplatelet drugs during the initial & short term treatment (up to 6 months), unless there is a history of recent (<12 months) acute coronary syndrome (&/or coronary intervention). Where there is doubt, a Cardiologist (preferably the operator for any intervention) should be consulted for advice.

If longer term anticoagulant treatment planned

- please review the risk-benefit balance with regards to resuming antiplatelet therapy, in consultation with appropriate specialists
- if concomitant antiplatelet therapy is warranted, consider using the low dose anticoagulant option (if available – see table: dosing regimens).
- Proton pump inhibitor (PPI e.g. lansoprazole) or Histamine receptor antagonist (H2RA e.g. ranitidine) protection may be considered.

Other interactions

Factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) are not recommended in patients receiving concomitant treatment with **strong CYP3A4 inhibitors** - azole-antimycotics (ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir), or **strong CYP3A4 inducers** (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort), as they may affect plasma drug concentrations. **Macrolide antibiotics** (e.g. clarithromycin and erythromycin) may inhibit metabolism of factor Xa inhibitors and therefore caution should be applied if co-prescribed. Co-administration of rivaroxaban with **dronedarone** should be avoided given limited clinical data**.** Concomitant treatment with **unfractionated heparin (UFH), Enoxaparin or fondaparinux** is contraindicated (except when UFH is being used to maintain patency of a central venous or arterial catheter). Concomitant treatment with **NSAIDs or antiplatelets** is generally not advised with an anticoagulant (see antiplatelet statement above).

Monitoring

Patients with poor compliance need careful assessment. Warfarin may be preferred if compliance issues remain unresolved. INR monitoring enables ongoing assessment of compliance.

Pregnancy & Breast feeding

Rivaroxaban and apixaban should be avoided in pregnant patients and those who are breast feeding. Treatment choices should be made in consultation with an Obstetrician / Obstetric Haematologist. Women of child-bearing potential should be counselled appropriately to avoid getting pregnant whilst on treatment with any anticoagulant.

Duration of therapy

Patients with proximal DVT or PE should be treated for at least 3 months. Long term treatment will be considered for recurrent thrombosis, patients with an on-going risk factor, or unprovoked proximal DVT or PE. It may be possible to decide on finite (3-6 months) or indefinite duration of anticoagulation, at the point of treatment initiation, in which situation ongoing monitoring can be handed over to primary care. However, for many patients (e.g. those with a first unprovoked proximal DVT or PE), a further review will be needed at three months to decide whether or not to stop anticoagulation, and the need for further tests to identify any underlying cause for VTE. This will be arranged at the point of discharge following initial diagnosis, with the DVT Clinic or the PE Clinic, as appropriate .

Patient / carer education

Standard practice with regards to safe anticoagulation therapy should be utilised. Verbal information about risk & benefit should be supplemented by an orange DOAC booklet (similar to the yellow booklet for Warfarin) and an alert card (available from pharmacy). Patients should be encouraged to carry the alert cards with them at all times.

Anticoagulant education has been shown to improve outcomes by reducing thrombotic and haemorrhagic adverse events. Outcomes improve when patients take responsibility for, understand and adhere to an anticoagulation care plan. There are many educational materials for warfarin, low molecular weight heparin and the DOACs although the emphasis is more on stressing adherence. Special attention should be directed at recognizing the signs of bleeding and stressing that any non-minor bleeding requires urgent attention.

Hospital discharge arrangements

Please ensure an adequate supply of anticoagulant medication (4 weeks) to avoid missed doses. Provide clear instructions to the patient / carer to ensure GP follow up within that time window. An ICE Anticoagulation Discharge Letter must be completed for all inpatient discharges, with clear instructions for GP to enable ongoing management and monitoring e.g. duration of therapy and/or plan for clinic review.

If there is uncertainty at Consultant level about plan of management, patients can be discussed with the PE clinic (use ED Ambulatory PE referral form, or ICE referral for inpatients needing specialist follow up) or DVT clinic (referral to thrombosis consultants – Dr Richard Gooding & Dr Bethan Myers) for specialist advice / review / follow up, as required.

Reversal

There is currently no specific reversal agent for Factor Xa inhibitors: apixaban, edoxaban and rivaroxaban. Treatment cessation and supportive therapy are advised.

For minor anticoagulant-related bleeding, temporary anticoagulant cessation is usually adequate. For **moderate to severe** anticoagulant-related bleeding, hospitalisation is required - please consult the oncall Haematologist for consideration of blood products, PCC and any specific antidotes available (e.g. Idarucizumab for patients on dabigatran only - available in the Emergency Department).

There is no role for Vitamin K in the management of DOAC associated bleeding, irrespective of coagulation profile.

Effect on coagulation tests

A coagulation profile is recommended for all anticoagulant-related bleeding. Currently, there is limited clinical value of these results to guide management of bleeding in the context of DOAC therapy. In general, if the PT and/or APTT are prolonged, levels are likely to be significant but a normal PT and APTT do not exclude significant drug levels (especially with apixaban).

Drug levels can be measured with a specific assay as part of an agreed pathway (in consultation with Haematology). Any local guidance for specific situations should be followed.

Surgical procedures

Elective surgery is not generally advised in the first 6 months following VTE diagnosis. Beyond that period, for patients undergoing elective surgery, please follow drug-specific guidance on peri-operative bridging.
Decisions regarding peri-operative care are the responsibility of the operating surgeon. Bridging guidance should be communicated in full to the responsible General Practitioner. Specific permission needs to be sought before delegating any responsibility for elements of an elective bridging plan to primary care.

Advice on bridging elective procedures is incorporated in the Anticoagulation Bridging Therapy for Elective Surgery and Procedures - UHL Guideline. If needed, further advice can be sought from the Thrombosis & Haemostasis Haematologists (Dr Richard Gooding / Dr Bethan Myers).

For emergency situations, please consult the on-call Haematologist for advice.

REFERENCES

1. Summary of Product Characteristics (SPC) for rivaroxaban (Xarelto®), *Bayer plc* accessed via www.medicines.org.uk.
2. Summary of Product Characteristics (SPC) for apixaban (Eliquis®), Bristol-Myers Squibb-Pfizer accessed via www.medicines.org.uk.
3. Bauersachs R et al. EINSTEIN - Oral Rivaroxaban for Symptomatic Venous Thromboembolism – The EINSTEIN Investigators. NEJM 363: 2499-2510
4. Agnelli G et al. AMPLIFY - Oral Apixaban for the Treatment of Acute Venous Thromboembolism. NEJM 369: 799-808
5. Weitz JI et al. EINSTEIN-CHOICE - Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism NEJM 2017;376:1211-22
6. Agnelli G et al. AMPLIFY-EXT - Apixaban for Extended Treatment of Venous Thromboembolism NEJM 2013;368:699-708
7. Medicines and Healthcare products Regulatory Agency (MHRA). Drug Safety Update October 2013 accessed via www.mhra.gov.uk 03/12/2013
8. Martin K et al., Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016; 14: 1308–13

3. Education and Training

The DOAC were introduced for clinical use for prevention of stroke in patients with atrial fibrillation in 2014. In light of new published evidence, the license for these agents now includes acute treatment and prevention of VTE. Dosing regimes are different for this indication as indicated in the guideline.

Education and training is ongoing with several presentations to various groups in the Trust (Friday Grand Round; Acute Medicine Meeting; Geriatrics Meeting; Cardiology Governance Forum; Stroke Education Meeting; CMT SUI Meeting; Geriatric SpR Meeting) and at various GP meetings and PLT events.

There remains a need for general upskilling for healthcare professionals, and an eLearning Program will be devised in line with user requirements.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
DATIX incidents associated with DOAC in the context of VTE	Medication Safety Pharmacist to report quarterly to Anticoagulation Task & Finish Group (ACTFG)	Elizabeth McKechnie – Medication Safety Pharmacist Elizabeth.McKechnie@uhl-tr.nhs.uk	Quarterly	ACTFG
GP Complaints / concerns related to DOAC use in VTE	Review of GP complaints / concerns & summary report to ACTFG	GP Engagement Lead	Quarterly	ACTFG

5. Supporting References (maximum of 3)

Included in text

6. Key Words

Venous thromboembolism; VTE; deep vein thrombosis; DVT; pulmonary embolism; PE; DOAC; apixaban; dabigatran; edoxaban; rivaroxaban; warfarin

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Details of Changes made during review:

2018-02	First version of document to support introduction and safe use of DOAC for VTE management in line with NICE technology appraisals. To be reviewed in light of new Trust guidelines being developed for management of DVT & PE.