

1. Before initiating or re-starting warfarin therapy

- Consider if the benefits of anticoagulation outweigh the risks (e.g. bleeding) for each patient (see section 5).
- Ensure **pre-treatment INR**, platelets and liver function tests are normal. If not, seek senior / specialist advice.

To remain in
end-of-bed folder

2. Dosing principles

- Warfarin should only be **prescribed** in the **designated area** of the medication chart.
- The initiating team must complete **target INR, indication, initial dose** and consider **duration** of therapy.
- If **admitted on warfarin**, an INR must be performed within 24 hours of admission, then every 2–3 days and documented in warfarin section of medication chart. If an INR has not been performed within 24 hours of admission, **warfarin is not to be administered until an INR is available** to guide dosing decisions.
- Check the patient has received **education** and **warfarin leaflets** before discharge. Ask your pharmacist to assist.

3. Starting warfarin therapy

- Acute DVT or PE:** Start warfarin on the same day as UFH / LMWH*. **Overlap warfarin** with therapeutic UFH / LMWH* for a minimum of five (5) days **and** until the INR has been in target range for at least two (2) consecutive days.
- Chronic AF and valve replacements:** Start **warfarin alone** (may overlap with prophylactic heparin).
- Post-operative patients:** Restart with their 'normal' pre-operative maintenance dose - **DO NOT RE-LOAD**.
- Assess** each patient for **risk factors** (see section 5) for increased sensitivity to warfarin and therefore bleeding.
- High loading doses**, such as 10 mg, should **not** be used due to an **increase in the risk of bleeding**.

4. Recommended starting nomogram for patients with no risk factors for increased sensitivity to warfarin

Day of Initiation	INR	Dose
1	Less than 1.4	5 mg
	Less than 1.8	5 mg
2	1.8–2	1 mg
	Greater than 2	Nil
3	Less than 2	5 mg
	2–2.5	4 mg
	2.6–2.9	3 mg
	3–3.2	2 mg
	3.3–3.5	1 mg
	Greater than 3.5	Nil
4	Less than 1.4	10 mg
	1.4–1.5	7 mg
	1.6–1.7	6 mg
	1.8–1.9	5 mg
	2–2.3	4 mg
	2.4–3	3 mg
	3.1–3.2	2 mg
	3.3–3.5	1 mg
Greater than 3.5	Nil	
After Day 4, dose is based on clinical judgement		

5. Risk factors for increased sensitivity to warfarin

If **no risk factors**, start at **5 mg daily**, monitor **INR daily** and adjust dose using **recommended nomogram**.

If **risk factors**, consider a smaller loading dose (**2 to 4 mg**) and seek senior / specialist advice.

- Age greater than 75 years
- History of bleeding
- Baseline INR greater than 1.4
- Concomitant drugs affecting warfarin metabolism (see "Warfarin Drug Interactions")
- Co-morbid diseases i.e. hypertension, cerebrovascular disease, ischaemic stroke, heart disease, renal insufficiency, hepatic impairment or low platelets
- Presence of malignancy
- History of falls
- Major surgery within the preceding 10–14 days

6. Recommended target INR ranges and minimum duration

Indication	Target INR Range	Minimum Duration
DVT / PE	2–3	3 months
AF; low risk heart valves (includes bioprostheses); irreversible, clinically hyper-coagulable states	2–3	Life-long, balanced against risks
Valve repairs	2–3	6 weeks post op
High risk mechanical heart valves - mitral valve, both aortic and mitral valves, or aortic valve with risk factors (AF, previous VTE, hypercoagulable state, left ventricular dysfunction, ejection fraction less than 30%, or older generation aortic valve replacement)	2.5–3.5	Life-long, balanced against risks

7. Perioperative thromboembolism risk stratification

Risk Stratum	Indication for Warfarin Therapy		
	Mechanical valve	Atrial fibrillation	Venous thromboembolism
Low risk Bridging unlikely to be required		<ul style="list-style-type: none"> AF and no history of cardiac embolism CHA2DS2–VASc score of 0–5 	<ul style="list-style-type: none"> One DVT or PE more than three months ago Prior VTE and low risk thrombophilia (heterozygous Factor V Leiden or prothrombin gene mutation)
Moderate to High risk Consider bridging	Present - discuss with cardiologist	<ul style="list-style-type: none"> Rheumatic AF (mitral valve disease stenosis / regurgitation) AF with history of cardiac embolism or mechanical heart valve in any position CHADS2–VASc score 6–9 	<ul style="list-style-type: none"> VTE within the past three months or very strong family history High risk thrombophilia: Deficiency of protein C, protein S or antithrombin III; homozygous factor V Leiden mutation; antiphospholipid antibody syndrome; more than one laboratory thrombophilic defect (compound heterozygotes). Two or more arterial or idiopathic venous thromboembolic events

8. Managing warfarin therapy during invasive procedures according to risk of thromboembolism

The decision to withhold, bridge and resume therapeutic anticoagulation in surgical patients should be made on a case-by-case basis in consultation with the surgeon, treating physician, and anaesthetist, with careful consideration of the risk of thromboembolism and bleeding.

Thrombosis risk	Before surgery	After surgery
Low	<ul style="list-style-type: none"> Withhold 4 daily doses of warfarin before surgery Night before surgery: If INR greater than 2, give 3 mg vitamin K[#] (phytomenadione) IV or oral Day of surgery: <ul style="list-style-type: none"> If INR less than or equal to 1.5, surgery can proceed If INR greater than 1.5, defer surgery or, if urgent give Prothrombinex™–VF 15–30 units / kg or, if Prothrombinex™–VF not available, give fresh frozen plasma (FFP) 10–15 mL / kg Employ pre-operative thrombo-prophylaxis as per hospital policy 	<ul style="list-style-type: none"> Start warfarin on the day of surgery at the previous 'normal' maintenance dose as long as there is no evidence of bleeding Employ thrombo-prophylaxis as per hospital policy
Moderate to High	<p>Option 1:</p> <ul style="list-style-type: none"> Withhold 4 daily doses of warfarin before surgery 2–3 days before surgery: When INR is less than 2 commence treatment dose of LMWH* subcutaneously or UFH IV: <ul style="list-style-type: none"> If using LMWH*, last dose should be given at least 24 hours before surgery If using UFH IV, cease infusion 4–6 hours before surgery <p>Option 2:</p> <ul style="list-style-type: none"> Night before surgery: If INR is stable at 2–3 in the 2–4 weeks preceding surgery, give 3 mg vitamin K[#] (phytomenadione) IV or oral Day of surgery: <ul style="list-style-type: none"> If INR less than or equal to 1.5, surgery can proceed If INR greater than 1.5, defer surgery or, if urgent give Prothrombinex™–VF 15–30 units / kg or, if Prothrombinex™–VF not available, give FFP 10–15 mL / kg <p>Option 3:</p> <ul style="list-style-type: none"> For urgent surgery, check INR before surgery and give Prothrombinex™–VF 15–30 units / kg For procedures with low risk of bleeding, warfarin may not need to be ceased 	<ul style="list-style-type: none"> Recommence warfarin as soon as possible at the previous 'normal' maintenance dose as long as there is no evidence of bleeding - DO NOT RE-LOAD Consider bleeding risk against thrombosis Start LMWH* or UFH 12–24 hours postoperatively: <ul style="list-style-type: none"> If using LMWH*, begin with prophylactic dose If using UFH IV, avoid bolus and aim to prolong APTT as recommended by your site Delay resumption of therapeutic LMWH* for 48–72 hours after surgery if no bleeding Continue LMWH* or UFH for minimum of 5 days and cease 48 hours after target INR is reached In surgery with high risk of bleeding, consider using prophylactic dose LMWH* or UFH IV only and cease 48 hours after target INR is reached

9. Recommendations for reversal of warfarin *Seek early advice if any bleeding occurs*

Clinical setting		Recommendation
No bleeding	INR greater than therapeutic range but less than 4.5 and NO bleeding	<ul style="list-style-type: none"> Reduce or withhold next dose of warfarin based on sensitivity risk factors (see section 5). Resume lower dose of warfarin once INR approaches therapeutic range. If INR is only minimally above therapeutic range (i.e. by 10%) dose reduction is generally not necessary.
	INR 4.5–10 and NO bleeding	<ul style="list-style-type: none"> Cease warfarin. Consider reasons for elevated INR and patient specific factors. Vitamin K is usually not required. If bleeding risk high^o, give vitamin K^o 1–2 mg orally or 0.5–1 mg IV. Check INR within 24 hours. Resume lower dose of warfarin once INR approaches therapeutic range.
	INR greater than 10 and NO bleeding	<ul style="list-style-type: none"> Cease warfarin. Give vitamin K^o 3–5 mg orally (the higher dose may lead to difficult re-warfarinisation) or 0.5–1 mg IV. If bleeding risk is high^o, consider Prothrombinex™-VF 15–30 units / kg. Check INR in 12–24 hours and continue to monitor every 1–2 days over the following week. Resume lower dose of warfarin once INR approaches therapeutic range.
Bleeding <small>SEEK SENIOR ADVICE</small>	INR greater than or equal to 1.5 with life-threatening (critical organ) bleeding	<ul style="list-style-type: none"> Cease warfarin. Give vitamin K^o 5–10 mg IV, Prothrombinex™-VF 50 units / kg and FFP 150–300 mL. If Prothrombinex™-VF is unavailable, increase FFP dose to 15 mL / kg. Assess INR frequently until INR less than 5 and bleeding stops.
	INR greater than or equal to 2 with clinically significant bleeding (not life-threatening)	<ul style="list-style-type: none"> Cease warfarin. Give vitamin K^o 5–10 mg IV and Prothrombinex™-VF 35-50 units / kg. If Prothrombinex™-VF is unavailable, increase FFP dose to 15 mL / kg. Assess INR frequently until INR less than 5 and bleeding stops.
	Any INR with minor bleeding	<ul style="list-style-type: none"> Omit warfarin. Repeat INR the following day and adjust warfarin dose to maintain INR in target therapeutic range. If bleeding risk is high^o or INR greater than 4.5, consider vitamin K 1–2 mg orally or 0.5–1mg IV. Assess INR frequently until INR less than 5 and bleeding stops.

10. Warfarin Drug Interactions

- Drug interactions are a common and significant cause of morbidity and mortality.
- Consider all concomitant therapy including herbal / complementary and over-the-counter medications (OTCs).
- Whenever starting or stopping a drug, particularly antibiotics, the INR must be re-checked 48 to 72 hours after change in therapy.
- Change in risk of bleeding may not be reflected in the INR (e.g. aspirin increases the risk of bleed however does NOT affect the INR).
- Do not pre-empt a change. Make dose adjustments only after checking INR at 48 to 72 hours.

Some potential drug interactions with warfarin are outlined below. Note: These lists are not comprehensive or exhaustive. Contact your pharmacist for further information.

Medications which can increase the risk of bleeding (NB: Change in risk of bleeding may not be reflected in the INR)

Anticoagulants / Antiplatelets: e.g. aspirin, dipyridamole, ticagrelor, clopidogrel, prasugrel, ticlopidine, abciximab, eptifibatid, tirofiban, bivalirudin, dabigatran, rivaroxaban, apixaban, fondaparinux, low molecular weight heparin (enoxaparin), tirofiban, and dalteparin), unfractionated heparin. (NB: For conversion between anticoagulants refer to guidelines for LMWH, dabigatran or factor Xa inhibitors)

Non-steroidal Anti-inflammatory Drugs (NSAIDs): e.g. ibuprofen, ketoprofen, naproxen

Antithrombotic agents: e.g. tenecteplase, alteplase

Complementary medicines / food with antiplatelet effects: e.g. fish oil, garlic (*Allium sativum*), ginger, ginkgo, ginseng (*Panax*), papaya, cranberry

Potential Drug Interactions

Severity of Interaction	Level of Evidence
Red ++ The interaction may be life-threatening and / or require medical intervention to minimise or prevent serious adverse effects; or the drugs are contraindicated for concurrent use.	A Controlled studies have clearly established the existence of the interaction.
	B Documentation strongly suggests the interaction exists, but well-controlled studies are lacking.
Black + The interaction may result in an exacerbation of the patient's condition and / or require an alteration in therapy.	C Available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or documentation is good for a pharmacologically similar drug.

Interacting Medication (Drug or Class)	Risk of Bleeding		Level of Evidence	Interacting Medication (Drug or Class)	Risk of Bleeding		Level of Evidence
	▲	▼			▲	▼	
Allopurinol	+		B	Proton Pump Inhibitors e.g. omeprazole, lansoprazole, esomeprazole, pantoprazole	+		B
Amiodarone	++		A	Quetiapine	+		B
Anabolic Steroids / Androgens e.g. nandrolone	++		C	Ropinirole	++		B
Antibiotics				Salicylates (topical) e.g. methyl salicylate	++		B
• amoxicillin, cephalosporins, isoniazid, macrolides, vancomycin	+		B	Sodium valproate i.e. valproic acid	++		B
• dicloxacillin, rifabutin, rifampicin			B	Statins			
• sulfamethoxazole i.e. in co-trimoxazole	++		A	• simvastatin	++		A
• fluoroquinolones – moxifloxacin	++		A	• fluvastatin	+		B
• fluoroquinolones – ciprofloxacin, norfloxacin	+		B	SSRIs e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine	++		B
• metronidazole	++		B	SNRIs e.g. desvenlafaxine, venlafaxine	++		B
Antifungals				Sulfasalazine	+		B
• fluconazole	++		A	Tamoxifen	++		B
• voriconazole	++		B	TCAs e.g. amitriptyline, doxepin	+		B
• itraconazole, ketaconazole, miconazole	+		B	Testosterone	++		B
• griseofulvin		+	B	Thyroxine	+		B
Antithyroid agents e.g. carbimazole, propylthiouracil		+	B	Tramadol	+		B
Aprepitant		++	B				
Azathioprine / Mercaptopurine		+	B	Interacting Complimentary Medication			
Carbamazepine		+	B	Co Enzyme Q10		+	B
Cholestyramine		+	B	Cranberry	+		B
COX-2 inhibitors e.g. celecoxib	++		B	Dan shen (also known as Tan shen) <i>Salvia miltiorrhiza</i>	+		B
Cyclosporin		+	B	Devil's claw <i>Harpagophytum procumbens</i>	+		B
Fibrates				Dong Quai <i>Angelica sinensis</i>	+		B
• fenofibrate	++		B	Fenugreek <i>Trigonella foenumgraecum</i>	+		B
• gemfibrozil	+		B	Glucosamine +/- Chondroitin	+		B
H2-Antagonists e.g. cimetidine, ranitidine	+		B	Goji berries <i>Lycium barbarum</i>	+		B
Imatinib	++		B	Green Tea		+	B
Infliximab		++	C	St John's Wort <i>Hypericum perforatum</i>		++	B
Influenza vaccine	++		B	Vitamin E	+		B
Leflunomide	++		B	Vitamin K		++	A
Methotrexate	++		B				
Paracetamol (within 1-2 weeks at 2-4 g / day)	+		A				

AF Atrial Fibrillation, APTT Activated Partial Thromboplastin Time, CHADS2 Score Risk Stroke With Af Estimate, CrCl Creatinine Clearance, DVT Deep Vein Thrombosis, FFP Fresh Frozen Plasma, INR International Normalised Ratio, LMWH Low, PE Pulmonary Embolism, TIA Transient Ischaemic Attack, UFH Unfractionated Heparin Molecular Weight Heparin, VTE Venous Thromboembolism

* Exercise caution in patients with impaired renal function (calculated CrCl less than 30mL / min) where LMWH can accumulate and contribute to bleeding. See Department of Health Guideline for anticoagulation and prophylaxis using low molecular weight heparin (LMWH) in adult inpatients.

Not for intramuscular injection; Konakion MM®, the intravenous preparation of vitamin K (phytonadione), may be given orally.

Φ Major bleed in previous four weeks, major surgery in previous two weeks, thrombocytopenia with platelets less than 50 x 10⁹ / L, known liver disease or concurrent antiplatelet therapy.