

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

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1.0 Clinical Guidance

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 4 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 score system has been validated in patients with atrial fibrillation.

	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.

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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 DOAC

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

2.0 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 in 1mg tablets.

- **Inanediones:**

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

- **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
First unprovoked DVT	2.5	3 months and review (long term if permanent risk factors)
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.

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- **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

Liver impairment

Low albumin <36g/L

Interacting medications

Weight <60kg

Increased bleeding risk (other causes)

Parenteral feeding

History of significant bleed

For all inpatients the prescriber must complete the warfarin details on CERNER, 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.

See Dosing section 1.4 for full information

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 enoxaparin 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.

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

- 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 (1 st dose)
	>1.4	Seek senior medical advice
2	<1.8	10
	1.8	1
	>1.8	0.5
3	<2	10
	2 - 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 - 3.1	2.5
	3.2 - 3.3	2
	3.4	1.5
	3.5	1
	3.6 - 4	0.5
	4	0
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-

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Algorithm B

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

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	1mg
	>2	0mg
3	<2	5mg
	2- 2.5	4mg
	2.6-2.9	3mg
	3-3.2	2mg
	3.3-3.5	1mg
	>3.5	0mg
Predicted Maintenance Dose		
4	<1.4	>7mg
	1.4-1.5	7mg
	1.6-1.7	6mg
	1.8-1.9	5mg
	2-2.3	4mg
	2.4-3	3mg
	3.1-3.2	2mg
	3.3-3.5	1mg
	3.6-4	0mg
	>4	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 2-3)		
Day	INR	Dose
1 to 7	< 1.4	2mg
8 to 10	<2	3mg
11 onwards	<2	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

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Age adjusted Fennerty

- Perform baseline INR (unless part of initial coagulation screen), and repeat INR daily on 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 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 adjustment 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	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	0	0	0
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			
		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.

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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	20% Increase	
2.1-3	No Change	
3.1-4	20% Reduction	4 days
4.1-6	Miss 2 days & 30% reduction	
>6.1	Miss 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.

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- **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 in the casenotes. The DVD 'Living with Warfarin' is available for patients to view in the anticoagulant outpatient clinic and on the intranet where access is possible

The OAT booklet is available online in different languages and can be downloaded when required.

<http://www.nrls.npsa.nhs.uk/resources/?EntryId45=61777>

- **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 the community check the INR 3 to 5 days after the interacting medicine is initiated.

Full information on interactions can be found in the BNF at <https://www.medicinescomplete.com/mc/> 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 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 enoxaparin will be supplied where $INR < 1.6$ and patient has had VTE within 30 days or is high risk for a thrombotic event.

See section 3.11 on reversal of high INR.

- **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

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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. See Appendix IV for warfarin discharge process.

A: Appointment All patients should be given an **appropriate** appointment to check their INR after discharge. This can be with the hospital anticoagulant outpatient clinic (Monday, Wednesday and Friday), with the patients usual anticoagulant service or with the DVT/unplanned care service.

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 CERNER. Ensure that this information is still correct and that any changes to interacting medication are communicated in the discharge letter by the practitioner.

- **Reversal of VKA (including high INR)**

Major Bleeding: Stop warfarin; give phytomenadione (vitamin K1) 5-10mg 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 after authorisation by a haematologist. Further information on these links:

<http://www.wuth.nhs.uk/media/572923/Prothrombin-Complex-Concentrate-Octaplex-Prescribing-Guideline-v2.pdf>

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-5mg by mouth using Konakion[®] MM Paediatric 2mg/0.2mL ampoules. If there is minor bleeding give phytomenadione 1-2mg 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 http://mm.wirral.nhs.uk/document_uploads/guidelines/HighINRPathway-FINALMay2016.pdf.

Note: oral and intravenous dose have same effect at 24 hours post dose.

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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 Bleeding - Management in patients taking oral anticoagulants Guidelines (Secondary Care Document).

- **Bridging therapy with LMWH or unfractionated heparin**

Where INR is below 2 (**for any INR target range**) and the patient is at higher risk of thromboembolism (e.g. within the first 30 days of acute VTE or has had recurrent VTE at lower levels of INR previously) then bridging therapy should be used. Enoxaparin is the preferred choice but in some cases it may be appropriate to use unfractionated heparin. The dose of enoxaparin should give full anticoagulation until the INR reaches 2. In the case of a newly diagnosed DVT or PE, the enoxaparin or UFH should be continued for a minimum of 5 days and until the INR is in range for 2 consecutive days.

There are various situations where bridging therapy may be required, e.g. restarting warfarin post INR above 8, patients admitted with a sub-therapeutic INR but at risk from thrombosis. Ensure the LMWH or UFH is reviewed daily and discontinued when INR > 2.

- **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 at <http://www.wuth.nhs.uk/media/1090055/Oral-anticoagulant-therapy-perioperative-management-during-elective-surgery-clinical-guideline-v2.pdf> (Secondary Care Document Only)

and

http://www.wuth.nhs.uk/media/575071/Oral-antithrombotic-therapy-management-in-patients-requiring-endoscopy_v1.pdf

- **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.

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Direct Oral Anticoagulants (DOACs)

3.0 APIXABAN

Apixaban (Eliquis®) is an anti-Xa inhibitor. It is available as 2.5mg and 5mg tablets.

3.1 Indications

Apixaban is indicated for

- Stroke prevention in non-valvular atrial fibrillation
- Prevention of thromboembolism post total knee replacement (TKR) and post total hip replacement (THR) (Not on WUTH formulary for this indication)
- Treatment of DVT and PE
- Prevention of recurrent DVT and PE

3.2 Contra-indications:

Active bleeding; significant risk of major bleeding (e.g. recent gastro-intestinal ulcer, oesophageal varices, recent brain, spine, or ophthalmic surgery, recent intracranial haemorrhage, malignant neoplasms, vascular aneurysm). Apixaban is not licensed for use in patients with prosthetic heart valves. Apixaban is contraindicated in severe liver disease. Apixaban should be used with caution in patients with elevated hepatic enzymes.

3.3 Initiation

- Baseline Activated Partial Prothrombin Time (aPTT), International Normalised Ratio (INR), haemoglobin, urea & electrolytes and liver function tests
- Weigh patient
- Obtain patient height
- Calculate baseline creatinine clearance (CrCl) using Cockcroft and Gault
- Informed discussion with patient regarding risks and benefits of apixaban
- Use reduced dose in patients with creatinine clearance 15-29ml/min. Avoid use in patients with creatinine clearance <15ml/min.
- If patient is anticoagulated on either LMWH or a different oral agent then follow the information below:
 - **Parenteral anticoagulants to apixaban** - Switching treatment from parenteral anticoagulants to apixaban can be done at the next scheduled dose
 - **Vitamin K antagonists to apixaban** - When converting patients from Vitamin K antagonist (VKA) therapy to apixaban discontinue warfarin or other VKA therapy and start apixaban when the international normalized ratio (INR) is < 2.0.

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3.4 Dosing

Dose is dependent on indication and CrCl

Indications	Creatinine clearance (Cockcroft and Gault)		
	<15ml/min	15-29ml/min	>30ml/min
Prophylaxis of VTE post knee replacement surgery	CONTRAINDICATED	Non- formulary at WUTH	
Prophylaxis of VTE post hip replacement surgery			
Treatment of deep vein thrombosis or pulmonary embolism		Use with caution as per SPC	Initial treatment 10mg twice daily for 7 days, then 5mg twice daily for continued treatment
Prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism			2.5mg twice daily (following completion of 6 months anticoagulant treatment)
Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation,		2.5mg twice daily*	5mg twice daily

*reduce to 2.5mg twice daily in patients over 80 years with body-weight \leq 60 kg

3.5 Monitoring

No monitoring is required to ensure therapeutic levels but regular monitoring of CrCl is recommended to avoid accumulation of apixaban in reduced renal function. Apixaban must be discontinued where CrCl<15ml/min.

Clotting tests are affected by the mechanism of action of apixaban. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability and cannot be used to monitor therapy.

3.6 Counselling

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

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3.7 Adverse effects

Apixaban should be used with caution in conditions with an increased risk of bleeding. Bleeding may occur at any site during therapy with apixaban. 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.

Other common adverse effects include nausea, bruising, anaemia; less commonly hypotension, thrombocytopenia, rash.

3.8 Discharge

The indication and duration of treatment with apixaban must be documented on the discharge information.

3.9 Management of adverse effects

Specific information on managing bleeding can be found in the Bleeding - Management in patients taking oral anticoagulants Guidelines (Secondary Care Document).

3.10 Surgery

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.

Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.

If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

3.11 Discontinuation of therapy

If patient has reached end of duration of treatment then apixaban can be discontinued immediately.

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Where switching from apixaban to alternative anticoagulant follow this guidance:

- **Apixaban treatment to parenteral anticoagulant.** Switching treatment to parenteral anticoagulants from apixaban can be done at the next scheduled dose
 - **Apixaban treatment to Vitamin K antagonists (VKA)** e.g. warfarin - when converting patients from apixaban to VKA therapy, continue administration of apixaban for at least 2 days after beginning VKA therapy. After 2 days of coadministration of apixaban with VKA therapy, obtain an INR prior to the next scheduled dose of apixaban. Continue coadministration of apixaban and VKA therapy until the INR is ≥ 2.0 . If stopping apixaban for inpatients then ensure VTE assessment is redone.
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4.0 DABIGATRAN

Dabigatran (Pradaxa®) is a direct thrombin inhibitor and is available as 75mg, 110mg and 150mg capsules.

4.1 Indications

- Stroke prevention in non-valvular atrial fibrillation
- Prevention of thromboembolism total knee replacement (TKR) and total hip replacement (THR) (Not on WUTH formulary for this indication)
- Treatment of DVT and PE
- Prevention of recurrent DVT and PE

4.2 Contra-indications

Active bleeding; significant risk of major bleeding (e.g. recent gastro-intestinal ulcer, oesophageal varices, recent brain, spine, or ophthalmic surgery, recent intracranial haemorrhage, malignant neoplasms, vascular aneurysm, haemorrhagic stroke); do not use as anticoagulant for prosthetic heart valve

4.3 Initiation

- Baseline Activated Partial Prothrombin Time (aPTT), International Normalised Ratio (INR), haemoglobin, urea & electrolytes and liver function tests
- Weigh patient and obtain height
- Calculate baseline creatinine clearance (CrCl) using Cockcroft and Gault
- If changing from another anticoagulant to dabigatran then follow the guidance below:
 - **Parenteral anticoagulants to dabigatran** Dabigatran should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be

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

due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH))

- **VKA to dabigatran** Stop the VKA. Give dabigatran as soon as the INR is <2.0.

4.4 Dosing

Dose is dependent on indication and CrCl. 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.

Indications	Creatinine clearance (Cockcroft and Gault)		
	<30ml/min	30-50ml/min	>50ml/min
Prophylaxis of VTE post knee replacement surgery	Contraindicated	Non-formulary at WUTH	
Prophylaxis of VTE post hip replacement surgery			
Treatment of deep-vein thrombosis or pulmonary embolism		110mg twice daily, following at least 5 days treatment with a parenteral anticoagulant.	150mg (elderly over 80 years or receiving concomitant treatment with verapamil, 110mg) twice daily, following at least 5 days treatment with a parenteral anticoagulant. (Lower dose of 110mg twice daily may be considered for patients aged 75–80 years, or with moderate renal impairment, or at increased risk of bleeding)
Prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism			
Prophylaxis of stroke and systemic embolism in atrial fibrillation		110mg twice daily	150mg (elderly over 80 years, or receiving concomitant treatment with verapamil, 110mg) twice daily. (Lower dose of 110mg twice daily may be considered for patients aged 75–80 years, or with moderate renal impairment, or at increased risk of bleeding)

4.5 Monitoring

No monitoring is required to ensure therapeutic levels but regular monitoring of CrCl recommended to avoid accumulation of dabigatran in reduced renal function. Dabigatran must be discontinued where CrCl<30ml/min.

For patients at risk of bleeding the aPTT provides an approximate indication of the anticoagulant intensity achieved with dabigatran. This test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. High aPTT values should be interpreted with caution. There is no requirement to monitor aPTT.

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4.6 Counselling

All patients should be given the dabigatran alert card and counselled. Ensure the patient understands the potential bleeding risks with dabigatran and is aware that there is currently no antidote. Patients should be advised on what action to take if they miss a dose of dabigatran. Patients should be counselled to inform their dentist or any other healthcare professional performing invasive treatments or surgery that they are taking dabigatran. Counselling should be documented in the casenotes when completed.

4.7 Adverse effects

Dabigatran should be used with caution in conditions with an increased risk of bleeding. Bleeding may occur at any site during therapy with dabigatran. 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

Nausea, dyspepsia, diarrhoea, abdominal pain, anaemia, haemorrhage less commonly hepatobiliary disorders, vomiting, dysphagia, gastro-intestinal ulcer, gastro-oesophageal reflux, oesophagitis, thrombocytopenia

4.8 Discharge

The indication and duration of treatment with dabigatran must be documented on the discharge letter

4.9 Management of adverse effects

Specific information on managing bleeding can be found in the Bleeding - Management in patients taking oral anticoagulants Guidelines (Secondary Care Document).

4.10 Surgery

If an acute intervention is required, dabigatran should be temporarily discontinued. Surgery or intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased and this should be weighed against the urgency of intervention.

Prior to elective surgical procedures and interventions temporarily discontinue dabigatran as there is an increased risk of bleeding. Clearance depends on renal function which will affect how long before the procedure to discontinue dabigatran.

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The following table can be used as a guide, but the opinion of the operating surgeon should be sought.

CrCl (ml/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk of bleeding
≥80	~13	2 days before	24 hours before
50 - <80	~15	2–3 days before	1-2 days before
30 - <50	~18	4 days before	2-3 days before

4.11 Discontinuation of therapy

If patient has reached end of duration of treatment then dabigatran can be discontinued immediately. Where switching from dabigatran to alternative anticoagulant follow the guidance in the SPC. If stopping dabigatran for inpatients then ensure VTE assessment is redone.

If changing from dabigatran to another anticoagulant then follow the guidance below:

Dabigatran treatment to Vitamin K antagonists (VKA) e.g. warfarin. 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

Dabigatran treatment to parenteral anticoagulant. It is recommended to wait 12 hours after the last dose before switching from dabigatran to a parenteral anticoagulant. If CrCl < 30mls/min wait 24 hours before initiating parenteral treatment.

5.0 Edoxaban

Edoxaban (Lixiana®) is a factor Xa inhibitor and is available as 15mg, 30mg and 60mg tablets

5.1 Indications

- Stroke prevention in adult patients with nonvalvular atrial fibrillation
- Treatment of deep vein thrombosis and pulmonary embolism and prevention of recurrent DVT and PE in adults

5.2 Contra-indications

- Clinically significant active bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of

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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.

5.3 Initiation

- Baseline Activated Partial Prothrombin Time (aPTT), International Normalised Ratio(INR), haemoglobin, urea & electrolytes and liver function tests
- Weigh patient and obtain height
- Calculate baseline creatinine clearance (CrCl)
- If switching from another anticoagulant to edoxaban:
 - **Parenteral anticoagulants to edoxaban** – Discontinue parenteral anticoagulant and start edoxaban at the time of the next scheduled dose.
 - **Vitamin K antagonists to edoxaban** VKA treatment should be stopped and edoxaban therapy should be initiated when the INR is ≤ 2.5
- If switching from edoxaban to VKA then refer to SPC for full information

5.4 Dosing

Dose is dependent on indication and CrCl.

Indication	Creatinine Clearance (Cockcroft and Gault)		
	<15ml/min	15-50ml/min	>50ml/min
Prophylaxis of stroke and systemic embolism in atrial fibrillation	Contraindicated	30mg once daily*	60mg once daily
Treatment of deep-vein thrombosis or pulmonary embolism		30mg once daily* Treat for at least 5 days with parenteral anticoagulant e.g. enoxaparin THEN switch to edoxaban	60mg once daily. Treat for at least 5 days with parenteral anticoagulant e.g. enoxaparin THEN switch to edoxaban
Prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism			

*Dose is 30mg once daily for patients with body weight ≤ 60 kg or if co-prescribed with ciclosporin or dronaderone or erythromycin or ketoconazole. Dose can be increased to 60mg once daily when course is completed.

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5.5 Monitoring

No monitoring is required to ensure therapeutic levels but regular monitoring of CrCl recommended to avoid accumulation of edoxaban in reduced renal function. Edoxaban must be discontinued where CrCl < 15 ml/min.

5.6 Counselling

All patients should be counselled. Ensure the patient understands the potential bleeding risks with edoxaban and is aware that there is currently no antidote. Patients should be advised on what action to take if they miss a dose of edoxaban. Patients should be counselled to inform their dentist or any other healthcare professional performing invasive treatments or surgery that they are taking edoxaban. Counselling should be documented in the casenotes when completed.

5.7 Adverse effects

Edoxaban should be used with caution in conditions with an increased risk of bleeding. Bleeding may occur at any site during therapy with edoxaban. Close clinical surveillance is recommended throughout the treatment period, especially if risk factors are combined

Side-effects include anaemia, hypersensitivity, , epistaxis, nausea, rash, pruritus.

5.8 Discharge

The indication and duration of treatment with edoxaban must be documented on the discharge letter if course is finite.

5.9 Management of adverse effects

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 edoxaban 30 minutes after completing the infusion.

5.10 Surgery

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, edoxaban should be stopped 36 to 48 hours before the procedure.

In deciding whether a procedure should be delayed until 24 hours after the last dose of edoxaban, the increased risk of bleeding should be weighed against the urgency

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of the intervention. Edoxaban should be restarted after the surgical or other procedures as soon as adequate haemostasis has been established, noting that the time to onset of the edoxaban anticoagulant therapeutic effect is 1 – 2 hours.

5.11 Discontinuation of therapy

If patient has reached end of duration of treatment then edoxaban can be discontinued immediately. Where switching from edoxaban to alternative anticoagulant follow the guidance in the SPC. If stopping edoxaban for inpatients then ensure VTE assessment is redone.

6.0 Rivaroxaban

Rivaroxaban (Xarelto®) is an anti-Xa inhibitor and is available in 2.5mg, 10mg, 15mg and 20mg tablets.

6.1 Indications

Rivaroxaban is indicated for:

- Prophylaxis of venous thromboembolism following knee replacement surgery
- Prophylaxis of venous thromboembolism following hip replacement surgery,
- Treatment of deep-vein thrombosis or pulmonary embolism,
- Prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism,
- Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation
- Prophylaxis of atherothrombotic events in acute coronary syndrome (with aspirin alone or aspirin and clopidogrel) (Not on WUTH formulary for this indication)

6.2 Contra-indications

Active bleeding; significant risk of major bleeding (e.g. recent gastro-intestinal ulcer, oesophageal varices, recent brain, spine, or ophthalmic surgery, recent intracranial haemorrhage, malignant neoplasms, vascular aneurysm); in *acute coronary syndrome*—previous stroke or transient ischaemic attack

6.3 Initiation

- Baseline Activated Partial Prothrombin Time (aPTT), International Normalised Ratio(INR), haemoglobin, urea & electrolytes and liver function tests
- Weigh patient and obtain height
- Calculate baseline creatinine clearance (CrCl)
- If switching from another anticoagulant to rivaroxaban:
 - **Parenteral anticoagulants to rivaroxaban** - Rivaroxaban should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a

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continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

- **Vitamin K antagonists to rivaroxaban** VKA treatment should be stopped and rivaroxaban therapy should be initiated when the INR is ≤ 3.0

6.4 Dosing

Dosing is dependent on indication and CrCl. There is limited data on use in patients with extremes of body weight and those with hepatic/renal impairment.

Indication	Creatinine Clearance (Cockcroft and Gault)			
	<15ml/min	15– 29ml/min	30-49ml/min	>50ml/min
Prophylaxis of VTE post knee replacement surgery	Contraindicated	Use with caution See SPC	10mg once daily for 2 weeks starting 6–10 hours after surgery	
Prophylaxis of VTE post hip replacement surgery			10mg once daily for 5 weeks starting 6–10 hours after surgery	
Prophylaxis of atherothrombotic events in acute coronary syndrome		Non-formulary at WUTH		
Treatment of deep-vein thrombosis or pulmonary embolism		15mg twice daily for 21 days then 20mg daily but consider reducing to 15mg if risk of bleeding outweighs risk of VTE	15mg twice daily for 21 days then 20mg daily	
Prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism		20mg daily but consider reducing to 15mg if risk of bleeding outweighs risk of VTE	20mg daily	
Prophylaxis of stroke and systemic embolism in atrial fibrillation,		15mg once daily		20mg once daily

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Use with caution in these patients.

6.5 Monitoring

No monitoring is required to ensure therapeutic levels but regular monitoring of CrCl is recommended to avoid accumulation of rivaroxaban in impaired renal function. Rivaroxaban must be discontinued where CrCl<15ml/min.

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine.

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6.6 Counselling

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

6.7 Adverse effects

Nausea, vomiting, diarrhoea, constipation, dyspepsia, abdominal pain, hypotension, dizziness, headache, renal impairment, haemorrhage, pain in extremities, pruritus, rash; *less commonly* dry mouth, thrombocythaemia, tachycardia, syncope, angioedema, malaise; *rarely* jaundice, oedema

6.8 Discharge

The indication and duration of treatment with rivaroxaban must be documented on the discharge letter.

6.9 Management of adverse effects

Specific information on managing bleeding can be found in the Bleeding - Management in patients taking oral anticoagulants Guidelines (Secondary Care Document).

6.10 Surgery

If an invasive procedure or surgical intervention is required, rivaroxaban should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Rivaroxaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established

6.11 Discontinuation of therapy

If patient has reached end of duration of treatment then rivaroxaban can be discontinued immediately. When switching from rivaroxaban to alternative

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anticoagulant follow the guidance in the SPC. If stopping rivaroxaban for inpatients then ensure VTE assessment is redone.

Rivaroxaban treatment to parenteral anticoagulant. Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose is due.

Rivaroxaban treatment to Vitamin K antagonists (VKA). There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR.

In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0 . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose.

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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

*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.

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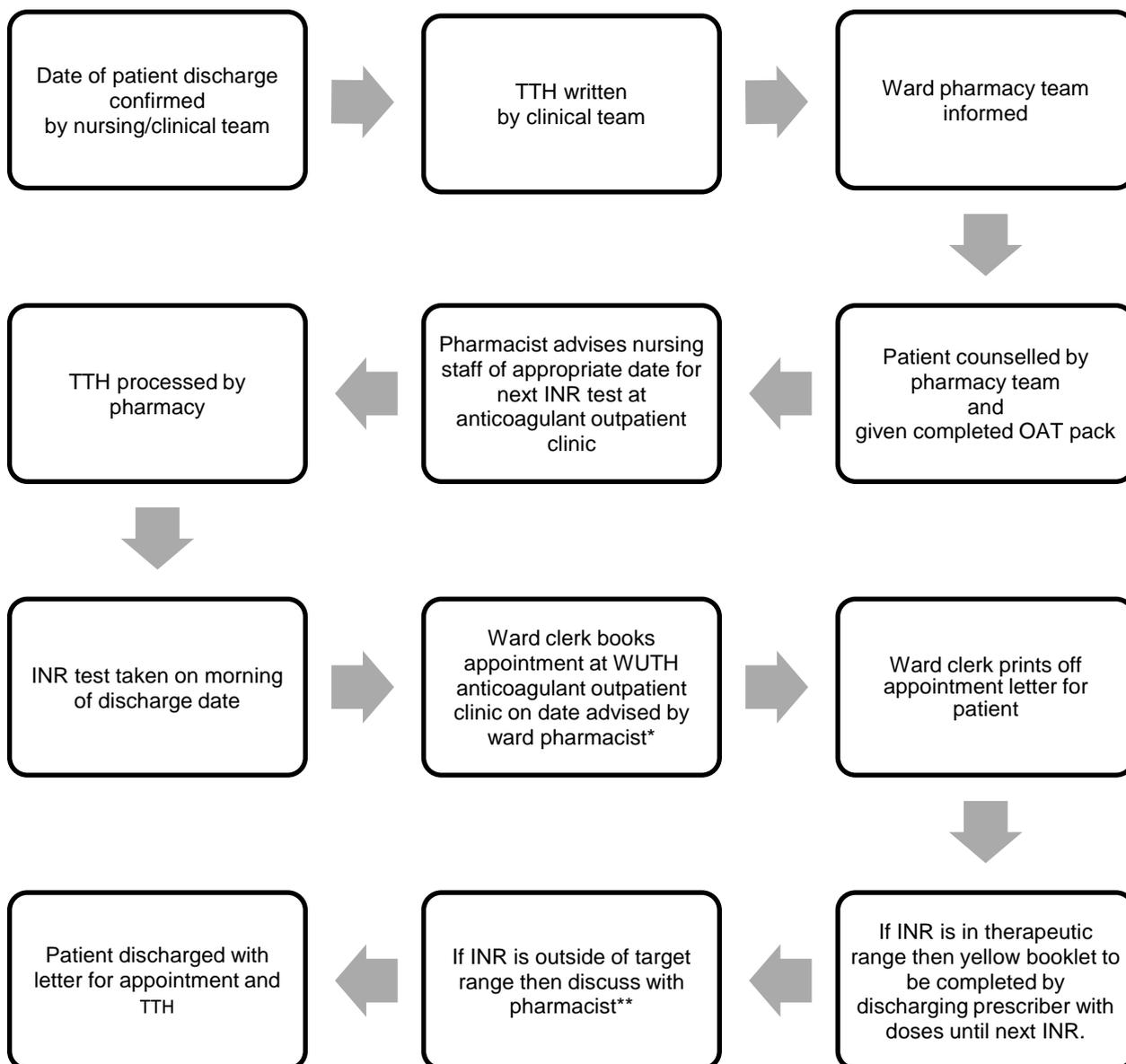
APPENDIX II Indication, target INR and duration for VKA

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
Calf vein thrombosis	2.5	Temporary risk factor 3 months Permanent risk factor -Life No risk factor -6 months
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. First unprovoked DVT 3 months and then review (long term if permanent risk factors)
Mechanical prosthetic heart valve: aortic bi-leaflet <ul style="list-style-type: none"> • 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	3 months and review Permanent risk factor -Life
Recurrent VTE when no longer on VKA therapy	2.5	Life
Recurrent VTE when VKA therapy in range	3.5	Life

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APPENDIX III

Discharge process for patients NEWLY started on warfarin, phenindione or acenocoumarol (VKA)

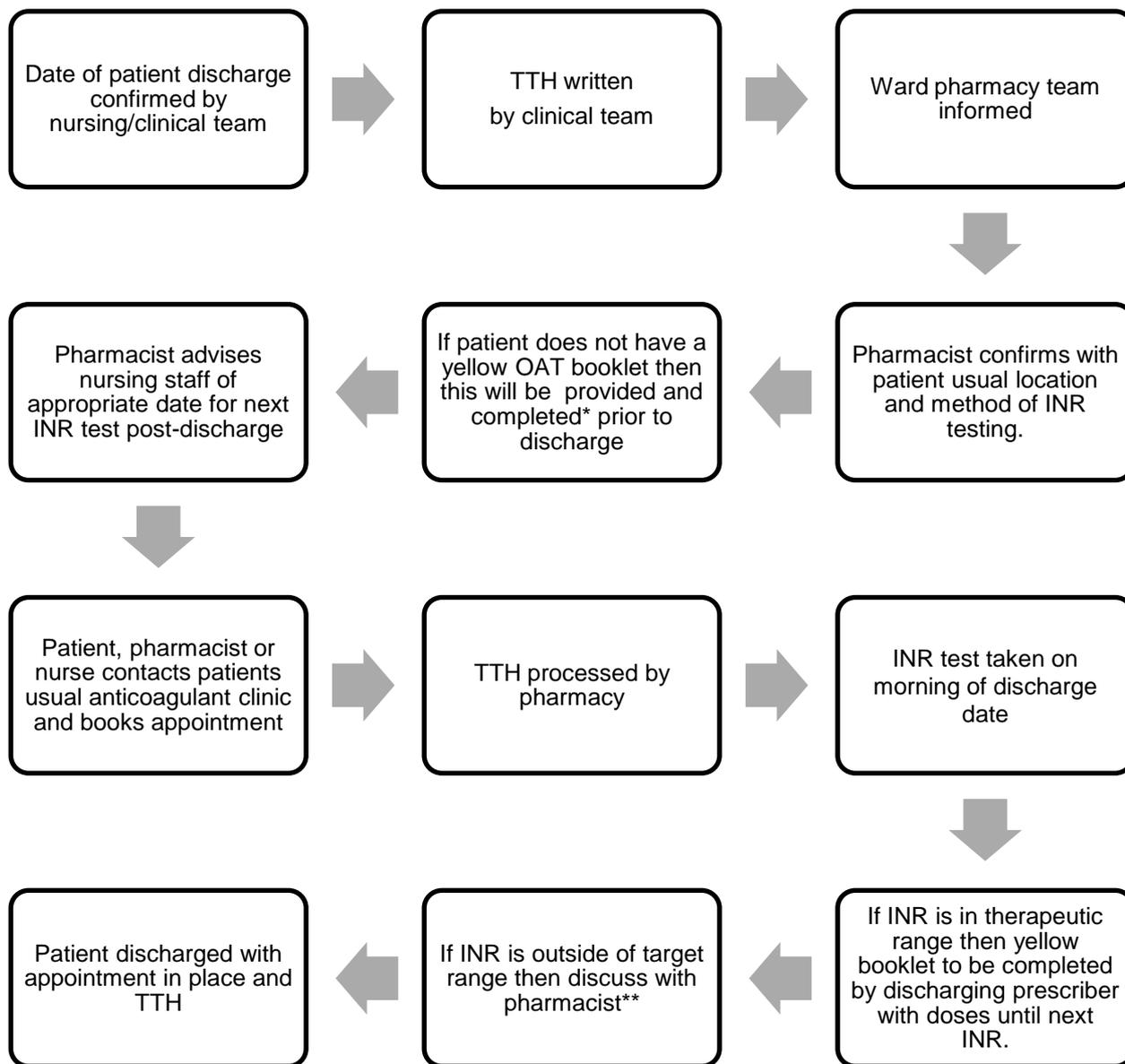


* If there is no ward clerk available then bleep 2044 for medical records team to book appointment
 ** Patient may be suitable for discharge with DVT/Unplanned care service. Contact via extension 6378

Note: If patient requires ambulance transport for clinic appointment then this must be arranged by the ward prior to discharge

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Discharge process for patients admitted on warfarin, phenindione or acenocoumarol (VKA)



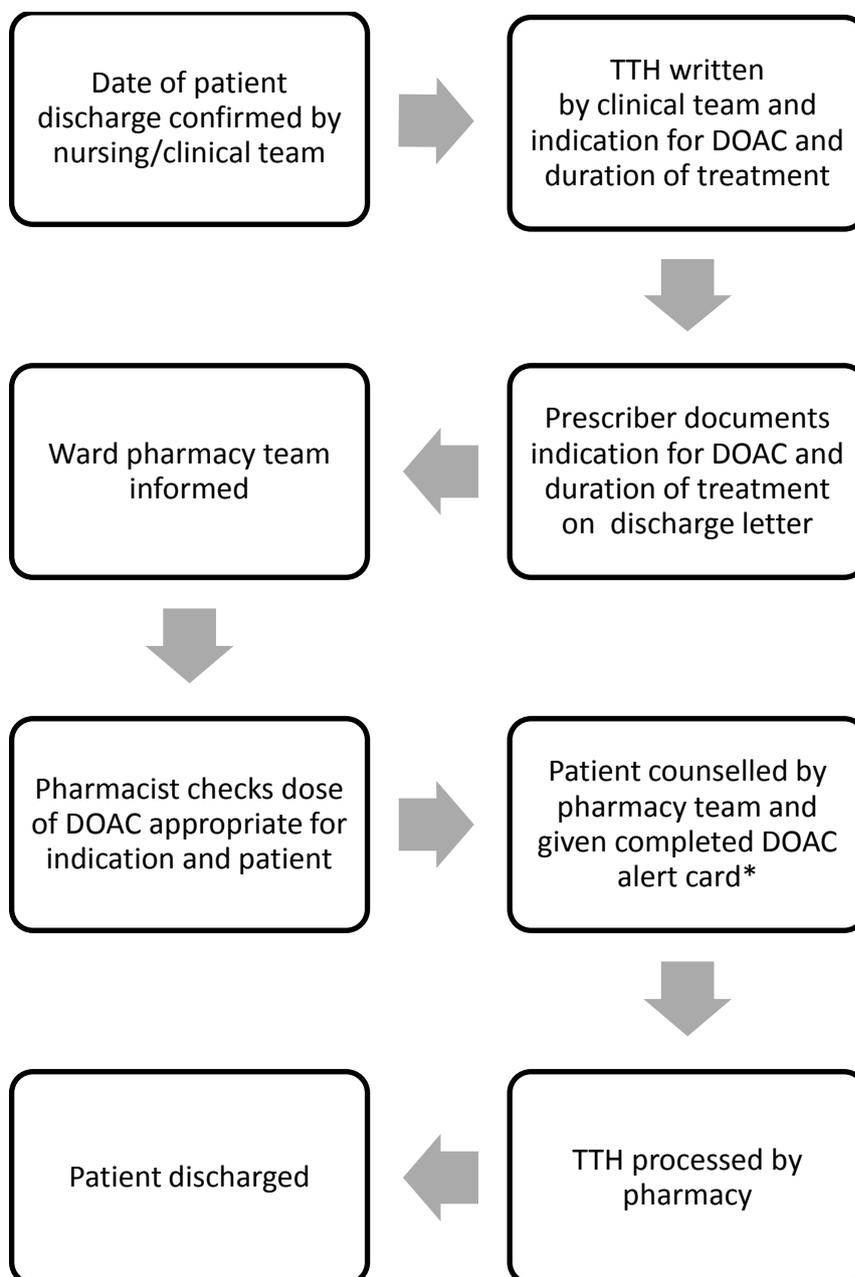
* If there is no ward clerk available then bleep 2044 for medical records team to book appointment

** Patient may be suitable for discharge with DVT/Unplanned care service. Contact via extension 6378

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APPENDIX IV

Discharge process for patients initiated on DOAC



*Individual alert cards for apixaban, dabigatran, edoxaban and rivaroxaban.

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APPENDIX V

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.

For more detail on each of these please see the full Patient Safety Alert at: www.npsa.nhs.uk/health/alerts

- 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