DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

GUIDELINE ON ORAL ANTICOAGULATION WITH WARFARIN

This guideline is intended to be used in Derbyshire to support the Primary care led INR monitoring service commissioned in Derbyshire. Only accredited practitioners who meet the service specification and sign up to the service level agreement should provide this service.

- It is recommended that only 1mg strength warfarin tablets are used for the majority of patients. Where patients are on doses of greater than 5mg and can manage different strengths, it may be considered appropriate to use higher strength tablets.
- Use of 0.5mg dosing is not recommended to avoid confusion with the 5mg.
- The patient should receive verbal and written information on anticoagulant therapy from the start of treatment and an induction process followed to ensure they understand the information.
- Each patient should be issued with an oral anticoagulation therapy (OAT) pack containing an anticoagulant record booklet (yellow booklet) which should be kept up to date.
- Practitioners managing oral anticoagulation with warfarin should meet the required competencies.
- Warfarin is classified as a "critical medicine" as defined by the National Patient Safety Agency Rapid Response Report 18: Preventing fatalities from medication loading doses. The use of loading doses of medicines can be complex and error prone. Incorrect use of loading doses or subsequent maintenance regimens may lead to severe harm or death.
- Particular attention should be placed on assessing concordance and checking changes in medication, food and lifestyle and the impact of these on the International Normalised Ratio (INR).
- Non-vitamin K antagonist oral anticoagulants (NOACs) are now available and indicated for certain conditions. Please see Derbyshire JAPC guideline: Atrial Fibrillation

Document updates	Date updated
Konakion MM paediatric 2mg in 0.2ml discontinued- brand removed and replaced with generic phytomenadione	Aug 2021

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References

1. Keeling, Baglin, Tait, Watson et al, British Committee for Standards in Haematology: Guidelines on oral anticoagulation with warfarin – fourth edition. British Journal of Haematology, 2011; 154: 311-324
2. Oates A, Jackson PR, Austin CA, Channer KS: A new regimen for starting anticoagulation in out-patients; British Journal of Clinical Pharmacology, 1998; 46:157-171
3. Channer, Kevin S. Starting warfarin as an outpatient. British Journal of General Practice, 2002; 52:238-239
4. www.cks.nice.org.uk/anticoagulation-oral 23/10/ 2019
5. Joint Formulary Committee British National Formulary (BNF) 65, March 2013; accessed online via medicines complete 23/10/ 2019
6. Shetty HG, Backhouse G, Bentley DP, Routledge PA. Effective reversal of Warfarin induced excessive anticoagulation with low dose vitamin K. Thrombosis and Haemostasis, 1992; 67(1):13-15
7. Hanley JP. Warfarin Reversal. Journal of Clinical Pathology, 2004; 57: 1132-1139
8. Makris M et al, British Committee for Standards in Haematology. Guideline on the management of bleeding in patients on antithrombotic agents. British Journal of Haematology, 2012; 160: 35-46.
9. McKernan A. Outpatient anticoagulation service: Management of high INR, without bleeding, due to vitamin K antagonists. February 2013.

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1. Introduction

- Warfarin has a narrow therapeutic index and regular titration of the dose against the anticoagulant effect in the blood, as assessed by the INR, is essential.
- The patient should be maintained within their therapeutic range, as documented in Table1. Deviation from the therapeutic range is associated with an increased risk of haemorrhage (if too high), or thrombosis and increased risk of stroke (if too low).
- Practitioners managing anticoagulation should have the necessary training and skills to do so. See appendix 2 for training resources.

2. Indications for oral anticoagulation

- The decision relating to diagnosis, indication for anticoagulation and INR target and range will be made in secondary care except for stroke risk reduction in atrial fibrillation patients. See AF guideline for further details.
- Accredited Pharmacists and nurses managing anticoagulation will not be required to make these decisions unless qualified as independent prescribers.
- Warfarin may be started in out-patients if immediate anticoagulation is not necessary.

Table 1. Indications for warfarin; target INR, therapeutic range and duration of treatment [1]

Indication	Target INR	& Range	Duration
Pulmonary embolus	2.5	2.0-3.0	3 months to long term (if unprovoked)
Proximal DVT	2.5	2.0-3.0	3 months to long term (if unprovoked)
Distal DVT • Isolated calf vein DVT • Provoked by surgery or other transient risk factors (e.g. COC use, pregnancy, plaster cast)	 2.5 2.5	 2.0-3.0 2.0-3.0	 6 weeks 3 months
Recurrent events PE &/or DVT • Whilst off warfarin or sub-therapeutic INR • Whilst on warfarin within therapeutic range	 2.5 3.5	 2.0-3.0 3.0-4.0	 6 months to long term Long term
Non-valvular AF with CHA_2DS_2-VASc score ≥2 (see AF guideline) CHA^2DS^2-VASc items / CHA^2DS^2-VASc Score: Congestive heart failure or left ventricular dysfunction: 1 Hypertension: 1 Age ≥75: 2 Diabetes: 1 Stroke or TIA: 2 Vascular disease (prior MI, peripheral artery disease, aortic plaque): 1 Age 65-74: 1 Sex category (female): 1	2.5	2.0-3.0	Long term
AF secondary to valvular (mitral stenosis related) heart disease	2.5	2.0-3.0	Long term
Cardioversion for AF	2.5	2.0-3.0	Minimum 3 weeks before to 4 weeks after
Rheumatic mitral valve disease	2.5	2.0-3.0	Long term
Dilated cardiomyopathy	2.5	2.0-3.0	Long term
LV mural thrombus post MI +/- LV aneurysm	2.5	2.0-3.0	3 months
Mechanical Prosthetic Heart Valves • Low thrombogenicity* No patient risk factors Patient related risk factors+ • Medium thrombogenicity* No patient risk factors Patient related risk factors+ • High thrombogenicity* No patient risk factors Patient related risk factors+	 2.5 3.0 3.0 3.5 3.5 3.5	 2.0-3.0 2.5-3.5 2.5-3.5 3.0-4.0 3.0-4.0 3.0-4.0	 Long term
Bioprosthetic Heart Valves • Mitral position • Previous systemic embolism • Left atrial thrombus at surgery • Other risk factors, e.g. AF, low LVEF	 2.5 2.5 2.5 2.5	 2.0-3.0 2.0-3.0 2.0-3.0 2.0-3.0	 3 months >3 months Until clot resolution Long term
Inherited thrombophilia with DVT &/or PE	2.5	2.0-3.0	Variable
Antiphospholipid syndrome	2.5	2.0-3.0	Long term

*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: mitral, tricuspid or pulmonary position; previous arterial thromboembolism; AF; left atrium diameter >50mm; mitral stenosis; left ventricular ejection fraction <35%; left atrial dense spontaneous echo contrast.

3. Initiation of Warfarin Therapy

- There are various schedules for initiating anticoagulation within an outpatient setting. In primary care initiation should only be done by accredited practitioners who have successfully completed the BMJ module - 'Starting patients on anticoagulants: how to do it' (see appendix 2).
- When starting warfarin you must stop antiplatelet therapy (aspirin/ clopidogrel/ dipyridamole/ ticagrelor/ prasugrel), once INR within therapeutic range; unless continuation is explicitly advised by a consultant in secondary care. This should be documented.
- All new patients should receive a structured induction to ensure that all the relevant information is provided. See https://cks.nice.org.uk/anticoagulation-oral click on Scenario: Warfarin- Advice.

Starting as an out-patient in primary care- Example safe slow loading regimen for AF[5,6,7] (where rapid anticoagulation is not necessary) with INR target 2.5. It normally takes 1-2 weeks to get warfarin in the therapeutic range.
This is a guide only- use approved clinical decision support software (CDSS) but clinical judgment must be applied in all cases to determine decisions.

Check baseline renal function, LFT & clotting factors
If results abnormal, investigate as appropriate prior to initiation of anticoagulation e.g. seek specialist advice if patient has prolonged baseline prothrombin time.

Discuss indication, risk/benefit of treatment and issue oral anticoagulation treatment pack

Day1 — Prescribe **2mg warfarin daily** (usually at 6pm)

Dav8 — Check INR

INR < 3	**INR > 3**
Continue 2mg warfarin daily	Discuss options with anticoagulation

Day15 — Check INR and prescribe predicted maintenance dose for **e.g target 2.5 ± 0.5** as below

Table 2. Predicted maintenance dosage of warfarin based on INR after 2 weeks of 2mg/day

MALE		FEMALE	
INR at Week 2	**Maintenance Dose**	**INR at Week 2**	**Maintenance Dose**
1.0	6mg/day	1.0-1.1	5mg/day
1.1-1.2	5mg/day	1.2-1.3	4mg/day
1.3-1.5	4mg/day	1.4-1.9	3mg/day
1.6-2.1	3mg/day	2.0-3.0	2mg/day
2.2-3.0	2mg/day	>3.0	1mg/day
>3.0	1mg/day		

Dav22 — Check INR

Bleeding	**INR > 4.0, not bleeding**	**INR between 2.0-3.0**	**INR <2**
See Table 5 Contact anticoagulation service (appendix 3)	Omit warfarin for 2 days then restart at a dose 1mg lower	Continue the same dose of warfarin	Check compliance/ interacting drugs/ drugs brought over the counter/ diet Continue and recheck in a week

- If there are two consecutive weeks where the INR is <2.0 after day 22 the dose of warfarin should be increased by 1mg if the patient has been assessed to be fully compliant.
- By the time the patient has been taking warfarin for 6 weeks the INR should be established and stable within the therapeutic range.

Changes in warfarin dosage should be kept to a minimum as there are natural fluctuations in the INR which occur on a daily basis and because of external factors.

4. Maintenance Dosing

- The dose required to achieve the therapeutic target is very variable between patients, but usually lies between 3 and 9mg daily [4].
- Dosage decisions should be supported using approved clinical decision support software (CDSS) but clinical judgment must be applied in all cases to determine decisions.
- The dose should be taken once a day at a fixed time, preferably 18.00 hours, or another **regular** time if more convenient, to aid compliance. Patients are mostly seen during the day therefore a late afternoon or evening dose enables the managing practitioner to ask the patient to miss a dose, when required. Management can be more difficult if the patient has already taken their anticoagulant.
- Warfarin tablet are colour coded - strengths available are: 0.5mg (white), 1.0mg (brown), 3.0mg (blue) and 5.0mg (pink).
- The use of the 1mg strength tablets has been agreed locally to avoid confusion over inappropriate dosing and the preferred option. By exception the use of other strengths i.e. higher doses greater than 5mg may be considered on a patient by patient basis. Avoiding more than two different strengths is strongly recommended.
- Use of 0.5mg dosing is not recommended to avoid confusion with the 5mg.
- The current INR and recommended dose should be recorded in the patient's yellow anticoagulant record book.
- The recommended dose should always be specified in milligrams, i.e. Xmg, not number of tablets.
- The NPSA recommends use of constant daily dosing and not alternate day dosing. In practice, fine tuning of dosage by using alternate day regimens of e.g. 2mg/3mg may need to be used if INR fluctuates too much.
- If a patient misses a dose of Warfarin they should be told **not** to take double the dose the next day but to continue with their normal dose. If the patient is very sensitive to changes, or at high risk if under dosed, they should contact the service provider as soon as possible. Other patients may be asked to arrange earlier monitoring if their appointment is not due for some time, depending on stability of patient and clinical judgment of managing practitioner.

5. Monitoring

- This service is based on near patient testing and venous samples should only be used in exceptional circumstances, as stated in the service specification.
- The frequency of monitoring will vary but patients should have their INR checked at least every 10 -12 weeks. Every patient must be seen at least once every 12 weeks. Less stable and new patients will require more frequent tests.
- More frequent monitoring of INR is required if there are risks of over-anticoagulation (e.g. severe, uncontrolled hypertension, liver disease, renal failure); or if there is an increased risk of bleeding (e.g. age 65 years or over, highly variable INRs, history of GI bleeding, cerebrovascular disease, serious heart disease, risk of falling etc.).
- Note: although INR may be measured daily or on alternate days, on starting warfarin and following a change in dose, a meaningful INR can only be obtained after 3-4 days.
- Recall dates will be suggested by the dosing support software; however, if the patient's clinical condition is changing, or there have been alterations in other medication, then the INR should be checked more frequently and clinical judgment should override the CDSS. See table 3 for suggested recall dates:

Table 3. Suggested recall periods during maintenance therapy (not initiation); (see table 1 for therapeutic ranges)

One INR high:	**recall in 7-14 days (stop treatment for 1-3 days) (maximum 1 week in prosthetic valve patients)**
One INR low:	Recall in 7-14 days
One INR therapeutic:	Recall in 4 weeks
Two INRs therapeutic:	Recall in 6 weeks (maximum for prosthetic valve patients)
Three INRs therapeutic:	Recall in 8 weeks (excluding prosthetic valve patients)
Four INRs therapeutic:	Recall in 10 weeks (excluding prosthetic valve patients)
Five INRs therapeutic:	Recall in 12 weeks (excluding prosthetic valve patients)

- Many clinical factors and drugs may affect the sensitivity of the patient to the effects of warfarin. Particular attention should be placed on checking changes in medication, food and lifestyle and the impact of these on the INR (see below).
- Records should be comprehensive and specific alert flags should be considered to highlight a specific warning, or a patient's particular sensitivity.
- Service providers should discuss concordance and, as with all prescribed medications, have mechanisms in place to regularly check compliance.
- A robust system should be in place to ensure all DNAs (did not attends) are followed up and monitored effectively. It must be stressed to the patient that careful monitoring of warfarin therapy is essential in order to avoid complications. Where patients repeatedly fail to attend, then the risks of continuing therapy should be considered against the benefits. Advice should be sought from the GP or specialist.

i) JAPC Consensus and agreement for the management of sub-therapeutic INR

It is not uncommon for patients INRs to fall below the target value in patients taking long term warfarin. There is though a lack of national guidance on what to do in this situation.
JAPC advises that for a patient with a single INR value below therapeutic value, the clinician should check medication compliance with the patient, and investigate any interacting medicines (prescribed, bought over the counter or herbal). Include questions on lifestyle or dietary changes to see if these are the cause. To decide on a patient by patient basis whether to increase the dose and/or address causes and then retest the INR accordingly within the next 7-14 days (as per table 3).

The use of LMWH is only advocated when the warfarin INR falls outside the therapeutic range, within the first four weeks of acute VTE, as recommended by the fourth edition of the British Committee for Standards in Haematology until the patient is within therapeutic range for warfarin. All other patients are deemed low risk. In patients with serial INRs (on more than 2 occasions) below therapeutic range where there is no improvement in control following interventions, advice should be sought from specialists in the area (e.g. in patients with artificial valves).

LMWH is commonly prescribed in patients where rapid anticoagulation is necessary and often used in conjunction with warfarin until target INR is reached (warfarin loading following acute VTE). The provider trusts will supply a suitable quantity of LMWH to meet the patients need. However in exceptional circumstances primary care clinicians may be requested to supply small quantities of LMWH where patients fail to reach their target INR at the request of a specialist or INR clinic. See LMWH guideline.

ii) Factors affecting warfarin sensitivity:

Conditions that may increase warfarin sensitivity (may warrant decrease in warfarin dose)	**Conditions that may decrease warfarin sensitivity (may warrant increase warfarin dose)**
• Hepatic dysfunction and/or jaundice • Alcohol abuse particularly "binge drinking" • Congestive heart failure • Anorexia • Hyperthyroidism • Acute pyrexial episode • Changes in diet which reduce the intake of vitamin K* • Dietary components: Cranberry juice • Drugs (see table 4) (this list is not exhaustive): - Allopurinol; NSAIDs; Amiodarone (marked effect) - Antibiotics (unpredictable / almost any antibiotic) - Antifungals; Disulfiram; Tamoxifen; Statins - Thyroid hormones; Cimetidine; - Antiplatelet agents (increased risk of bleeding)	• Hypothyroidism • Changes in diet which increase the intake of vitamin K * • Dietary components: Dasheen • Herbal remedies: St John's Wort, Gingko Biloba • Drugs: (this list is not exhaustive): ▪ Anti-convulsants ▪ Barbiturates ▪ Rifampicin ▪ Estrogens & progestogens ▪ Sucralfate Note: When these drugs are discontinued the dose must be reduced to avoid dangerous over-anticoagulation.

***The following foods and supplements are rich in vitamin K:** dark green vegetables: spinach, kale, spring greens, cabbage, Brussels sprouts, broccoli; asparagus, watercress, parsley, beef liver, rapeseed oil, green tea

Additional circumstances where changes in dose may be required

The following also may exaggerate the effect of warfarin and necessitate a reduction of dosage:	The following may reduce the effect of warfarin and require the dosage to be increased:
• Loss of weight • Acute illness • Cessation of smoking	• Weight gain • Diarrhoea • Vomiting

iii) COMMON Warfarin Drug Interactions: [5]

The drugs in this list are more usually associated with loss of INR control in patients already established on warfarin. **This list is not exhaustive** - refer to the British National Formulary (BNF) for further information. If any of the drugs below are to be started in these patients then the use of alternatives in the same therapeutic class may be considered. If this is not possible then the patient's INR should be monitored as detailed below. Those drugs highlighted in **bold** are significant interactions and should be avoided or used with caution.

- **Drugs marked * are liver enzyme inhibitors and increase the INR. They act very quickly (can be within 24 hours) and if the drug is withdrawn the effect disappears quickly depending on the drug half-life. The INR should if possible be monitored within 72 hours of starting the interacting drug and on withdrawal.**

- **Drugs marked $ are liver enzyme inducers and decrease the INR. They act more slowly (up to a week) with peak effect at 2-3 weeks and can persist for up to 4 weeks after stopping depending on drug half-life. The INR will need checking after 1 week of concurrent therapy.**

- **Drugs with neither have other mechanisms, which affect the INR.**

N.B. If a patient on warfarin were started on ANY other new medication a repeat INR after 1 week would be sensible.

Table 4. Common Warfarin Drug Interactions

	Drugs that increase the INR and risk of bleed
Gastrointestinal	**cimetidine*,** omeprazole* esomeprazole
Cardiovascular	**amiodarone*** (liver enzyme inhibition is slow and may persist long after withdrawal requiring weekly monitoring over 4 weeks), **fibrates**, ezetimibe, **propafenone*,** propranolol, statins – no clinically relevant interaction will normally be seen however it is prudent to check INR in the weeks after initiation and at any dose change
CNS	**Entacapone, fluvoxamine***, SNRIs, **SSRIs*, tramadol**
Anti-infectives (anti-infectives in general may cause raised INR's)	**azole antifungals*** (esp. miconazole including oral gel and vaginal), **co-trimoxazole*, macrolides*** (can be serious but unpredictable), **metronidazole***, **quinolones*** (can be serious but unpredictable), **tetracyclines,** influenza vaccine
Endocrine	**anabolic steroids (and danazol), high dose corticosteroids, glucagon (high dose 50mg+ over 2 days), flutamide, levothyroxine**
NSAIDs	Ibuprofen at lowest effective dose (+/-PPI) is probably safest if NSAID is required **N.B. All NSAIDs can increase the risk of bleeds and should be avoided if possible**
Antiplatelets – increased bleed risk	**Aspirin, clopidogrel, dipyridamole, ticagrelor** and **prasugrel**
Anti-coagulants	**Fondaparinux, heparin; low molecular weight heparin eg enoxaparin, tinzaparin; NOACs eg apixaban, dabigatran, rivaroxaban**

Cytotoxics	**Erlotinib, etoposide, fluorouracil, gefitinib,** gemcitabine, imetinib, **sorafenib, vemurafenib**
Miscellaneous	Alcohol (acute), **actiretin,** allopurinol*, **benzbromarone*,** colchicine, **disulfiram,** interferon, paracetamol (prolonged use at high dose), **sulfinpyrazone**, **tamoxifen**, **topical salicylates**, zafirlucast*
Herbal preparations/Food supplements	Carnitine, chamomile, **cranberry juice***, curbicin, dong quai, fenugreek, fish oils, garlic, gingko biloba**, glucosamine**, grapefruit juice*, lycium*, mango, quilinggao
Drugs that decrease the INR	
Miscellaneous	**Alcohol$ (chronic), azathioprine, barbiturates$,** bosentan$, **carbamazepine$, carbimazole, griseofulvin$, mercaptopurine, nevirapine$, OCP/HRT**, **phenobarbital, phenytoin, propylthiouracil,** raloxifene, **rifampicin$(most potent inducer),** trazodone
Herbal preparations etc	Avocado, co-enzyme Q10, green tea, natto, soya beans, **St Johns wort$ (avoid**)
Binding agents	Colestyramine, sucralfate
Warfarin antagonist	**Vitamin K**
Drugs that increase or decrease the INR	
Anti-virals	Atazanavir, **efavirenz, ritonavir, telapravir**
Miscellaneous	Ginseng, phenytoin, quinidine, **tricyclic antidepressants**

* liver enzyme inhibitors and increase the INR.
$ liver enzyme inducers and decrease the INR.
Drugs with neither have other mechanisms, which affect the INR.

6. Management of bleeding and over-anticoagulation [1,6,7,8,9]

NOTE: ANY SIGNS OF BLEEDING REQUIRE MEDICAL ADVICE AND/OR DIRECT REFERRAL TO SECONDARY CARE (see table for further guidance)

Coagulometers using capillary blood may not be accurate when the INR is elevated. For CoaguChek XS plus, **when the INR is >8.0 the capillary blood INR result should be confirmed with a second test and in addition a sample obtained by venepuncture and sent to the laboratory to determine the exact INR reading**.

The therapeutic decision around dosing and clinical management of the patient should not be delayed until the laboratory result is obtained. Clinical management will depend on whether there is bleeding or not which will also indicate need for vitamin K (see table 5 below). [1]

- The risk of haemorrhage increases significantly when the INR is >5.0.
- **Factors associated with higher risk of bleeding*: older age, uncontrolled hypertension; diabetes; renal or liver failure; previous gastrointestinal or cerebral bleed; use of anti-platelet medications; previous history of bleeding; postoperative. [1,9]**
- **All patients with any active bleeding should be evaluated to determine whether there is a local anatomical cause for the haemorrhage.**
- Unexpected bleeding at therapeutic levels – always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal pathology
- A PGD for administration of oral vitamin K (phytomenadione 2mg in 0.2ml) is available for use by accredited practitioners across Derbyshire.

Table 5. Management of Bleeding and Over-anticoagulation [1,5,9]

Bleeding/over-anticoagulation	ACTION
Major bleeding, irrespective of INR	• **Stop warfarin** **Urgent referral to secondary care who will-** • Give 5mg IV vitamin K (phytomenadione) • Give 25-50units/kg prothrombin complex concentrate (PCC) – factors II, VII, IX, X – see BNF section 2.11
Minor bleeding, INR ≥5.0	• **Stop warfarin** **Refer to secondary care who will-** • Give 1-3mg IV vitamin K • Repeat dose if INR still high after 24 hours • Restart warfarin when INR <5.0
Minor bleeding, INR <5.0	• Withhold warfarin • Seek advice from GP or specialist and/or arrange hospital
INR >8.0, no bleeding	• Stop warfarin • Give 2mg vitamin K (using phytomenadione 2mg in 0.2ml - IM / oral preparation to be given **orally**) – **see associated PGD** • Repeat dose if INR still high after 24 hours • Do not give more than 3 consecutive doses of vitamin K – seek specialist advice if INR not falling. • Restart warfarin when INR <5.0 • Investigate cause of elevated INR
INR 6.0-8.0, no bleeding	• Omit 1-2 doses of warfarin • Reduce maintenance dose of warfarin • Consider 2mg vitamin K (using phytomenadione 2mg in 0.2ml - IM / oral preparation to be given **orally**) if bleeding risks* or induction – seek medical advice • Repeat INR within 7 days or next day after vitamin K • Investigate cause of elevated INR
INR 3.0-6.0 (target 2.5) *or* INR 4.5-6.0 (target 3.5), no bleeding	• Reduce maintenance dose of warfarin, or omit one dose then reduce • Repeat INR in 1-2 weeks • Investigate cause of elevated INR

In primary care - the oral route (phytomenadione 2mg in 0.2ml ampoule) is slower and will readily reverse INRs within 16 to 24 hours to therapeutic levels.
In secondary care - IV Vitamin K administration leads to INR reversal within 6-8 hours and is the fastest means of INR reversal. Do not give subcutaneously (inconsistent correction) or intramuscularly (risk of intramuscular haematoma)[4].

Dosage reduction

In general when adjusting the dose of warfarin, a 15% change in dose is expected to result in a change in the INR of 1, and a 10% dose adjustment is expected to result in a 0.7-0.8 change in the INR.

7. Contraindications to Anticoagulation [4]

This list is not absolute and each patient must be individually evaluated.

- Haemorrhagic stroke
- Pregnancy: exposure of the embryo to warfarin during the 6th to 12th weeks of gestation may be associated with the development of an embryopathy and throughout gestation there is a continuing risk of foetal haemorrhage. Women of child bearing age should be warned of the risks and counseled in the use of effective contraception.

8. Exclusions

Patients with the following conditions/problems should be excluded from the primary care service:
A known hereditary or acquired bleeding disorder;

- Children under 16;
- Pregnant women;
- Other conditions the Consultant Haematologist considers should exclude the patient from management in primary care.

Excluded patients will continue to be managed by secondary care clinicians.

9. Cautions

There are certain conditions/problems where caution should be taken when monitoring patients and, where required, advice from the Haematology department should be sought. These include severe heart failure, liver failure, DVT /PE in the previous month, thyroid disorders and chronic alcohol intake.

Risk factors for bleeding should be considered. The following patient characteristics are indicative of a high risk for bleeding: Age >65, uncontrolled hypertension, diabetes, renal failure, previous MI, previous CVA, previous gastrointestinal or cerebral bleed, patients with liver disease [1]. AF patients see guideline for further details (including assessing bleeding risk using HAS-BLED tool).

Reports of calciphylaxis, a very rare but serious condition causing vascular calcification and skin necrosis have been reported to the MHRA. The mortality rate is high. Patients should consult their doctor if they develop a painful skin rash. See MHRA, July 2016 for further details.

10. Anticoagulation in special circumstances

All practitioners providing this service should be aware of special circumstances and know how to manage these patients, following hematology advice. These are circumstances such as Protein C deficiency, Protein S deficiency, Antiphospholipid syndrome, Factor V Leiden.

Anticoagulation in Cancer Patients:

Patients with cancer who are receiving antithrombotic therapy are thought to be at higher risk of bleeding than patients without cancer. For practical purposes, the recommended therapeutic levels of anticoagulation remain the same as long as patients are educated about the risks and the anticoagulation levels are strictly monitored.

Patients with cancer are at a higher risk than non-cancer patients of recurrence of thromboembolism despite adequate anticoagulation.

Patients with cancer who develop thromboembolism should be considered for treatment with long-term low molecular weight heparin (LMWH). Therapeutic anticoagulation with LMWH in this circumstance reduces the risk of recurrent events compared with warfarin therapy. Alternatively the use of DOACs may be considered on specialist advice.

Anticoagulation in dental surgery:

The British Committee for Standards in Haematology (BCSH) has published a document to provide healthcare professionals, including primary care dental practitioners, with clear guidance on the management of patients on oral anticoagulants requiring dental surgery, which can be accessed online at: http://www.nature.com/bdj/journal/v203/n7/full/bdj.2007.892.html

See appendix 1 for summary of key points.

11. Discontinuation of Warfarin Therapy

- The duration of required anticoagulation should always be stated in the medical notes when the patient is first started on therapy.
- Concern of a 'rebound hypercoagulable state' after stopping oral anticoagulant therapy has resulted in uncertainty as to whether treatment should be stopped abruptly or gradually.
- Having considered the evidence, the BCSH guidelines state that there is no need for gradual withdrawal of anticoagulant therapy. The guidelines recommend that oral anticoagulant therapy can be discontinued abruptly when the duration of therapy is completed.

APPENDIX 1: ANTICOAGULATION IN DENTAL SURGERY

Guidelines for the management of patients on oral anticoagulants requiring dental surgery

D. J. Perry, T. J. C. Noakes & P. S. Helliwell
British Dental Journal **203**, 389 - 393 (2007)

Summary of key recommendations

1. The risk of significant bleeding in patients on oral anticoagulants and with a stable INR in the therapeutic range 2-4 (ie <4) is very 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 (grade A level Ib)
2. For patients stably anticoagulated on warfarin (INR 2-4) and who are prescribed a single dose of antibiotics as prophylaxis against endocarditis, there is no necessity to alter their anticoagulant regimen (grade C, level IV)
3. The risk of bleeding in patients on oral anticoagulants undergoing dental surgery may be minimised by:
   - The use of oxidised cellulose (Surgicel) or collagen sponges and sutures (grade B, level IIb)
   - 5% tranexamic acid mouthwashes used four times a day for two days (grade A, level Ib). Tranexamic acid is not readily available in most primary care dental practices. (Tranexamic acid mouthwash is listed in Derbyshire A-Z specials)
4. For patients who are stably anticoagulated on warfarin, a check INR is recommended 72 hours prior to dental surgery (grade A, level Ib)
5. Patients taking warfarin should not be prescribed non-selective NSAIDs and COX-2 inhibitors as analgesia following dental surgery (grade B, level III).

Grading of evidence
•Ia: systematic review or meta-analysis of RCTs.
•Ib: at least one RCT.
•IIa: at least one well-designed controlled study without randomisation.
•IIb: at least one well-designed quasi-experimental study, such as a cohort study.
•III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case-control studies and case series.
•IV: expert committee reports, opinions and/or clinical experience of respected authorities.

Grading of recommendations
•A: based on hierarchy I evidence.
•B: based on hierarchy II evidence or extrapolated from hierarchy I evidence.
•C: based on hierarchy II evidence or extrapolated from hierarchy I or II evidence.
•D: directly based on hierarchy IV evidence or extrapolated from hierarchy I, II or III evidence

APPENDIX 2: RESOURCES

Implementing Patient safety alert 18: Actions that can make anticoagulant therapy safer.
https://www.sps.nhs.uk/articles/implementing-patient-safety-alert-18/
Anticoagulants are one of the classes of medicines most frequently identified as causing preventable harms and admissions to hospitals. The Specialist Pharmacy Sservice has updated this patient safety alert and support materials to help manage the risks associated with anticoagulants and reduce the risks of patients being harmed in the future.

BMJ e- learning modules - Registration with BMJ Learning is required (can be accessed via Athens)

- Starting patients on anticoagulants: how to do it
  http://www.bmjlearning.com/planrecord/servlet/ResourceSearchServlet?keyWord=All&resourceId=5004325&viewResource=
- Maintaining patients on anticoagulants: how to do it
  http://www.bmjlearning.com/planrecord/servlet/ResourceSearchServlet?keyWord=All&resourceId=5004429&viewResource

Local Supplies
The complete OAT pack or individual items such as the yellow record book can be obtained from Primary Care Support England (PCSE) through the following link http://pcse.england.nhs.uk/ using your practice log in details.

Other useful resources:
British Committee for Standards in Haematology: http://www.b-s-h.org.uk/guidelines/
NICE Clinical Knowledge Summaries: https://cks.nice.org.uk/anticoagulation-oral

APPENDIX 3: USEFUL CONTACTS

Chesterfield Royal Hospital Foundation Trust (CRHFT)
Anticoagulation clinic: 01246 512 159
On call consultant haematologist via switchboard (also out of hours): 01246 277271

University Hospitals of Derby and Burton NHS Foundation TRUST
Dr Angela McKernan, Consultant Haematologist (angela.mckernan@nhs.net)) Tel 01332 254770
Derby Hospitals Anticoagulation Team: 01332 789422

Queens Burton Hospital
Anticoagulation team 01283 511511 ext 4040; fax 01283 593064

Other Hospitals:
Nottingham Hospitals QMC Campus
Anticoagulation team 0115 9249924 ext 68412, fax 0115 8754600
Direct line 0115 9194413.
Nottingham anticoagulation service Manager: Steve Davidson 01159249924 Bleep 808274

Sheffield Teaching Hospitals – Royal Hallamshire Hospital
Dr Rhona MacLean, Consultant Haematologist (rhona.maclean@sth.nhs.uk) Tel 0114 2711900
Northern General Hospital anticoagulation clinic – Tel. 0114 2714399

Out of Hours
Derbyshire Health United (DHU) direct line for health professionals - 0844 412 2235
Central Nottinghamshire Clinical Services based at Byron House, Kingsmill Hospital, Mansfield 01623 622515 ext 3601