Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis

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ABSTRACT

- For most warfarin indications, the target maintenance international normalised ratio (INR) is 2–3.
- Risk factors for bleeding complications with warfarin use include age, history of past bleeding and specific comorbid conditions.
- To reverse the effects of warfarin, vitamin K_1 can be given. Immediate reversal is achieved with a prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP). Vitamin K_1 is essential for sustaining the reversal achieved by PCC and FFP.
- When oral vitamin K_1 is used for warfarin reversal, the injectable formulation of vitamin K_1 is preferable to tablets because of its flexible dosing; this formulation can be given orally or injected.
- To temporarily reverse the effect of warfarin when there is a need to continue warfarin therapy, vitamin K_1 should be given in a dose that will quickly lower the INR to a safe, but not subtherapeutic, range and will not cause resistance once warfarin is reinstated.
- Prothrombinex-HT is the only PCC approved in Australia and New Zealand for warfarin reversal. It contains factors II, IX and X, and low levels of factor VII. FFP should be added to Prothrombinex-HT as a source of factor VII when used for warfarin reversal.
- Simple dental or dermatological procedures may not require interruption to warfarin therapy.
- If necessary, warfarin therapy can be withheld 5 days before elective surgery, when the INR usually falls to below 1.5 and surgery can be conducted safely.
- Bridging anticoagulation therapy for patients at high risk for thromboembolism should be undertaken in consultation with the relevant experts.

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Anticoagulation is very effective for primary and secondary prevention of thromboembolic events. However, questions persist about the risks and management of over-anticoagulation.

Major bleeding, which includes intracranial haemorrhage and bleeding leading to death or hospitalisation, has been reported in 1.2%–8.1% of patients during each year of long-term warfarin therapy.[1,2] Despite these bleeding risks, warfarin use in Australia has increased between 6% and 9% per annum in the last 4 years, with current growth at about 9% per year.[3] It is commonly used in the community setting for indications such as uncomplicated deep vein thrombosis and stroke prophylaxis in atrial fibrillation. By understanding the pharmacokinetics and pharmacodynamics of warfarin, and therefore the potential modifiers of warfarin's effects, these bleeding risks can be minimised through preventive strategies with or without warfarin reversal.

These consensus guidelines offer advice on these preventive strategies and the principles of warfarin reversal, as well as bridging therapy in the face of different clinical settings. The recommendations draw on available evidence and the clinical experience of the panel of author practitioners.

Warfarin pharmacokinetics and pharmacodynamics

Warfarin and other coumarin anticoagulants act by inhibiting the synthesis of functional vitamin K-dependent coagulation factors II, VII, IX and X.[4] Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischaemic tissue damage. However, once thrombosis has occurred, anticoagulation therapy aims to prevent further clot progression and prevents secondary thromboembolic complications.[4]

The effective half-life of warfarin ranges from 20 to 60 hours, with a mean of about 40 hours. The duration of effect is 2–5 days.[5] The drug is completely absorbed after oral administration, and peak concentrations occur within 4 hours. The elimination of warfarin is almost entirely by metabolism, with very little excreted unchanged in the urine and bile. Metabolism occurs mainly in the liver, involving the cytochrome P450, and in particular the CYP2C9, isoenzyme.[4]

Understanding the difference between the antithrombotic and anticoagulant effects of warfarin is useful in clinical practice. Initial increases in international normalised ratio (INR) are typically noted 24–36 hours after giving the first dose of warfarin. This early effect is related to the clearance of coagulation factor VII, which has a short half-life *in vivo* of 6 hours. However, the initial elevation of the INR is not thought to be associated with a clinically important antithrombotic effect, as warfarin is thought to exert its antithrombotic effect mostly through reductions in factor II (prothrombin) and factor X levels. If the ability of warfarin to curb existing clot growth and prevent further clot formation depends largely on the clearance of prothrombin with its half-life of 60–72 hours, then it should take a minimum of two prothrombin half-

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lives, or up to 5 days, to fully express the antithrombotic effect in patients.[6] Because the effect of warfarin on the INR is dependent on the clearance of preformed coagulation factors, the maximum effect of a dose occurs up to 48 hours after administration, and the effect lasts for the next five days.[2]

These observations form the basis of the current recommendations that, unless there is reason to believe that the patient will be unusually sensitive, warfarin therapy is best initiated with a daily dose of 5 mg (about the usual maintenance dose) rather than by using a loading regimen. Much higher loading doses may expose patients to an increased risk of bleeding, and increase the required frequency of monitoring.[6,7] Starting doses above 10 mg per day should be avoided.

Modifiers of warfarin response

Drug interactions can critically interfere with warfarin control. Common examples of drugs that can influence the absorption or metabolic clearance of warfarin include antibiotics, amiodarone, statins and anticonvulsants. Some herbal medications, such as St John's wort, are recognised as important modifiers of the anticoagulant effects of warfarin, and patients should be carefully questioned about the use of these medications.[8] Elderly patients can also exhibit an exaggerated response to warfarin, in part because they tend to store less vitamin K than younger people.[9]

The INR should be tested more frequently after starting, stopping or changing the dose of concomitant medication. It takes several days for enzyme induction or other drug effects to take place, so that an INR measured about one week after a change in medication should reflect clinically significant interactions.

Alcohol in small to moderate amounts probably has little effect on warfarin metabolism. In heavy drinkers, however, factors such as increased falls, alcohol-induced gastritis, poor diet and poor compliance increase the risk of bleeding.[10]

The amount of vitamin K in the diet partly determines the sensitivity to warfarin. This is important to consider in situations when diet changes, such as during illness, travel, fad diets, hospitalisation and postoperatively. Dark green vegetables such as spinach and broccoli are typically high in vitamin K. However, it takes a very large daily intake of "greens" to influence the INR. Rather than restricting vegetable intake, it is better to recommend a balanced and consistent diet.[10]

Bleeding complications of warfarin therapy

The most common complication of warfarin therapy is bleeding. A major determinant is the INR. In one study, the bleeding rate was doubled as the INR increased from 2.0–2.9 to 3.0–4.4, and quadrupled when the INR increased to 4.5–6.0.[11] In another study, each increase in INR by 0.5 multiplied the absolute risk of major bleeding (mostly intracranial) by 1.43.[12] Although the bleeding risk increases as the INR increases, 50% of bleeding episodes occur while the INR is less than 4.0.[10]

Observational studies suggest that the risk of bleeding is also related to age, history of past bleeding and specific comorbid conditions. Generally, elderly people have increased sensitivity to the anticoagulant effect of warfarin and require a lower mean daily dose than younger patients. One study showed a 46% increase in major bleeding for every 10-year increase above the age of 40.[15] This increase is not necessarily linked to age itself, but may be related to comorbidity associated with age. Box 1 lists the patient-related risk factors.[16,17]

1 Risk factors for bleeding complications of anticoagulation therapy

Risk factor category	Specific risk factors
Age[16,17]	> 65 years
Cardiac[16,17]	Uncontrolled hypertension
Gastrointestinal[16,17]	History of gastrointestinal haemorrhage, active peptic ulcer, hepatic insufficiency
Haematologic/oncologic[16,17]	Thrombocytopenia (platelet count, < 50 10^9/L), platelet dysfunction, coagulation defect, underlying malignancy
Neurologic[16,17]	History of stroke, cognitive or psychological impairment
Renal[16,17]	Renal insufficiency
Trauma[16,17]	Recent trauma, history of falls (> 3 per within previous treatment year, or recurrent, injurious falls)
Alcohol[16,17]	Excessive alcohol intake
Medications*[16,17]	Aspirin, COX-I-specific non-steroidal anti-inflammatory drugs (COX-II inhibitors do not impair platelet function, but can influence warfarin effect), "natural remedies" that interfere with haemostasis.

* Careful monitoring of warfarin effect is critical to minimise risk in patients taking multiple medications.

A patient's risk of bleeding is greatest in the first three months after starting therapy. Bleeding during the early months of therapy, particularly from the gastrointestinal or renal tracts, often indicates an underlying lesion and should be thoroughly investigated.[14]

Many bleeding episodes are not clinically significant (although many patients are unlikely to view their bleeds in these terms). Such episodes include nosebleeds, bruising and excessive bleeding after minor injury, such as shaving. Patients should be made aware of these problems, and simultaneously reassured that, although common, they are not serious.[13]

Risk factors can be additive. Patients with two or three risk factors have a much higher incidence of warfarin-associated bleeding than those with none or one.[9]

General principles for preventing high INR

Warfarin is a highly effective medication. Bleeding because of an excessive INR is minimised by therapeutic monitoring and when other precautionary measures are adopted.

Starting warfarin therapy

- Avoid high loading doses of warfarin, as they are not warranted and may result in bleeding episodes. An example would be the use of a 10 mg starting dose in a frail elderly individual. In general it is preferable to start treatment using an initial daily dose of 5 mg, or one that is closer to the usual maintenance dose of about 4–6 mg per day, as there is normally no immediate time constraint for achieving a target level of INR.[7,9,18-21]

2 Key patient education components[17]

Explain the

- Reason for treatment
- Mechanism of action of warfarin
- Time of day to take warfarin (same time of day)
- The INR, target range and need for regular testing
- Signs and symptoms of bleeding
- Effect of illness, injury or any changes in physical status
- Potential effect of invasive procedure, surgery or dental work
- The effects of common over-the-counter (OTC) medication interactions
- The need for consistent intake of vitamin K-rich foods
- Effects of alcohol intake
- Appropriate action if diarrhoea or vomiting occurs

Some patients may consider the use of a Medic Alert bracelet/necklace and warfarin identification card.

- Potential warfarin–drug interactions need to be considered.
- Aim for an INR level that balances the therapeutic goal with the risk factors of bleeding on an individual basis. This will minimise haemorrhagic complications and maximise antithrombotic effect. The desirable target INR for most clinical indications is 2.5 (range, 2–3). The optimal INR for people with mechanical heart valves is still being debated, with the 2001 American College of Chest Physicians guidelines suggesting a reduced target of 2.5 for most recent-model prosthetic valves,[22] while a recent meta-analysis suggests the target should remain above 3.0.[23]
- A reduced target INR range (1.5–2.0) has not been proven to reduce bleeding risk, and is likely to lead to some reduction in effectiveness of therapy.[24-26]
- Avoid frequent dose adjustments. A change in warfarin dose will take several days to influence the INR, so testing the INR within 24 or 48 hours of a dose change may not truly reflect the steady-state response to the dose adjustment.
- Avoid excessive increases in dose when the INR drifts below the target INR range.
- Effective patient education can minimise compliance problems. Box 2 lists the key components of patient education.

Warfarin reversal

There is a close relationship between the INR and risk of bleeding. The risk of bleeding increases noticeably once the INR exceeds 4, and the risk rises sharply with values greater than 5. The management options for warfarin reversal are outlined in Box 3 and depend on the INR level and whether or not bleeding is present.[27,28]

In addition to stopping warfarin when the effect is excessive, vitamin K_1 can be given, and coagulation factors replaced by infusing a prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP). The choice of approach is based largely on clinical judgement, because no randomised trials have compared these strategies in terms of clinical outcomes.[9]

Vitamin K_1

Vitamin K_1 is available as oral tablets or as ampoules for intravenous (IV) or oral administration. The ampoules are not recommended for intramuscular or subcutaneous use.[29] Intramuscular vitamin K_1 for reversal of warfarin is not recommended, as it exhibits depot characteristics that may interfere with recommencement of anticoagulation therapy. Furthermore, intramuscular

3 Guidelines for the management of an elevated international normalised ratio (INR) in adult patients with or without bleeding

Clinical setting	Action
INR higher than the therapeutic range but < 5.0; bleeding absent	• Lower the dose or omit the next dose of warfarin. Resume therapy at a lower dose when the INR approaches therapeutic range. • If the INR is only minimally above therapeutic range (up to 10%), dose reduction may not be necessary.
INR 5.0–9.0;* bleeding absent	• Cease warfarin therapy; consider reasons for elevated INR and patient-specific factors. • If bleeding risk is high, give vitamin K_1 (1.0–2.0 mg orally or 0.5–1.0 mg intravenously). • Measure INR within 24 hours,† resume warfarin at a reduced dose once INR is in therapeutic range.
INR > 9.0; bleeding absent	• Where there is a low risk of bleeding, cease warfarin therapy, give 2.5–5.0 mg vitamin K_1 orally or 1.0 mg intravenously. Measure INR in 6–12 hours, resume warfarin therapy at a reduced dose once INR < 5.0. • Where there is high risk of bleeding,‡ cease warfarin therapy, give 1.0 mg vitamin K_1 intravenously. Consider Prothrombinex-HT (25–50 IU/kg) and fresh frozen plasma (150–300 mL), measure INR in 6–12 hours, resume warfarin therapy at a reduced dose once INR < 5.0.
Any clinically significant bleeding where warfarin-induced coagulopathy is considered a contributing factor	• Cease warfarin therapy, give 5.0–10.0 mg vitamin K_1 intravenously, as well as Prothrombinex-HT (25–50 IU/kg) and fresh frozen plasma (150–300 mL), assess patient continuously until INR < 5.0, and bleeding stops.§ OR • If fresh frozen plasma is unavailable, cease warfarin therapy, give 5.0–10.0 mg vitamin K_1 intravenously, and Prothrombinex-HT (25–50 IU/kg), assess patient continuously until INR < 5.0, and bleeding stops.§ OR • If Prothrombinex-HT is unavailable, cease warfarin therapy, give 5.0–10.0 mg vitamin K_1 intravenously, and 10–15 mL/kg of fresh frozen plasma, assess patient continuously until INR < 5.0, and bleeding stops.§

* Bleeding risk increases exponentially from INR 5 to 9;[13] INR ≥ 6 should be monitored closely. † Vitamin K effect on INR can be expected within 6–12 hours. ‡ Examples of patients in whom the bleeding risk would be expected to be high include those with active gastrointestinal disorders (such as peptic ulcer or inflammatory bowel disease), those receiving concomitant antiplatelet therapy, those who underwent a major surgical procedure within the preceding two weeks, and those with a low platelet count. See Box 1 for a list of bleeding risk factors. § In all situations carefully reassess the need for ongoing warfarin therapy.

4 Recommended dose range for vitamin K_1 preparations available in Australia and New Zealand for reversing anticoagulation*

Dosage route	Oral†	Intravenous†
Usual dose for anticoagulation reversal	1.0–2.0 mg	0.5–10.0 mg

*These recommendations may not be consistent with the approved product indications[29] of Konakion in Australia and New Zealand. †Konakion injectable paediatric or adult formulation; Roche Products Pty Ltd.

injection in patients on anticoagulation therapy (particularly when over-anticoagulated) poses a significant risk of causing a haematoma to form.[29] Studies have also shown that the response to intramuscular or subcutaneous vitamin K_1 is unpredictable and sometimes delayed.[30-33]

- Ideally, unless the patient is actively bleeding, vitamin K_1 should be administered in a dose that will quickly lower the INR into a safe, but not subtherapeutic, range without causing resistance once warfarin is reinstated.[9]

Oral vitamin K_1 is the treatment of choice unless very rapid reversal of anticoagulation is required.[9] For most patients, 1.0–2.0 mg of oral vitamin K_1 is sufficient. If the INR is particularly high, 5 mg orally may be required.[2] The formulation of injectable vitamin K_1 (Konakion MM, Roche Products Pty Ltd), while not approved for oral use by government regulatory agencies in Australia and New Zealand, is preferred for the reversal of anticoagulation because of its dosing flexibility.

Although IV injection produces a more rapid response, it may be associated with anaphylactic reactions. There is no evidence that this rare, but serious, complication can be avoided by using low doses.[9] In Australia and New Zealand, vitamin K_1 is a mixed micelle-based formulation, and may not carry the same risk of allergies, including anaphylaxis, as earlier formulations.

The optimal IV dose of vitamin K_1 for partial reversal of over-anticoagulation with warfarin is 0.5–1.0 mg. If correction of the INR (rather than just return to the usual therapeutic range) is desired, larger doses of vitamin K_1 are needed (see Box 3). The INR can usually be normalised within 24 hours with an IV dose of 5–10 mg of vitamin K_1.[34]

Large doses of vitamin K_1 may produce some resistance to re-anticoagulation with warfarin, and this can be avoided by giving smaller doses. Larger doses are appropriate if a clinical decision has been made to discontinue further warfarin treatment.[27]

Box 4 presents the recommended dose ranges of vitamin K_1 preparations available in Australasia for anticoagulation reversal.

Prothrombin complex concentrate and fresh frozen plasma

The full effect of vitamin K_1 in reducing the INR takes up to 24 hours to develop, even when given in larger doses with the intention of complete reversal. For immediate reversal of clinically significant bleeding, the combination of prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP) covers the period before vitamin K_1 has reached its full effect.

- Vitamin K_1 is essential for sustaining the reversal achieved by a PCC and FFP.[27]

Prothrombinex-HT is the only PCC approved in Australia and New Zealand for warfarin reversal. It is a three-factor concentrate, containing factors II, IX and X, but only low levels of factor VII. Therefore, the adjunctive use of FFP should be considered as a source of factor VII.[27]

Box 5 provides a summary of the characteristics of Prothrombinex-HT and FFP.[35,36]

The overall management of over-anticoagulation depends on:

- the risk of bleeding,
- the clinical significance of the bleed, and
- the level of INR.

5 Summary of characteristics of Prothrombinex-HT* and fresh frozen plasma (FFP)

	Prothrombinex-HT†	Fresh frozen plasma†
Description	Prepared from plasma collected from voluntary donors. Sterile freeze-dried powder containing coagulation factors II, IX and X and low levels of factor VII.	Separated and frozen within 18 hours of collection from volunteer donors. Contains all coagulation factors.
Contra-indications	Patients showing signs of thrombosis or disseminated intravascular coagulation.	Do not use when coagulopathy can be corrected more effectively with specific therapy, such as vitamin K, cryoprecipitate or other specific factor concentrates.
Specifications	Available in vials containing 500 IU of factor IX, II and X to be reconstituted in 20 mL of water for injections. Each vial also contains 25 IU of antithrombin and 200 IU of heparin.	Available in 150–300 mL sizes. May be stored in blood refrigerator at 2–6°C for up to 5 days once thawed, and relabelled "thawed plasma". Thawed plasma has levels of factors II, VII, IX and X adequate for warfarin reversal.
Availability	From relevant blood service or hospital blood bank. No need to consider ABO group.	Available in all ABO groups and should be ABO-group compatible with patient's red cells (or use AB plasma).
Considerations for use	Known allergies to prothrombin complex concentrates. Predisposition to venous thrombosis, disseminated intravascular coagulation and myocardial infarction.‡	Most common adverse events — allergic reactions and volume overload. Potential for transmission of infections, transfusion-related acute lung injury and other transfusion reactions.

CSL Limited. †For more comprehensive information on these products, refer to Prothrombinex-HT Australian[35] and New Zealand[37] approved product information, the Australian Red Cross Blood Service *Circular of information 2003*,[36] the Australian Red Cross Blood Service *Transfusion medicine manual 2003*[27] and the New Zealand Blood Service *Transfusion medicine handbook 2003*.[38] ‡From its date of issue in 1992 to date there have been no instances reported to CSL Bioplasma of thrombotic episodes with Prothrombinex-HT.

6 Managing oral anticoagulation during invasive procedures according to risk of thromboembolism

Time	Patients at relatively low risk	Patients at relatively high risk
Before surgery	• Withhold warfarin therapy 4–5 days before surgery. • *Night before surgery:* If INR > 2, give 1–5 mg vitamin K_1 intravenously. • *Day of surgery:* If INR ⩽ 1.5 surgery can proceed. If INR > 1.5, defer surgery, or if surgery is urgent, give Prothrombinex-HT (25–50 IU/kg) plus 150–300 mL fresh frozen plasma or 10–15 mL/kg of fresh frozen plasma if Prothrombinex-HT is not used.	• Withhold warfarin therapy 4–5 days before surgery. • *2–3 days before surgery:* Start giving daily or twice-daily treatment doses of unfractionated heparin intravenously or low-molecular-weight heparin (LMWH)* subcutaneously. • If using LMWH, the last dose (maximum dose of enoxaparin 1mg/kg or dalteparin 100 U/kg) should be at least 24 hours before surgery. If using unfractionated heparin, it should be discontinued 4–6 hours before surgery.
After surgery	• Start warfarin therapy on the day of surgery, at the previous maintenance dose. • Employ thromboprophylaxis as per usual practice.	• Recommence warfarin therapy as soon as possible. • Start heparin or LMWH 12–24 hours postoperatively. • If using LMWH, give a thromboprophylactic dose. • If using unfractionated heparin, aim to prolong the APTT by 1.5 times. • Fully anticoagulate the patient with warfarin 72 hours postoperatively as long as there is no evidence of bleeding. • Cease heparin or LMWH therapy 48 hours after the target INR is reached.

INR = international normalised ratio. APTT = activated partial thromboplastin time.
* Exercise caution in patients with impaired renal function (calculated creatinine clearance rate, < 30 mL/hour). LMWH can accumulate and contribute to bleeding.

Box 3 summarises the consensus reached on the management of an elevated INR in different clinical settings. Note, however, that expert advice on management should be sought whenever there is bleeding in patients taking warfarin who have a high risk of a disabling thromboembolic event in the absence of anticoagulation therapy (as with prosthetic heart valves or a recent pulmonary embolism or extensive venous thrombosis).

Pre- and postoperative management of anticoagulation

Opinion varies about how to manage anticoagulation in patients who have been taking warfarin long-term and who need to undergo surgery, as the evidence is mainly anecdotal.

• For most patients, warfarin can be withheld 5 days before elective surgery; the INR usually falls to below 1.5 in this time, and surgery can be conducted safely.

There are some procedures, however, which entail a low risk of bleeding, and so do not require interruption to warfarin therapy if the INR is within the therapeutic range. Examples include simple dental procedures, periodontal therapy, and minor dermatological procedures where pressure can be applied if required.

If withholding warfarin preoperatively is necessary, a number of issues need to be considered. These include:

Background and evidence basis of recommendations

These consensus guidelines for warfarin reversal were produced by the Warfarin Reversal Consensus Group on behalf of the Australasian Society of Thrombosis and Haemostasis. The writing committee consisted of Hatem Salem (Chair), Ross Baker, Paul Coughlin, Alex Gallus and Paul Harper. The guidelines were developed after extensive consultation, including several workshops and teleconferences. The guidelines draw on review of all available evidence from published studies and from clinical experience. The aim of the Warfarin Reversal Consensus Group is to provide an Australian and New Zealand perspective on the safe and effective management of bleeding risks resulting from warfarin therapy.

• Prolonged immobility during surgery and afterward increases the risk of venous thromboembolism.

• The potential risk of thrombosis should be assessed. The need for bridging therapy is very much dependent on the risk of the thrombosis recurring during the period that patients are not receiving anticoagulation therapy.

Unfractionated heparin offers some advantages as an anticoagulant in the 24 hours preceding surgery because of its faster onset and offset of action. There is significant disagreement about who should and should not receive such bridging therapy, principally because there is a lack of randomised controlled trial data.

In some situations, clinical experience suggests that bridging anticoagulation is not required. Patients who take anticoagulants because of atrial fibrillation, or in whom the index event requiring anticoagulation occurred more than 3 months ago, can be safely managed without bridging anticoagulation. These patients are at relatively low risk of thromboembolism. Box 6 lists an appropriate approach for these patients.

Patients with prosthetic valves and those who have suffered an acute thrombosis within the preceding 3 months should receive bridging anticoagulation in the perioperative and postoperative period. This should be done in consultation with the relevant experts in this area. Box 6 lists the recommended plan of management for these patients who are at relatively high risk of thromboembolism.

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