Oxford University Hospitals NHS
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OXFORD HAEMOPHILIA AND THROMBOSIS CENTRE PROTOCOLS FOR OUT-PATIENT ORAL ANTICOAGULATION WITH VITAMIN K ANTAGONISTS

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It is available at

http://ouh.oxnet.nhs.uk/anticoagulation

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Indications and target INR

This guideline refers to target INRs rather than target ranges though the target range is generally taken to be within 0.5 of the target, i.e. a target INR 2.5 equates to a target range of 2.0 to 3.0. Specifying tighter target ranges for fully anticoagulated patients e.g. 2.0 – 2.5 or 3.5 – 4.0 does not achieve tighter anticoagulation control but results in more blood tests and worse INR control (Meier, *et al* 2007).

The most common target INR is 2.5. Others are:

Recurrent VTE (DVT or PE) despite adequate anticoagulation	3.5
Cardioversion	Pre - 3.0 Post - 2.5
Mechanical Heart Valves	See below

Warfarin is not usually indicated for ischaemic stroke without atrial fibrillation (except in antiphospholipid syndrome), retinal vessel occlusion, peripheral artery thrombosis, coronary artery graft or coronary angioplasty and stents.

Atrial fibrillation

Anticoagulation is normally offered to patients with a CHADSVASc score ≥ 2 and considered in men with a CHADSVASc score of 1 (NICE 2014).

	Condition	**Points**
C	Congestive heart failure	1
H	Hypertension (or treated hypertension)	1
A_2	Age >75 years	2
D	Diabetes	1
S_2	Prior Stroke or TIA	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Female	1

CHADSVASc Score	**Stroke Risk %**
0	0.2
1	0.6
2	2.2
3	3.2
4	4.8
5	7.2
6	9.7
7	11.2
8	10.8
9	12.2

Using http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/

Cardioversion

The BSH recommend anticoagulation for 3 weeks before and for 4 weeks after cardioversion (Keeling*, et al* 2011). However the policy in Oxford is to anticoagulate for 4 weeks before and for 3 months afterwards. To minimise cardioversion cancellations due to low INRs on the day of the procedure we recommend a target INR of 3.0 prior to the procedure and 2.5 afterwards.

Heart valve prostheses

The risk of systemic embolism from prosthetic heart valves depends on the type of valve, its position and other factors that contribute to the patients' risk of developing thrombosis, such as cardiac rhythm and dilatation.

Mitral bioprosthetic valves

The target INR is 2.5 for the first 3 months after valve insertion, after which oral anticoagulation is usually discontinued (long term anticoagulation may be required for other reasons such as atrial fibrillation) and replaced with aspirin (Whitlock*, et al* 2012).

Aortic bioprosthetic valves

Can start aspirin straight away with no need for initial warfarin (long term anticoagulation may be required for other reasons such as atrial fibrillation) (Whitlock*, et al* 2012).

Mechanical valves

The types of mechanical valves used in modern practice are typically less thrombogenic than older valves (see below) but there still are surviving patients with old style valves such as the Starr-Edwards in place. The BSH (Keeling*, et al* 2011) decided to adopt the European Society of Cardiology guidelines (Vahanian*, et al* 2007) but to restrict the highest recommended target INR to 3.5.

Prosthesis Thrombogenicity*	INR target No patient risk factors	INR target Patient-related risk factors** present
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	3.5***

*Prosthesis thrombogenicity:
Low: Carbomedics (aortic position), Medtronic Hall, St Jude Medical (without silzone)
Medium: Bjork-Shiley, other bileaflet valves
High: Starr-Edwards, Omniscience, Lillehei-Kaster.

**Patient-related risk factors for thrombosis:
Mitral, tricuspid or pulmonary position
Previous arterial thromboembolism
Atrial fibrillation
Left atrium diameter >50 mm
Mitral stenosis of any degree
Left ventricular ejection fraction <35%
Left atrial dense spontaneous echo contrast.

***Was 4.0 in ESC guideline.

We will take advice from the referring physician but will use this as a guide when the required information is available. The ACCP (Whitlock*, et al* 2012) suggest a target of 2.5 for mechanical aortic valves and 3.0 for mechanical mitral valves. This is simple and fits what ESC/BSH recommends for low risk valves, it is reasonable for us to recommend this if we have no other data but note that for patients at low risk of bleeding the ACCP recommend the addition of aspirin.

Duration of treatment in venous thromboembolism (VTE)

Patients with proximal DVT or PE should be treated for at least 3 months. A recent analysis of data from seven trials (Boutitie*, et al* 2011) concluded that three months of treatment achieves a similar risk of recurrent venous thromboembolism after stopping anticoagulation as a longer course of treatment. This was also found in a British study (Campbell*, et al* 2007).

It is clear that patients with unprovoked proximal DVT or PE are at a higher risk of recurrence than those with a transient precipitating factor (Iorio*, et al* 2010) and it is therefore recommended that they should be considered for long-term anticoagulation (Kearon*, et al* 2012), we should take into account information that may help predict risk of recurrence and risk of bleeding in the individual patient. This includes the increased risk of recurrence in males, those with post thrombotic syndrome and perhaps those with a raised D-dimer after completing anticoagulation. It should also be taken into account that patients with an initial symptomatic PE are 3 to 4 times more likely to suffer recurrence with PE rather than DVT as compared with patients who present with an initial DVT.

Commencement of oral anticoagulant therapy

Standard induction regimen commenced with heparin cover

Patients with VTE will commence treatment with (LMW) heparin. Warfarin can be started as soon as the diagnosis is confirmed. Heparin should be continued until the INR has been ≥ 2 for at least two consecutive days or for five days – whichever is the longer.

Our warfarin induction schedule is shown in the table. We prefer starting with 5 mg rather than 10 mg as over-anticoagulation is less likely, particularly in the elderly and those with liver disease or cardiac failure.

If the baseline INR≤1.3 the patient will receive 5mg of warfarin once daily on days 1 and 2. The INR is checked on day 3 and 4 and the warfarin dose is adjusted according to the schedule.

days 1 & 2	day 3		day 4	
	INR	dose	INR	dose
Give 5 mg each day if baseline INR ≤ 1.3	< 1.5	10 mg	< 1.6	10 mg
	1.5-2.0	5 mg	1.6-1.7	7 mg
	2.1-2.5	3 mg	1.8-1.9	6 mg
	2.6-3.0	1 mg	2.0-2.3	5 mg
	> 3.0	0 mg*	2.4-2.7	4 mg
			2.8-3.0	3 mg
			3.1-3.5	2 mg
			3.6-4.0	1 mg
			> 4.0	0 mg*

* if required the thrombosis nurse (bleep 5035) or the haematology SpR can be contacted for advice on further management.

Slow induction of anticoagulation in patients with atrial fibrillation without heparin cover (Janes*, et al* 2004)

Exclusions

- Patients with baseline INR of >1.3 (discuss with a haematology doctor)
- Patients concurrently starting amiodarone, a statin, antibiotics or other drugs known to potentiate warfarin. Patients who have been on these drugs prior to starting warfarin can be included.
- If a patient has taken warfarin in the past their previous dose requirements should be considered.

INR	Dose
Day 1-7	3 mg daily and check in 1 week
Day 8*	**This protocol is only valid if the patient has taken 7 days warfarin before the day 8 INR: otherwise it is invalid. You should be aware of early tests as the dose may be seriously overestimated.*
<1.4	Increase to 6 mg and check in 1 week (see Day 15 below)
1.4-1.5	Increase to 5 mg and check in 1 week
1.6-1.8	Increase to 4 mg and check in 1 week
1.9-2.1	Maintain 3 mg and check in 1 week
2.2-2.5	Reduce to 2.43 mg (17 mg per week) and check in 1 week
2.6-2.7	Reduce to 2 mg and check in 1 week
2.8-3.0	Omit 1 day, reduce to 1 mg and check in 1 week
>3.0	Stop, check in 3-5 days. Restart at 1mg when INR <3.0 (if > 8.0 give phytomenadione according to protocol)

Additional dosing protocol *only* for patients who have 3mg/day for one week followed by 6 mg/day for one week

Day 15 **	***Only* to be followed if the patient received 6 mg during the second week because of inadequate response to 3 mg.*
<1.4	Increase to 10 mg and check in 1 week (NB check compliance/inhibiting drugs)
1.4-1.6	Increase to 8 mg and check in 1 week
1.7-1.8	Increase to 7 mg and check in 1 week
1.9-2.4	Maintain 6 mg and check in 1 week
2.5-2.9	Reduce to 5 mg and check in 1 week
3.0-4.0	Omit 1 day and reduce to 4 mg and check in 1 week
4.1-5.0	Omit 2 days and reduce to 4 mg and check in 1 week
>5.0	Omit 3 days and recheck INR (if > 8.0 give phytomenadione according to protocol)

Management of anticoagulation in the peri-operative period for major surgery or procedure which requires the INR to be normalized

Pre-operative assessment

For patients on warfarin the pre-operative assessment team must liaise with the patient's anticoagulation service (bleep 1857 for Oxfordshire patients). Warfarin should be stopped 5 days before surgery.

The main decision is whether to give bridging anticoagulant therapy with full treatment doses of low molecular weight heparin (LMWH) or, less commonly with unfractionated heparin (UFH) once the INR is less than 2.0. Patients on warfarin for mechanical heart valves (MHV), atrial fibrillation (AF) or for treatment or prevention of venous thromboembolism (VTE) are considered for bridging therapy if they are regarded as at high risk of thrombosis (see **table**).

All patients who do not require bridging with full treatment dose heparin over the operative period should be risk assessed and given prophylactic dose LMWH as appropriate.

	Consider bridging with full treatment dose heparin in
VTE	Patients with a VTE within previous 3 months. Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3.5.
AF	Patients with a previous stroke/TIA in last three months. Patients with a previous stroke/TIA and three or more of the following risk factors: • Congestive cardiac failure • Hypertension (greater than 140/90 mmHg or on medication) • Age over 75 years • Diabetes mellitus
MHV	All Mechanical Heart Valve patients except those with a bileaflet aortic valve and no other risk factors

There is no need to monitor the INR in patients who are at home for the 5 days before surgery. The last dose of warfarin should be taken on the evening of day -6. LMWH is started on the morning of day -3 and is continued until day -1 (i.e. 24 hours before surgery). If the surgery poses a high risk of bleeding, this final dose of LMWH on day -1 should only be half the full anticoagulant dose. **NB** according to Oxfordshire Shared Care guidelines, supply of LMWH for patients who need bridging at home should come from the hospital. This should be discussed and arranged during the pre-operative assessment.

In patients who are in hospital in the run up to surgery and who are receiving bridging anticoagulation with therapeutic dose UFH the heparin should be stopped 4-6 hours before surgery (discuss timing with the operating surgeon). Refer to MIL vol.5 no.6 "Guidelines on when to use and how to monitor unfractionated heparin in adults" for full guidance on the use of UFH.

In all patients whose warfarin has been stopped 5 days before surgery, the INR should be measured on the day before surgery, allowing correction with oral phytomenadione (vitamin K) if it is greater than or equal to 1.5 (suggested dose 2mg). If correction with phytomenadione is required, the INR should be re-checked on the morning of surgery.

Full dose bridging after major surgery

In patients undergoing a procedure which carries a high risk of bleeding, the perioperative anticoagulation depends on a balance between the risk of bleeding and the risk of thrombosis. The choices are:

- Avoid all heparin after surgery
- Give prophylactic dose LMWH or UFH after surgery once haemostasis has been secured
- Give therapeutic dose LMWH or UFH no sooner than 48 hours if haemostasis is secured

i.e. therapeutic dose LMWH or UFH must not be given for at least 48 hours after high bleeding risk surgery. Instruction for the provision of post-operative heparin is the responsibility of the operating surgeon.

Warfarin can be resumed, at the normal maintenance dose, the evening of surgery or the next day if there is adequate haemostasis, following discussion with the operating surgeon.

Minor surgery or procedure with low bleeding risk

For some operations the surgeon may advise that the INR need only be reduced (to 1.5-2.0 for example) for the procedure in which case bridging anticoagulation may not be required. In these cases, the surgical team should liaise with the anticoagulation service in good time to make necessary dose adjustments and arrange an INR test the day before surgery as described above.

Some procedures, such as joint injections and cataract surgery, can be carried out without interrupting warfarin therapy. However, the person performing the procedure may advise that the INR is reduced to 1.5-2.0.

Endoscopy in patients on warfarin (Veitch*, et al* 2016)

In general, low risk diagnostic procedures including mucosal biopsy can be performed when the INR is up to and including 3 without altering anticoagulation. For therapeutic procedures, the risk of post-procedure bleeding is higher and reduction of anticoagulation is preferred. There are, however, no absolute rules and the risks and benefits should be discussed with the patient prior to the procedure and an individual decision made.

If warfarin is stopped, it is safe to reinstate anticoagulation on the evening of the procedure unless the endoscopist advises otherwise.

The risk of thromboembolism and risk of bleeding after a procedure can be divided into high and low, see **table.** The recommendations for action following risk assessment are summarized below:

High Risk Procedure
Warfarin should be discontinued 5 days before the procedure. Bridging therapy with heparin (UFH or LMWH) should be considered for high risk conditions while the INR is below therapeutic level.

Low Risk Procedure
No change in anticoagulation is recommended unless the INR is greater than 3.

Condition	Procedure
High Risk Conditions Prosthetic metal heart valve in mitral position Prosthetic heart valve and AF AF and mitral stenosis Less than 3months after VTE	**High Risk Procedures** Polypectomy ERCP with sphincterotomy Ampullectomy EMR/ESD Dilation of strictures Therapy of varices PEG EUS with FNA Oesophageal, enteral or colonic stenting
Low Risk Conditions Prosthetic metal heart valve in aortic position Xenograft heart valve AF without valvular disease Greater than 3months after VTE	**Low Risk Procedures** Diagnostic procedures +/- biopsy Biliary or pancreatic stenting Device-assisted enteroscopy without polypectomy

Dentistry in anticoagulated patients

The risk of significant bleeding in patients on oral anticoagulants and with an INR of . ≤ 4.0 is small and the risk of thrombosis may be increased in patients in whom oral anticoagulants are temporarily discontinued. Oral anticoagulants should not be discontinued in the majority of patients requiring out-patient dental surgery including dental extraction.

The risk of bleeding may be minimised by:

- The use of oxidised cellulose (Surgicel) or collagen sponges and sutures.
- 5% tranexamic acid mouthwashes used four times a day for 2 days (but note tranexamic acid is not readily available in most primary care dental practices).

For patients who are stably anticoagulated on warfarin, a check INR is recommended 72 hours prior to dental surgery.

Patients taking warfarin should not be prescribed NSAIDs as analgesia following dental surgery.

The National Patient Safety Agency (NPSA), with support from the British Dental Association & BCSH, has produced a useful poster '**Managing patients who are taking warfarin and undergoing dental treatment'.** Dentists enquiring about patient management should be referred to this.

Management of bleeding and of high INR in the absence of bleeding

For a patient with bleeding check the APTT as well as the INR. An APTT > 50s associated with a therapeutic INR suggests there may be another problem such as a low factor VIII due to acquired haemophilia or (in a male) a very low factor IX due to an Ala -10 mutation.

The cause of the elevated INR as well as the source of bleeding should always be investigated.

Major / life threatening bleeding requiring immediate complete reversal

This relates to patients with intracranial or rapid-onset neurological signs, intra-ocular (not conjunctival) bleeds, compartment syndrome, pericardial bleeds or those with active bleeding and shock, or any bleeding that requires complete reversal of anticoagulation within 6-8 hours. These patients need urgent clinical assessment of clotting.

Anticoagulation due to warfarin can be effectively reversed with PCC **and** phytomenadione 5mg by slow intravenous injection:

Dose of PCC for reversal of anticoagulation

Weight	**Dose of PCC**
less than 60kg	1500 units
60-75kg	2000 units
76-90kg	2500 units
greater than 90kg	3000 units

Non-major bleeding

INR 5.0 or greater

- Omit warfarin
- Give IV phytomenadione 1-3mg (or 5-10mg if anticoagulation is to be stopped)

INR less than 5

- A clinical decision needs to be made as to whether lowering the INR is required. If this is the case, consider giving IV phytomenadione 1-3 mg and modifying warfarin dose

High INRs in non-bleeding patients

The cause of the elevated INR should be investigated

INR ≥ 5.0 and < 8.0

- stop warfarin for 1-2 days and reduce maintenance dose

INR ≥ 8.0

- stop warfarin until INR< 5.0
- give oral phytomenadione 5 mg

Oral vitamin K will have an effect within 16-24 hours

Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology

Please notify the outpatient anticoagulation team (57555/57557) if a patient on warfarin is admitted with bleeding issue.

Management of subtherapeutic anticoagulation

If the INR falls to < 1.7 in the first 4 weeks after starting treatment for acute VTE we recommend re-starting LMWH until the INR is back to ≥2.0.

Warfarin and antiplatelet medication

The following recommendations are from the BSH guideline (Keeling*, et al* 2011)

Patients on antiplatelet therapy who develop an indication for warfarin

- Patients receiving an anti-platelet agent as primary prophylaxis for CVD on developing an indication for warfarin should stop their antiplatelet agent (1B)
- Patients with peripheral artery disease or previous ischaemic stroke on antiplatelet therapy should stop this agent if warfarin is commenced (1B)
- Patients on aspirin or clopidogrel as secondary prophylaxis with stable ischaemic heart disease [often defined as >12 months following acute MI] should stop their antiplatelet agent while being treated with warfarin (2B)
- Patients on a single antiplatelet agent <12 months following an ACS, who require to start warfarin therapy should continue aspirin therapy until 12 months post ACS, unless they are regarded as having a high bleeding risk (2B)
- Patients on aspirin and clopidogrel, following an ACS or stent placement, who develop an indication for warfarin should be carefully assessed for bleeding risk and discussed with their cardiologist, with a view to introducing warfarin and minimising the duration of triple therapy (2C)
- When combined warfarin and single antiplatelet agent are indicated, consideration should be given to use of aspirin given the higher bleeding risk associated with clopidogrel (2C)

Patients on warfarin who develop an indication for antiplatelet agents

- Patients requiring coronary artery stenting, should be considered for bare metal stent (rather than drug-eluting stent) which would only necessitate triple therapy for 4 weeks, followed by aspirin and warfarin to 12 months (2B).
- Patients who do not undergo PCI should be considered for 4 weeks triple therapy, after which clopidogrel should be stopped, and aspirin continued for a further 11 months (2C)

Outpatient monitoring and dose adjustment
Patients under the care of the Oxfordshire Anticoagulation Service have their anticoagulation monitored and dose adjusted using computer decision support software (RAID - Hirumed® Ltd). Monitoring is by nurse specialists trained and deemed competent in the use of RAID, under the clinical lead of a consultant haematologist.

Point of Care Devices

Outpatients
For a small number of patients it is problematic obtaining venous INR samples (eg difficult to bleed/needle phobic). These patients can have their INR testing using CoaguChek XS Plus point of care testing device. This service is only available for outpatients.

Self-testing
The Anticoagulation Service will facilitate self-testing for outpatients who have bought their own Coaguchek XS machine. The patient must get approval from their GP to prescribe the testing strips.

Swapping to/from other oral vitamin K antagonists

There is very little evidence available to suggest a suitable transition protocol for patients switching from one VKA to another.

Warfarin, acenocoumarol and phenindione are the only VKA licenced in the UK. Patients started on oral anticoagulants in different countries may need converting from fluindione and phenprocoumon as these are not available in the UK.

Approximate dose conversions				
Warfarin	Acenocoumarol	Phenindione	Fluindione	Phenprocoumon
0.5mg, 1mg 3mg, 5mg	1mg	10mg, 25mg 50mg	20mg	3mg
(scored ½)	(scored ½)		(Scored ¼)	(scored ¼)
t ½: 40 hours	t ½: 8-11 hours	t ½: 5-10 hours	t ½: 31 hours	t ½: 5-6 days
Relative dose = 1	**x 0.5***	**x 10***	**x 3***	**x 0.5***
1mg	0.5mg	10mg	-	0.75mg
2mg	1.0mg	20mg	5mg	0.75mg
3mg	1.5mg	30mg	10mg	1.5mg
4mg	2.0mg	40mg	10mg	2.25mg
5mg	2.5mg	50mg	15mg	2.25mg
6mg	3.0mg	60mg	20mg	3mg
7mg	3.5mg	70mg	20mg	3.75mg
8mg	4.0mg	80mg	25mg	4.5mg
9mg	4.5mg	90mg	25mg	4.5mg
10mg	5.0mg	100mg	30mg	5.25mg

*The table above is a guide to the half-lives of the available agents and a rough approximation of their equivalent doses in terms of potency and clinical effect. It is based on only a small amount of data and all patients switching VKAs should be closely monitored over this period.

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