Clinical Guidance

Oral Anticoagulants (VKA and DOAC)
Guidelines for prescribing, monitoring and management

Anticoagulants are one of the classes of medicines which frequently cause harm and admission to hospital. Managing the risk associated with anticoagulants was the subject of The National Patient Safety Agency Patient Safety Alert number 18 March 2007.

High risks identified with prescribing anticoagulation include:

- Failure to initiate oral anticoagulant therapy where indicated
- Poor documentation of reason and treatment plan at commencement of therapy
- Incorrect prescribing of oral anticoagulant doses (especially loading doses)

The formulary has 5 different anticoagulants to choose from. For the majority of patients, the choice of anticoagulant is guided by indication, clinician and patient choice after appropriate discussion of risks and benefits of the different options.

Anticoagulation is not advisable if the risk of harm is likely to outweigh the benefits of treatment. Consideration should be given to the safety of initiating oral anticoagulants in patients with:

- cognitive impairment
- risk of falls/ with a history of falls,
- history of bleeding,
- excess alcohol intake
- liver disease
- impaired visual acuity

The HASBLED score can be used to give an indication of the overall risk of bleeding. This scoring system has been validated in patients with atrial fibrillation (it is not validated in the VTE setting).

	Clinical characteristic	**Points awarded**
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

A score of 3 or more indicates increased one year bleed risk on anticoagulation sufficient to justify caution or more regular review.

Patients on VKA who fail to attend for regular blood tests and those with poor compliance should be counselled and consideration given to whether or not it is safe to continue with treatment and/or switch to a Direct Oral Anticoagulant (DOAC).

Oral anticoagulants should not be prescribed in pregnancy except in the case of mechanical prosthetic valves where this should be done in conjunction with consultant obstetrician, consultant haematologist, and consultant cardiologist and with counselling and consent of the patient.

Vitamin K antagonists (VKA)

Coumarins:

Warfarin is the most commonly used oral anticoagulant in the UK. It is available as 0.5mg (white) 1mg (brown), 3mg (blue) and 5mg (pink) tablets (Note that 0.5mg tablets should not be used to avoid confusion with other white tablets and 5mg doses). The 1mg tablets can be broken in half or cut with a tablet cutter to achieve a 0.5mg dose. Acenocoumarol is occasionally used in patients who cannot tolerate warfarin. It is available as 1mg tablets.

Inanediones:

Phenindione (Dindevan) is occasionally used in patients who cannot tolerate warfarin. It is available as 10mg, 25mg and 50mg tablets (unlicensed).

Indications for VKA and target INR

The most common indications and target INR are documented in the table below.
Further details can be found in Appendix II

Indication	Target INR	Duration
Atrial fibrillation.	2.5	Life
Cardioversion (higher target values, such as an INR of 3, can be used for up to 4 weeks before the procedure to avoid cancellations due to low INR).	2.5	Minimum 4 weeks post cardioversion
First provoked proximal DVT/PE	2.5	3 months (longer if risk factors persist)
First unprovoked DVT	2.5	3 months and review (many patients would be advised anticoagulation for life/long term after an unprovoked event)
First PE	2.5	3 months and review
First PE with permanent risk factor	2.5	Life
Recurrent VTE when no longer on VKA/DOAC therapy	2.5	Life
Recurrent VTE when on VKA/DOAC therapy	3.5	Life

Contra-indications

VKAs are contraindicated in patients with haemorrhagic stroke or clinically significant bleeding. Avoid within 72 hours of major surgery with risk of severe bleeding. Avoid in pregnancy and within 48 hours postpartum.

Initiation

Check baseline LFTs, FBC and clotting screen (i.e. APTT and INR). Seek senior medical advice if any abnormalities.
NB: There are no dosing guidelines for patients with a baseline INR of >1.4.
Consideration should be given to the safety of initiating therapy in patients who have a raised baseline INR. Aim to identify reason for elevated INR and seek advice from haematology.

Check for the following risk factors:

Age>70 years	Weight <60kg
Liver impairment	Increased bleeding risk (other causes)
Low albumin <36g/L	Parenteral feeding
Interacting medications	History of significant bleed

For all inpatients the prescriber must complete the warfarin details on Wirral Millennium, documenting the indication, target INR and duration of treatment. This also applies for patients admitted on warfarin.

Secondary care:
If the patient has no risk factors and does not have chronic atrial fibrillation – use standard initiation algorithm A.
If risk factors are present- consider if anticoagulation is still appropriate. For those patients requiring smaller loading doses consider using the "Reduced Dose Initiation of Warfarin" - algorithm B.
In chronic atrial fibrillation not needing cardioversion, consider using Algorithm C.

Primary care:
Only Algorithm C should be used.

Dosing

Algorithm A
This regimen is recommended where rapid anticoagulation is desired AND the patient has no risk factors outlined above.

Day	INR	Warfarin dose (mg) Given at 6pm
A baseline INR must be taken and then daily INR for at least three days		
1	<1.4 (before treatment)	10 (1st dose)
	>1.4	Seek senior medical advice
2	<1.8	10
	1.8	1
	>1.8	0.5
3	<2.0	10
	2.0 - 2.1	5
	2.2 - 2.3	4.5
	2.4 - 2.5	4
	2.6 - 2.7	3.5
	2.8 - 2.9	3
	3.0 - 3.1	2.5
	3.2 - 3.3	2
	3.4	1.5
	3.5	1
	3.6 – 4.0	0.5
	>4.0	Omit
Predicted Maintenance Dose		
4	<1.4	>8
	1.4	8
	1.5	7.5
	1.6 - 1.7	7
	1.8	6.5
	1.9	6

Ref: Based on Fennerty.A, et.al. BMJ 1984; 288: 1268-

Algorithm B

This regimen is recommended where patient has one or more risk factors and requires rapid anticoagulation

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Day	INR (9-11am)	Warfarin dose (mg) Given at 6pm
A baseline INR must be taken and then daily INR for at least three days		
1	<1.4(before treatment)	10mg
	>1.4	Seek senior medical advice
2	<1.8	5mg
	1.8 - 2.0	1mg
	>2.0	omit
3	<2.0	5mg
	2.0 - 2.5	4mg
	2.6 - 2.9	3mg
	3.0 - 3.2	2mg
	3.3 - 3.5	1mg
	>3.5	omit
Predicted Maintenance Dose		
4	<1.4	>7mg
	1.4 - 1.5	7mg
	1.6 - 1.7	6mg
	1.8 - 1.9	5mg
	2.0 - 2.3	4mg
	2.4 - 3.0	3mg
	3.1 - 3.2	2mg
	3.3 - 3.5	1mg
	3.6 - 4.0	omit
	>4.0	Seek senior medical advice

Ref: Based on Gedge et al. Age and Ageing 2000:29:31-34

Algorithm C

In the treatment of atrial fibrillation in elderly patients (>75years) who **do not** require cardioversion, slow induction of anticoagulation is suitable to avoid over anticoagulation. This algorithm is used in both primary and secondary care.

Low dose initiation with warfarin for AF: target INR 2.5 (range 2 to3)		
Day	**INR**	**Dose**
1 to 7	< 1.4	2mg
8 to 10	< 2.0	3mg
11 onwards	< 2.0	4mg
Continue to monitor INR at least weekly and increase warfarin by 1mg daily until therapeutic INR achieved. Continue on this warfarin dose until next INR		

Ref: Based on Barrett, J et al Age and Ageing 2000; 29: 457

Age adjusted Fennerty

- Perform baseline INR (unless part of initial coagulation screen), and repeat INR daily for the first four days.
- When the INR result is towards the upper end of a range in the INR column, it is recommended that a warfarin dose is chosen towards the lower end of the suggested dose range in the age-appropriate dose column; and vice versa when INR result is towards the lower end of an INR range.

- Beyond day four dosage adjustments may still be required, especially between days five and 14 when INR may need to be assessed every two to three days until stable and the patient has been transferred to an appropriate outpatient INR monitoring service.
- More careful dosing and monitoring may be required in elderly patients or where there is co-administration with drugs known to increase or decrease INR (consult the BNF or seek advice from clinical pharmacists).

Day	INR	Dose for age (mg)			
		≤50 years	51-65 years	66-80 years	>80 years
1	<1.4	10	9	7.5	6
2	<1.6	10	9	7.5	6
	≥1.6	0.5	0.5	0.5	0.5
3	<1.8	10	9	7.5	6
	1.8 - 2.5	4 - 5	3.5 - 4.5	3 - 4	2.5 - 3
	2.6 - 3.0	2.5 - 3.5	2.5 - 3.5	2 - 2.5	1.5 - 2
	3.1 - 3.5	1 - 2	1 - 2	0.5 - 1.5	0.5 - 1.5
	3.6 - 4.0	0.5	0.5	0.5	0.5
	≥ 4.0	omit	omit	omit	omit
4	<1.6	10 - 15	9 - 13	7.5 - 11	6 - 9
	1.6 - 1.9	6 - 8	5.5 - 7	4.5 - 6	3.5 - 5
	2.0 - 2.6	4.5 - 5.5	4 - 5	3.5 - 4.5	2.5 - 3.5
	2.7 - 3.5	3.5 - 4	3 - 3.5	2.5 - 3	2 - 2.5
	3.6 - 4.0	3	2.5	2	1.5
	4.1 - 4.5	OMIT DOSE AND THEN follow dose guidance below:			
		1 – 2	0.5 – 1.5	0.5 – 1.5	0.5 – 1.5
	>4.5	Withhold warfarin until INR back between 2.0 – 3.0 (then restart on 0.5 - 1mg)			

Before initiating acenocoumarol or phenindione seek advice from haematology.

Approximate dosage conversions		
Phenindione dose	**Acenocoumarol dose**	**Warfarin dose**
20mg	0.5mg	1mg
35mg	1.0mg	2mg
50mg	1.5mg	3mg
70mg	2.0mg	4mg
80mg	2.5mg	5mg
100mg	3.0mg	6mg
120mg	3.5mg	7mg
135mg	4.0mg	8mg
150mg	4.5mg	9mg
170mg	5.0mg	10mg

Monitoring

Inpatient:

- Monitor INR daily for acutely unwell patients. INR test taken in the morning so that result is available for dosing by 14:00. This will ensure the team caring for the patient manage the prescribing safely.
- Consider reducing frequency of monitoring for medically stable patients.
- **All** patients to have an INR on day of discharge.

Outpatient anticoagulation clinic:

- INR to be monitored at each appointment, frequency dependent on clinical decision.

GP practice:

- As per local protocol. This should be done with a computerised dosing system in stable patients.

Outpatients: Dose adjustment of established (maintenance) warfarin i.e. in patients who have been taking warfarin for 7 days or longer		
Target INR 2.5		
INR	**Dose change**	**Next INR**
<1.5	30% Increase	3 days
1.5 - 2.0	20% Increase	
2.1 - 3.0	No Change	
3.1 - 4.0	20% Reduction	
4.1 - 6.0	Omit 2 days & 30% reduction	4 days
>6.1	Omit 3 days	Measure INR daily if there is a high concern for bleeding

NOTE: This guide cannot be used in acutely unwell patients, where daily INR must be monitored.

Counselling

A yellow oral anticoagulant therapy booklet (OAT pack) must be provided for all patients initiated on warfarin. All inpatients must be counselled prior to discharge by the pharmacy team. This is then documented on the oral anticoagulant chart and on Wirral Millennium. The OAT booklet is available online in different languages and can be downloaded when required.

Adverse effects

Prescribers and pharmacists must check the potential interaction of any medicine that is to be prescribed concomitantly with oral anticoagulants. In patients who are stabilised on warfarin and whose INR is within the target range on oral anticoagulants, control can be disrupted by:

- Initiating a new medicine which potentiates or inhibits the oral anticoagulant effect.
- Stopping an interacting medicine, the effect of which has already been compensated for through dose adjustment with the oral anticoagulant.

It may be an option to withhold the warfarin for a few days when an interacting medicine is prescribed, or to reduce the usual dose by 20-30%. For inpatients check the INR daily, but in primary care check the INR 3 to 5 days after the interacting medicine is initiated.

Full information on interactions can be found in the BNF. For inpatients, INR must be checked daily after starting the new medicine and the oral anticoagulant dose adjusted accordingly. When the new medicine is stopped, a return to the previous maintenance dose may be needed.

As the INR rises there is an increased risk of bleeding or if the INR drops there is an increased risk of a thrombotic event. Careful monitoring will avoid harm to the patient and ensure a therapeutic INR is maintained. For patients seen in the anticoagulant clinic or in the community, full anticoagulation with low molecular weight heparin (LMWH) will be supplied where INR<1.6 and patient has had VTE within 30 days or is high risk for a thrombotic event.

Reversal of VKA (including high INR)

Major Bleeding: Stop warfarin; give phytomenadione (vitamin K1) 5mg to10mg by slow intravenous injection; give prothrombin complex concentrate: factors II, VII, IX and X (Octaplex®) within 1 hour of presentation. Check INR at 6 hours to ensure full and ongoing reversal. This is issued by the blood transfusion laboratory. Further information can be found in the clinical guideline 'Prothrombin Complex Concentrate Octaplex Therapy'.

INR >8 no bleeding or minor bleeding: Stop warfarin, restart when INR <5; if there are other risk factors for bleeding (Age >65 years, hypertension, diabetes mellitus, renal failure, liver failure, previous gastrointestinal bleed, previous cerebral bleed, concomitant antiplatelet therapy) give phytomenadione (vitamin K1) 1mg to 5mg by mouth using Konakion® MM Paediatric 2mg/0.2mL ampoules.
If there is minor bleeding give phytomenadione 1mg to 2mg intravenously (Konakion MM®). Repeat dose of phytomenadione if INR is still too high after 24 hours. Daily INR required and restart warfarin when INR <5. Refer to specific guidance if reviewing in primary care setting.
Note: oral and intravenous dose have same effect at 24 hours post dose.

INR 6 – 8 no bleeding or minor bleeding: Stop warfarin, restart when INR<5.

INR <6 but more than 0.5 units above target value: Reduce dose or stop warfarin, restart when INR < 5.

Unexpected bleeding at therapeutic levels: Always investigate possibility of underlying cause (e.g. unsuspected renal or gastro-intestinal tract pathology).

Further information on managing over anticoagulation and bleeding can be found in the clinical guideline 'Bleeding – Management in patients taking oral anticoagulants'.

Discharge
The process for discharge at WUTH is documented below, referred to as ABCD, and aims to achieve safe anticoagulant management for all patients. The discharge section of the oral anticoagulant chart should be completed as follows.

It is the responsibility of the prescriber to ensure that A, B, C and D have been completed. It is pharmacist's responsibility to check A, B, C and D when fulfilling the TTH and the discharging nurse's responsibility to check A, B, C and D at the point of discharge. Ward stock of warfarin will be used for patients during the admission period. Warfarin tablets will only be supplied on the TTH when ABCD have been confirmed by the pharmacist.

A: Appointment All patients should be given an **appropriate** appointment to check their INR after discharge. Refer to 'Discharging warfarin patients' guide in the pharmacy resource section of the intranet under 'other guides' to determine the most appropriate place for the patient to have their INR checked and the timescale in which this should occur. Appointments can be with the patients usual anticoagulant service, with the hospital anticoagulant outpatient clinic (Monday, Wednesday and Friday), or with the DVT/unplanned care service.

Wirral Community Service DVT /Anticoagulant Service
The service provided is as follows:

1. Initiate anticoagulation for patients diagnosed with a DVT or PE and who are medically stable. When treatment with warfarin and a LMWH is initiated, patients will be monitored daily until their INR is in the range 2-3 for 48 hours.
2. Initiate warfarin for patients diagnosed with atrial fibrillation.
3. Manage anticoagulation for medical and surgical patients requiring monitoring to facilitate discharge, and patients requiring additional monitoring for unstable anticoagulation.

Once anticoagulation is stable the care will then be transferred to the GP or to the Countess of Chester hospital (COCH) monitoring service where applicable
Referrals to COCH should be made by phone on 0151 514 6475

B: Anticoagulant Therapy Record Book. All patients newly started on warfarin must be given an OAT pack, other patients on warfarin should be supplied with the dosing booklet with the following information completed by the doctor or pharmacist or registered nurse, checking that the information is correct. The doses post discharge may only be entered by the prescriber.

- Patient name, address, date of birth, MRN number, NHS number
- Warfarin details (e.g. indication, target INR and duration of treatment)
- Last 5 INR results and doses. The warfarin dose to be taken until the appointment must be clearly written and signed by the prescriber
- Date of the next anticoagulant clinic appointment

C: Counselling. Ensure that the patient has been counselled. See counselling section above.
D: Warfarin Details. The indication for therapy, target INR and duration of treatment selected will be electronically transferred to the discharge letter from Wirral Millennium. Ensure that this information is still correct and that any changes to interacting medication are communicated in the discharge letter by the practitioner.

Bridging therapy with LMWH or unfractionated heparin for sub-therapeutic INR
Bridging anticoagulation therapy should be used to ensure adequate anticoagulation in situations where the INR is sub-therapeutic and the patient is at a high risk of thromboembolism (e.g. within first 30 days of acute VTE, recurrent VTE on anticoagulation, patients acutely in atrial fibrillation, mechanical prosthetic heart valves).

In the case of newly diagnosed DVT or PE, the LMWH or unfractionated heparin (UFH) should be continued for a minimum of 5 days **and** until the INR is in range for 2 consecutive days.

For bridging therapy in patients with mechanical prosthetic heart valves: LMWH or UFH should be continued until INR $\geq$2.0 for **aortic** valves and INR $\geq$2.5 for **mitral** valves.

In all cases INR should be checked **daily**.

Surgery
Continuation of anticoagulation during surgery and invasive procedures is likely to increase bleeding. Discontinuation will, however, be associated with a temporary increase in thrombosis risk.

For elective surgery and endoscopic procedures see WUTH guidelines; ‘Oral anti-thrombotic therapy-management in patients requiring endoscopy’ and ‘Warfarin therapy perioperative management during elective surgery’.

Discontinuation
If warfarin is no longer required it can be stopped immediately without any further INR monitoring. Hospital in-patients who have their warfarin discontinued need to be re-assessed for thromboprophylaxis.

Direct Oral Anticoagulants (DOACs)

	Drug	Brand	Strengths available
Anti-Xa inhibitor	Apixaban	Eliquis®	2.5mg and 5mg tablets
	Edoxaban	Lixiana®	15mg, 30mg and 60mg tablets
	Rivaroxaban	Xarelto®	2.5mg, 10mg, 15mg and 20mg tablets
Direct thrombin inhibitor	Dabigatran	Pradaxa®	75mg, 110mg and 150mg capsules

Indications
All DOACs indicated for the following at WUTH:

- Stroke prevention in non-valvular atrial fibrillation
- Treatment of DVT and PE
- Prevention of recurrent DVT and PE

Rivaroxaban is also indicated for:

- Prevention of thromboembolism post total knee replacement (TKR) and post total hip replacement (THR)
- Prophylaxis of atherothrombotic events in acute coronary syndrome (with aspirin alone or aspirin and clopidogrel) (Not on WUTH formulary for this indication)

The Pan Mersey APC recommends in the absence of a specific clinical reason to select a particular DOAC, that the least costly DOAC is the first line DOAC for patients with non-valvular AF.

Contra-indications:

- Clinically significant active bleeding.
- 'Valvular' atrial fibrillation (patients with atrial fibrillation and mechanical prosthetic heart valves or mitral stenosis).
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see SPC for further information).
- Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms 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 malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Uncontrolled severe hypertension.
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives, oral anticoagulants except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Pregnancy and breast-feeding.

Dosing
Each DOAC has individual criteria for dosing based on renal function, weight and age. See tables below for dosing information for prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and treatment of deep vein thrombosis or pulmonary embolism and prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism.

<table>
<tr><th colspan="6">Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF)</th></tr>
<tr><th rowspan="2"></th><th colspan="5">Creatinine clearance (Cockcroft and Gault using actual body weight)</th><th rowspan="2"></th></tr>
<tr><th><15mL/min</th><th>15-29mL/min</th><th>30-49mL/min</th><th>50-80mL/min</th><th>>80mL/min</th></tr>
<tr><td>Apixaban</td><td rowspan="4">Contraindication</td><td>2.5mg TWICE daily</td><td colspan="3">5mg TWICE daily*</td><td>*reduce dose to 2.5 mg twice daily in patients with at least two of the following characteristics: age 80 years and over, body weight ≤60 kg, or serum creatinine 133 micromol/litre and over</td></tr>
<tr><td>Dabigatran</td><td>Contraindication</td><td colspan="3">150mg TWICE daily

<u>Reduce</u> dose to 110mg twice daily in elderly patients over 80 years or patients receiving concomitant treatment with verapamil
Lower dose of 110mg twice daily may be <u>considered</u> for patients aged 75–80 years, or with moderate renal impairment (CrCl 30-50mL/min), or at increased risk of bleeding.</td><td>Clinical data is limited for dabigatran in patients with CrCl 30-50ml/min and so should be used with caution. Likewise, there is limited clinical data in use in patients <50kg or >100kg bodyweight.</td></tr>
<tr><td>Edoxaban</td><td colspan="2">30mg ONCE daily</td><td>60mg ONCE daily**</td><td>Decreased efficacy with increasing CrCl was observed for edoxaban compared to well-managed warfarin. Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.</td><td>**Dose is 30mg once daily for patients with body weight ≤60kg or if co-prescribed with ciclosporin or dronaderone or erythromycin or ketoconazole. Dose can be increased to 60mg once daily when course is completed.</td></tr>
<tr><td>Rivaroxaban</td><td colspan="2">15mg ONCE daily</td><td colspan="2">20mg ONCE daily</td><td>Limited clinical data for patients with severe renal impairment (CrCl 15 - 29 mL/min) indicate that rivaroxaban plasma concentrations are increased. Use with caution in these patients.</td></tr>
</table>

<table>
<tr><th colspan="6">Treatment of deep vein thrombosis or pulmonary embolism and prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism</th></tr>
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<tr><td>Apixaban</td><td rowspan="4">Contraindication</td><td>Use with caution as per SPC</td><td colspan="2">Initial treatment 10mg twice daily for 7 days, then 5mg twice daily* for continued treatment</td><td>Recurrent DVT/PE: Reduce to 2.5mg twice daily (following completion of 6 months anticoagulant treatment)</td></tr>
<tr><td>Dabigatran</td><td>Contraindication</td><td colspan="2">Treat for at least 5 days treatment with a parenteral anticoagulant prior to starting dabigatran 150mg twice daily.

<u>Reduce</u> dose to 110mg twice daily in elderly patients over 80 years or patients receiving concomitant treatment with verapamil
Lower dose of 110mg twice daily may be <u>considered</u> for patients aged 75–80 years, or with moderate renal impairment (CrCl 30-50mL/min), or at increased risk of bleeding.</td><td>Clinical data is limited for dabigatran in patients with CrCl 30-50ml/min and so should be used with caution. Likewise, there is limited clinical data in use in patients <50kg or >100kg bodyweight.</td></tr>
<tr><td>Edoxaban</td><td colspan="2">Treat for at least 5 days with parenteral anticoagulant prior to edoxaban 30mg once daily</td><td>Treat for at least 5 days with parenteral anticoagulant prior to edoxaban 60mg once daily^</td><td>^Dose is 30mg once daily for patients with body weight ≤60kg or if co-prescribed with ciclosporin or dronaderone or erythromycin or ketoconazole. Dose can be increased to 60mg once daily when course is completed.</td></tr>
<tr><td>Rivaroxaban</td><td>15mg twice daily for 21 days then 20mg daily but consider reducing to 15mg if risk of bleeding outweighs risk of VTE</td><td colspan="2">15mg twice daily for 21 days then 20mg daily</td><td>Limited clinical data for patients with severe renal impairment (CrCl 15 - 29 mL/min) indicate that rivaroxaban plasma concentrations are increased. Use with caution in these patients.

Recurrent DVT/PE: 10mg once daily
(following completion of 6 months therapy for DVT or PE) In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with 10 mg once daily, a dose of 20 mg once daily should be considered.</td></tr>
</table>

Initiation

- Baseline Activated Partial Prothrombin Time (aPTT), International Normalised Ratio (INR), haemoglobin, urea & electrolytes and liver function tests
- Weigh patient and obtain patient height
- Calculate baseline creatinine clearance (CrCl) using Cockgroft and Gault using actual body weight. Informed discussion with patient regarding risks and benefits of a DOAC.

Weight

See specific dosing regarding dose reduction criteria for individual DOACs in the dosing table.

Caution is advised in patients at extremes of body weight. Patients with a low body weight (<50kg) have an increase haemorrhagic risk, patients with a high body weight (>120kg) have a lower exposure and may have reduced efficacy. Warfarin would be the preferred option in these patients.

When calculating creatinine clearance for patients with extremes of body weight, use both ideal and actual body weight and use clinical judgement to identify the most appropriate dose and DOAC to be used.

Switching between anticoagulants

See advice in table below regarding switching between anticoagulation. Ensure VTE risk assessment is updated as required.

Patients should not take a loading dose of warfarin in order to promptly achieve a stable INR between 2 and 3

Switching between anticoagulants

From → / To ↓	LMWH	Apixaban	Edoxaban	Dabigatran	Rivaroxaban	Vitamin K antagonists
LMWH		Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose. If CrCl <30mls/min wait 24 hours before initiating parenteral treatment.	Start at the time of the next scheduled dose.	Start when INR <2.0.
Apixaban	Start at the time of the next scheduled dose.		Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose.	Discontinue VKA and start apixaban when the INR is <2.0.
Edoxaban	Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose.		Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose.	Discontinue VKA and start edoxaban should when the INR is ≤ 2.5
Dabigatran	Dabigatran should be started 0 to 2 hours before the time of the next scheduled dose of the LMWH.	Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose.		Start at the time of the next scheduled dose.	Discontinue VKA and start dabigatran when the INR is <2.0.
Rivaroxaban	Rivaroxaban should be started 0 to 2 hours before the time of the next scheduled dose of the LMWH.	Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose.	Start at the time of the next scheduled dose.		Discontinue VKA and start rivaroxaban when: INR is ≤ 3.0 (AF) INR is ≤ 2.5 (Prevention and treatment PE/DVT)
Vitamin K antagonists	Commence warfarin in combination with treatment dose LMWH and monitor INR. Continued for a minimum of 5 days **and** until the INR is in range for 2 consecutive days.	Continue administration of apixaban for at least 2 days after beginning VKA therapy. Continue co-administration of apixaban and VKA therapy until the INR is ≥ 2.0.	If on 60mg dose give 30mg edoxaban OD plus an appropriate warfarin dose. If on 30mg dose, give 15mg edoxaban OD plus an appropriate warfarin dose. Once an INR ≥ 2.0 is achieved, Edoxaban should be discontinued. See SPC for further details.	Adjust the starting time of the VKA based on CrCl as follows: CrCl ≥ 50 ml/min, start VKA three days before discontinuing dabigatran CrCl 30 - < 50 ml/min, start VKA two days before discontinuing dabigatran	Continue co-administration of rivaroxaban and VKA therapy until the INR is ≥ 2.0.	

Monitoring
No monitoring is required to ensure therapeutic levels of DOACs but regular monitoring of CrCl is recommended to avoid accumulation in reduced renal function. This should be considered on a 3 to 6 monthly.

Counselling
All patients should be given an information booklet and alert card and counselled on the details. Ensure patients understand the potential bleeding risks with DOACs and are aware that there is currently no antidote for apixaban, edoxaban and rivaroxaban. Patients should be advised on what action to take if they miss a dose and should be advised to inform their dentist or any other healthcare professional performing invasive treatments or surgery that they are taking a DOAC. Counselling should be documented in the casenotes when completed.

Adverse effects
DOACs should be used with caution in conditions with an increased risk of bleeding. Bleeding may occur at any site during therapy with DOAC. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to an investigation to identify a bleeding site. Close clinical surveillance is recommended throughout the treatment period, especially if risk factors are combined.

	Common and very common	Uncommon	Rare or very rare	Frequency not known
Apixaban	Anaemia; haemorrhage; nausea; skin reactions	Administration site reactions; CNS haemorrhage; hypotension; post procedural haematoma; thrombocytopenia; wound complications		
Dabigatran	Hepatic function abnormal	Anaemia; diarrhoea; haemorrhage; hyperbilirubinaemia; nausea; post procedural complications; vomiting; wound complications	Angioedema; dysphagia; gastrointestinal discomfort; gastrointestinal disorders; incision site haemorrhage; intracranial haemorrhage; post procedural drainage; skin reactions; thrombocytopenia; wound drainage	Bronchospasm
Edoxaban	Anaemia; haemorrhage; nausea; skin reactions	CNS haemorrhage		
Rivaroxaban	Anaemia; asthenia; constipation; diarrhoea; dizziness; fever; gastrointestinal discomfort; haemorrhage; headache; hypotension; menorrhagia; nausea; oedema; pain in extremity; post procedural anaemia; renal impairment; skin reactions; vomiting; wound complications	Allergic oedema; angioedema; dry mouth; hepatic disorders; intracranial haemorrhage; malaise; syncope; tachycardia; thrombocytopenia; thrombocytosis	Vascular pseudoaneurysm	

Management of adverse effects

Specific information on managing bleeding can be found in the clinical guideline 'Bleeding- Management in patients taking oral anticoagulants'.

Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

For life-threatening bleeding that cannot be controlled with the measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of anti-factor Xa inhibitors 30 minutes after completing the infusion.

Discharge

The indication and duration of treatment with DOAC must be documented on the discharge information. All patients newly started on a DOAC must be counselled where appropriate prior to discharge.

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9. Edoxaban SPC https://www.medicines.org.uk/emc/medicine/30512

10. Rivaroxaban SPC http://www.xarelto.com/en/information-on-xarelto/summary-of-product-characteristics/

11. WUTH http://www.wuth.nhs.uk/staff/clinical/clinical-guidance/clinical-guidelines/ Select above link and then click on anticoagulation tab for full list of guidance

12. British Committee for Standards in Haematology (BCSH) http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=All&dpage=0&sspage=0&ipage=0#gl

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Appendix I Summary of oral anticoagulants

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	VKA **Warfarin, phenindione, acenocoumarol**
Dose form available	2.5mg and 5 mg tablets	75mg, 110mg and 150mg capsules	15mg, 30mg and 60mg tablets	2.5mg, 10mg, 15mg and 20mg tablets	**Warfarin**: 0.5mg, 1mg, 3mg, 5mg tablets **Phenindione:** 10mg, 25mg, 50mg tablets **Acenocoumarol**: 1mg tablets
Regular therapeutic level monitoring	N/A	N/A	N/A	N/A	INR
Regular monitoring	Renal function	Renal function	Renal function	Renal function	None
Contraindicated where CrCl is 30 - 50ml/min	No	Reduced dose applies	Reduced dose applies	Reduced dose applies	No
Contraindicated where CrCl is 15 - 29ml/min	Reduced dose applies	Contraindicated	Reduced dose applies	Reduced dose applies	No
Contraindicated where CrCl<15ml/min	Yes	Yes	Yes	Yes	No
Use in patients with prosthetic valves	No	No	No	No	Yes
Suitable for dosette dispensing	Yes	No	Yes	Yes	No (due to variable dosing)
Can be crushed and administered via enteral feeding tube	Yes	No	Yes	Yes	Yes
Stroke prevention in valvular AF	No	No	No	No	Yes
Stroke prevention in non-valvular AF	Yes	Yes	Yes	Yes	Yes
VTE prophylaxis post THR and TKR	No*	No*	No	Yes	No
Treatment of DVT/PE**	Yes	Yes (Requires at least 5 days of LMWH treatment before initiation)		Yes	Yes
Prevention of recurrent DVT/PE	Yes	Yes	Yes	Yes	Yes
Treatment and prevention of thromboembolism in other veins	No	No	No	No	Yes
Use post-thrombolysis	No	No	No	No	As per guidelines
Reversal agent	No	Idarucizumab	No	No	Phytomenadione PCC (Octaplex)

*Drugs are licensed for this indication but not in WUTH formulary.

****Note**: VKA, apixaban, dabigatran, edoxaban and rivaroxaban are **not** recommended for use in patients with both DVT/PE and active cancer.

APPENDIX II Indication, target INR and duration for VKA

Indication	Target INR	Duration
Atrial fibrillation.	2.5	Life
Antiphospholipid syndrome	2.5	Life
Arterial grafts (if anticoagulated)	2.5	Life
Bioprosthesis in the mitral position.	2.5	Life
Bioprosthetic valve and history of systemic embolism	2.5	Life
Bioprosthetic valve and left atrial thrombus at surgery.	2.5	Life
Bioprosthetic valves and other prothrombotic risk factors such as atrial fibrillation and low ventricular ejection fraction.	2.5	Life
Symptomatic isolated calf vein thrombosis	2.5	6 weeks
Cardiomyopathy	2.5	Life
Cardioversion (higher target values, such as an INR of 3, can be used for up to 4 weeks before the procedure to avoid cancellations due to low INR).	2.5	Minimum 4 weeks post cardioversion
Coronary artery thrombosis (if anticoagulated)	2.5	Life
Dilated cardiomyopathy.	2.5	Life
Deep Vein Thrombosis	2.5	First provoked proximal DVT 3 months. (longer if ongoing risk factors) First unprovoked DVT 3 months and then review (many patients would be advised anticoagulation for life/long term after an unprovoked event)
Mechanical prosthetic heart valve: aortic bi-leaflet • aortic bi-leaflet • aortic tilting disk • aortic caged ball or caged disk • mitral bi-leaflet • mitral tilting disk • mitral caged ball or caged disk	 2.5 3.0 3.5 3.0 3.0 3.5	Life
Mitral stenosis or regurgitation with atrial fibrillation or history of systemic embolism or left atrial thrombus or enlarged left atrium	2.5	Life
Mural thrombus	2.5	Life
Pulmonary Embolism	2.5	First provoked PE 3 months (longer if ongoing risk factors) First unprovoked PE review at 6 months. Consider long term anticoagulation after assessing risks/benefits
Recurrent VTE when no longer on VKA therapy	2.5	Life
Recurrent VTE when VKA therapy in range	3.5	Life

APPENDIX III

Competencies

This Trust Guideline is based on British Committee for Standards in Haematology (BCSH) and National Patient Safety Agency (NPSA) guidance. The NPSA recommends that NHS and independent sector organisations in England and Wales take the following steps:

- Ensure all staff caring for patients on anticoagulant therapy have the necessary work competencies. Any gaps in competence must be addressed through training to ensure that all staff may undertake their duties safely
- Review and, where necessary, update written procedures and clinical protocols for anticoagulant services to ensure they reflect safe practice, and that staff are trained in these procedures.
- Ensure that patients who are prescribed anticoagulants receive appropriate verbal and written information at the start of therapy, at hospital discharge, on the first anticoagulant clinic appointment, and where necessary throughout the course of their treatment. The BSH and the NPSA have updated the patient-held information (yellow) booklet.
- Promote safe practice amongst prescribers and pharmacists to ensure that INR's are not only monitored regularly but also that levels are safe before issuing or dispensing repeat prescriptions for oral anticoagulants.
- All staff caring for or managing patients on anticoagulant therapy must have completed the necessary Trust training. Any gaps in competence must be addressed through training to ensure that all staff may undertake their duties safely. BMJ e-learning modules are available and accessible:
    - Starting patients on anticoagulants in secondary care: how to do it http://learning.bmj.com/learning/search-result.html?moduleId=5004325
    - Maintaining patients on anticoagulants http://learning.bmj.com/learning/search-result.html?moduleId=5004429

This is currently under review and will be updated when information is available