Queensland Government

Guidelines for Anticoagulation using Warfarin - Adult

1. Prescribing principles

- Consider if the benefits of anticoagulation outweigh the risks (e.g. bleeding) for each patient (see section 4).
- Ensure **pre-treatment INR**, platelets and liver function tests are normal. If not, seek senior / specialist advice.
- 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 to 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.

2. Starting warfarin therapy

- **Acute DVT** or **PE**: Start warfarin on same day as therapeutic UFH / LMWH* and overlap for a minimum of 5 days, until target INR reached for at least 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**.

NB: High loading doses, such as 10 mg, should **not** be used due to an **increase in the risk of bleeding**.

3. 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
2	Less than 1.8	5 mg
	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		

4. Risk factors for increased sensitivity to warfarin

- Age greater than 75 years
- History of bleeding or falls
- Baseline INR greater than 1.4
- Concomitant drugs affecting warfarin metabolism (see section 9)
- Co-morbidities i.e. hypertension, cerebrovascular disease, ischaemic stroke, heart disease, renal insufficiency, hepatic impairment or low platelets, malignancy
- Major surgery within the preceding 10 to 14 days

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

If no risk factors, follow the recommended nomogram and monitor INR daily.

5. Recommended target INR ranges and minimum duration

To remain in end-of-bed folder

Indication	Target INR Range	Minimum Duration
Valve repairs; Bioprosthetic valve	2–3	6 weeks post op
DVT / PE	2–3	3 months
AF; Irreversible, clinically hyper-coagulable states; Mechanical AVR with no risk factors[∞]	2–3	Life-long, balanced against risks
High risk mechanical heart valves; Mechanical MVR; Mechanical AVR with risk factors[∞]	2.5–3.5	Life-long, balanced against risks

[∞]Risk factors: AF, previous VTE, hypercoagulable state, left ventricular dysfunction or older generation AVR

6. Perioperative thromboembolism risk stratification

Thrombosis risk	Indication for Warfarin Therapy		
	Mechanical valve	Atrial fibrillation	Venous thromboembolism
Low Bridging unlikely to be required	Present - discuss with cardiologist	• AF and no history of cardiac embolism • CHA_2DS_2–VASc score of 0–4[Ω]	• 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 Consider bridging	Present - discuss with cardiologist	• Rheumatic AF (mitral valve disease stenosis / regurgitation) • AF with history of cardiac embolism or mechanical heart valve in any position • CHA_2DS_2–VASc score 5–9[Ω]	• 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

[Ω]There is uncertainty with CHA_2DS_2-VASc scores 4–6 and an individualised approach may be required

7. Managing warfarin therapy during invasive procedures

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	• Withhold 4 daily doses of warfarin before surgery • Night before surgery: If INR greater than 2, give 3 mg vitamin K[#] IV or oral • Day of surgery: » 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 depending on initial and target INR or, if Prothrombinex™-VF not available, give FFP 10–15 mL/kg » Employ pre-operative thromboprophylaxis as per hospital policy	• Start warfarin on the day of surgery at the **previous** '**normal**' maintenance dose as long as there is no evidence of bleeding • Employ thromboprophylaxis as per hospital policy
Moderate to High	**Option 1: Planned surgery** • Withhold 4 daily doses of warfarin before surgery • 2 to 3 days before surgery: When INR is less than 2 commence treatment dose of LMWH* subcutaneously or UFH IV: » If using LMWH*, last dose should be given at least 24 hours before surgery » If using UFH IV, cease infusion 4 to 6 hours before surgery **Option 2: Planned surgery with stable INR in preceding weeks** • Night before surgery: If INR is stable at 2–3 in the 2 to 4 weeks preceding surgery, give 3 mg vitamin K[#] IV or oral • Day of surgery: » 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 depending on initial and target INR or, if Prothrombinex™-VF not available, give FFP 10–15 mL/kg **Option 3: Urgent surgery** • For urgent surgery, check INR before surgery and give Prothrombinex™-VF 15–30 units/kg depending on initial and target INR • For procedures with low risk of bleeding, warfarin may not need to be ceased	• 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 to 24 hours postoperatively: » If using LMWH*, begin with prophylactic dose » If using UFH IV, avoid bolus and aim to prolong APTT as recommended by your site • Consider delaying resumption of therapeutic LMWH* for 48 to 72 hours after major surgery • 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

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8. 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	• Reduce or withhold next dose of warfarin based on sensitivity risk factors (see section 4) • 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	• Cease warfarin. Consider reasons for elevated INR and patient specific factors. Vitamin K is usually not required. If bleeding risk high$^{\Phi}$, give vitamin K$^{\#}$ 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	• Cease warfarin. Give vitamin K$^{\#}$ 3–5 mg orally (the higher dose may lead to difficult re-warfarinisation) or 0.5–1 mg IV. If bleeding risk is high$^{\Phi}$, consider Prothrombinex^{TM}–VF 15–30 units/kg • Check INR in 12 to 24 hours and continue to monitor every 1 to 2 days over the following week • Resume lower dose of warfarin once INR approaches therapeutic range
Bleeding SEEK SENIOR ADVICE	INR greater than or equal to 1.5 with life-threatening (critical organ) bleeding	• Cease warfarin. Give vitamin K$^{\#}$ 5–10 mg IV, Prothrombinex^{TM}-VF 50 units/kg and FFP 150–300 mL. If Prothrombinex^{TM}-VF is unavailable, increase FFP dose to 15 mL/kg • Assess INR frequently until clinically stable
	INR greater than or equal to 2 with clinically significant bleeding (not life-threatening)	• Cease warfarin. Give vitamin K$^{\#}$ 5–10 mg IV and Prothrombinex^{TM}-VF 35–50 units/kg. If Prothrombinex^{TM}-VF is unavailable, give FFP 15 mL/kg • Assess INR frequently until clinically stable
	Any INR with minor bleeding	• Omit warfarin. Repeat INR the following day and adjust warfarin dose to maintain INR in target therapeutic range. If bleeding risk is high$^{\Phi}$ or INR greater than 4.5, consider vitamin K$^{\#}$ 1–2 mg orally or 0.5–1 mg IV

9. Potential drug interactions *List is not comprehensive or exhaustive. Contact pharmacist for further information*

- 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
- Do not pre-empt a change. Make dose adjustments only after checking INR at 48 to 72 hours

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

Anticoagulants: e.g. apixaban, dabigatran, rivaroxaban, heparin, LMWH

Antiplatelet agents: e.g. aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine

Antithrombotic agents: e.g. alteplase, tenecteplase

Non-steroidal anti-inflammatory drugs (NSAIDs): e.g. ibuprofen, ketoprofen, naproxen

Complementary medicines / foods with antiplatelet effects: e.g. cranberry, fish oil, garlic, ginger, ginkgo, papaya extract

Severity of Interaction		Level of Evidence	
Major ++	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
Moderate +	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 ▲	Risk of Bleeding ▼	Level of Evidence
Allopurinol	+		B
Amiodarone	++		A
Antibiotics			
• cephalosporins, penicillins (except dicloxacillin), metronidazole	++		B / C
• dicloxacillin		++	A
• doxycycline	++		C
• isoniazid, vancomycin	+		B
• macrolides, quinolones	++		A / B
• sulfamethoxazole i.e. in co-trimoxazole	++		A
• rifabutin, rifampicin		+	B
Antifungals			
• azoles e.g. fluconazole, voriconazole	++		A / B
• griseofulvin		+	B
Antithyroid agents e.g. carbimazole, propylthiouracil		+	B
Aprepitant		++	B
Azathioprine / Mercaptopurine		++	B
Carbamazepine		+	B
Cholestyramine		+	B
COX-2 inhibitors e.g. celecoxib	++		B
Cyclosporin		+	B
Fibrates			
• fenofibrate	++		C
• gemfibrozil	+		B
H2-Antagonists e.g. cimetidine, ranitidine	+		B
Imatinib	++		B
Infliximab		++	C
Influenza vaccine	++		B
Leflunomide	++		B
Methotrexate	++		B
Nandrolone	++		C

Interacting Medication (Drug or Class)	Risk of Bleeding ▲	Risk of Bleeding ▼	Level of Evidence
Paracetamol (within 1 to 2 weeks at 2–4 g/day)	+		A
Phenytoin	+ initially	+ long-term	C
Proton pump inhibitors e.g. omeprazole	+		B
Quetiapine	+		B
Ropinirole	++		B
Salicylates (topical) e.g. methyl salicylate	++		B
Sodium valproate i.e. valproic acid	++		B
Statins			
• simvastatin	++		A
• fluvastatin, rosuvastatin	+		B
SSRIs e.g. citalopram, fluoxetine, sertraline	++		B
SNRIs e.g. desvenlafaxine, venlafaxine	++		B
Sulfasalazine	+		B
Tamoxifen	++		B
TCAs e.g. amitriptyline, doxepin	+		B
Testosterone	++		B
Thyroxine	+		B
Tramadol	+		B

Interacting Complimentary Medication	Risk of Bleeding ▲	Risk of Bleeding ▼	Level of Evidence
Black Tea, Green Tea		+	A / B
Co Enzyme Q10		+	B
Dan shen / Tan shen *Salvia miltiorrhiza*	++		B
Dong Quai *Angelica sinensis*	+		B
Ginseng		+	B
Glucosamine +/- Chondroitin	+		B
St John's Wort *Hypericum perforatum*		++	B
Vitamin A, Vitamin E	+		B
Vitamin K		++	A

AF Atrial Fibrillation, **APTT** Activated Partial Thromboplastin Time, **AVR** Aortic Valve Replacement, **CHA_2DS_2-VASC score** Estimate for stroke risk with AF, **CrCl** Creatinine Clearance, **DVT** Deep Vein Thrombosis, **FFP** Fresh Frozen Plasma, **INR** International Normalised Ratio, **LMWH** Low Molecular Weight Heparin, **MVR** Mitral Valve Replacement, **PE** Pulmonary Embolism, **TIA** Transient Ischaemic Attack, **UFH** Unfractionated Heparin, **VTE** Venous Thromboembolism

* Exercise caution in patients with impaired renal function (calculated CrCl less than 30 mL/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 (phytomenadione), may be given orally.

$^{\Phi}$ Major bleed in previous four weeks, major surgery in previous two weeks, thrombocytopenia with platelets less than 50 x 10^9/L, known liver disease or concurrent antiplatelet therapy.