Guidelines

An update of consensus guidelines for warfarin reversal

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doi: 10.5694/mja12.10614

An abridged version of this article appeared in the printed journal

Summary

- Despite the associated bleeding risk, warfarin is the most commonly prescribed anticoagulant in Australia and New Zealand. Warfarin use will likely continue for anticoagulation indications for which novel agents have not been evaluated and among patients who are already stabilised on it or have severe renal impairment.
- Strategies to manage over-warfarinisation and warfarin during invasive procedures can reduce the risk of haemorrhage.
- For most warfarin indications, the target international normalised ratio (INR) is 2.0–3.0 (venous thromboembolism and single mechanical heart valve excluding mitral). For mechanical mitral valve or combined mitral and aortic valves, the target INR is 2.5–3.5.
- Risk factors for bleeding with warfarin use include increasing age, history of bleeding and specific comorbidities.
- For patients with elevated INR (4.5–10.0), no bleeding and no high risk of bleeding, withholding warfarin with careful subsequent monitoring seems safe.
- Vitamin K_1 can be given to reverse the anticoagulant effect of warfarin. When oral vitamin K_1 is used for this purpose, the injectable formulation, which can be given orally or intravenously, is preferred.
- For immediate reversal, prothrombin complex concentrates (PCC) are preferred over fresh frozen plasma (FFP). Prothrombinex-VF is the only PCC routinely used for warfarin reversal in Australia and New Zealand. It contains factors II, IX, X and low levels of factor VII. FFP is not routinely needed in combination with Prothrombinex-VF. FFP can be used when Prothrombinex-VF is unavailable. Vitamin K_1 is essential for sustaining the reversal achieved by PCC or FFP.
- Surgery can be conducted with minimal increased risk of bleeding if INR $\leq$ 1.5. For minor procedures where bleeding risk is low, warfarin may not need to be interrupted. If necessary, warfarin can be withheld for 5 days before surgery, or intravenous vitamin K_1 can be given the night before surgery. Prothrombinex-VF use for warfarin reversal should be restricted to emergency settings. Perioperative management of anticoagulant therapy requires an evaluation of the risk of thrombosis if warfarin is temporarily stopped, relative to the risk of bleeding if it is continued or modified.

Warfarin is effectively used in a wide range of thromboembolic disorders for primary and secondary prevention. Patients on long-term therapy have a risk of 1%–3% per year for haemorrhage leading to hospitalisation or death.[1,2] Therefore, strategies to manage over-warfarinisation and warfarin during invasive procedures are important.[3,4] Despite the associated bleeding risk, warfarin remains the most commonly prescribed anticoagulant in Australia and New Zealand. Common indications for the use of warfarin in the community include stroke prevention in atrial fibrillation (AF), preventing thrombus formation in patients with mechanical heart valves (MHV), and treatment of venous thromboembolism (VTE). For most warfarin indications, the target international normalised ratio (INR) is 2.0–3.0 (VTE and single MHV excluding mitral). For mechanical mitral valve or combined mitral and aortic valves, the target INR is 2.5–3.0.[5] New anticoagulants such as oral direct factor Xa inhibitors and direct thrombin inhibitors are becoming available as alternatives to warfarin.[6-8] However, it is likely that warfarin will continue to be widely used in the community among patients who are already stable on warfarin or have severe renal impairment (creatinine clearance, <30 mL/min), and for anticoagulation indications for which these novel agents have not been evaluated, such as MHV.[9,10]

This update of the previous consensus guidelines[11] is again on behalf of the Australasian Society of Thrombosis and Haemostasis (ASTH) and offers advice on strategies to prevent over-anticoagulation, the principles of warfarin reversal, and bridging anticoagulation therapy in different clinical settings. In particular, the focus is on managing:

- warfarin therapy complicated by bleeding;
- a supratherapeutic INR with no bleeding; and
- warfarin therapy during invasive procedures.

The recommendations draw on available evidence and the clinical experience of the panel of author–practitioners.

Guideline development

As Australian and New Zealand-based experts in the field of thromboembolic disorders, we were invited to join the panel leading guideline development. The process included reviewing up-to-date evidence and existing high-quality evidence-based international guidelines for warfarin reversal. We conducted a face-to-face meeting on 21 March 2011 at which specific questions and drafting of the guidelines were discussed. Further revisions were made by consensus via email. All six members of the panel are the authors of this article.

We based our recommendations on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the local setting.

Relevant clinical questions guided systematic review of the evidence. We followed the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method to generate recommendations. The strength of recommendations, designated strong (1) or weak (2), is based on the quality of the body of evidence, which can be high (A), moderate (B) or low (C).[12] For recommendations where the quality of evidence was not sufficient to allocate a grade, the term "good practice point" (GPP) indicates the recommendation is based on the consensus opinion of the ASTH writing panel (Box 1). Consensus recommendations were reached in an equitable manner. Agreement of all members of the expert panel was required in order to proceed with making the recommendation.

Potential conflicts of interest were declared and recorded. Funding for this update was provided by a restricted educational grant from CSL Bioplasma that was administered by the ASTH.

1 Grades of guideline recommendations

Grade of recommendation	Quality of supporting evidence
Strong recommendation, high-quality evidence **(1A)**	Evidence obtained from a systematic review of all relevant randomised controlled trials (RCTs) or exceptionally strong evidence from observational studies
Strong recommendation, moderate-quality evidence **(1B)**	Evidence from at least one RCT or very strong evidence from observational studies
Strong recommendation, low-quality evidence **(1C)**	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence
Weak recommendation, high-quality evidence **(2A)**	Evidence obtained from a systematic review of all relevant RCTs or exceptionally strong evidence from observational studies
Weak recommendation, moderate-quality evidence **(2B)**	Evidence from at least one RCT or very strong evidence from observational studies
Weak recommendation, low or very low-quality evidence **(2C)**	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence
Good practice point **(GPP)**	Supporting evidence is insufficient to meet even the lowest grade of evidence. Recommendation is therefore based on consensus opinion of the writing panel of Australasian Society of Thrombosis and Haemostasis ◆

Bleeding complications of warfarin therapy

Bleeding is the most common complication of warfarin therapy and is related to the INR value. Although incremental rises in INR increase the risk of bleeding, most intracranial bleeds are in patients with an INR in the therapeutic range; they occur in 0.5%–1.0% of patients with AF per year.[13,14] Bleeding risk is also related to patient factors including age, a prior bleeding history and specific comorbidities. Elderly patients are generally more sensitive to warfarin and need a lower mean daily dose.[15,16] Bleeding risk is greatest in the first 3 months after starting warfarin. An occurrence suggests an underlying organ-specific lesion and should be appropriately investigated.[1,17]

Changes in concomitant medication potentially alter a patient's response to warfarin anticoagulation and increase their risk of bleeding. Drugs that commonly alter warfarin metabolism include antibiotics, amiodarone, statins, anticonvulsants and some herbal medications, such as St John's wort. Alcohol in small to moderate amounts probably has little effect on warfarin metabolism. Among heavy drinkers, however, associated factors such as increased falls, alcohol-induced gastritis, poor diet and poor compliance all increase the risk of bleeding. Bleeding prediction scores, such as HAS-BLED (hypertension, abnormal liver or renal function, stroke, bleeding history or predisposition, labile INR, elderly [>65 years], alcohol or drugs concomitantly) for AF, may help to identify factors that can be modified to reduce the risk of warfarin-related bleeding but should not result in withholding of anticoagulation therapy.[18]

General principles for preventing high INR include careful therapeutic monitoring and adopting other precautionary measures that can minimise bleeding risk due to high INR (Box 2).[19-22]

2 Principles for preventing high international normalised ratio (INR)*

- When starting warfarin therapy, avoid high loading doses of warfarin. In general, it is preferable to start treatment using an initial daily dose of 5 mg, or even lower in elderly patients.[19-21] However, some guidelines have suggested that patients who are considered sufficiently healthy may receive warfarin 10 mg daily for the first 2 days with subsequent doses to be determined by the INR **(2C)**[12]
- Consider potential warfarin–drug interactions. Avoid concomitant non-steroidal anti-inflammatory drugs and certain antibiotics **(2C)**. Avoid concomitant antiplatelet therapy except where clinical benefit is known, such as mechanical heart valves, acute coronary syndrome, or recent insertion of coronary stents **(2C)**
- Test the INR more frequently after starting, stopping or changing the dose of concomitant medication
- 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
- Pharmacogenetic testing to guide warfarin dosing is not necessary **(1B[22])**

* Level of evidence in parentheses in **bold**. Details, Box 1. Recommendations with no evidence level are standard practice and not based on gradable evidence. ◆

Warfarin reversal

Vitamin K_1 for reversal of warfarin-associated coagulopathy

Vitamin K_1 is an effective antidote to the anticoagulant effect of warfarin. Despite this, data are lacking to show that its use improves outcome in life-threatening bleeds. Currently, phytomenadione is the only injectable formulation available in Australia and New Zealand. While intravenous or oral routes of administration can be used and are effective in reversing an INR that is raised because of warfarin therapy, the intravenous route achieves a more rapid response compared with oral administration, with an onset of action seen within 6–8 hours. However, both routes achieve a similar correction of INR by 24 hours.[23]

Vitamin K_1 should not be administered by subcutaneous or intramuscular routes. Subcutaneous administration is no more effective than placebo, while intramuscular injection in an over-anticoagulated patient may lead to hae-

3 Characteristics of Prothrombinex-VF* and fresh frozen plasma

	Prothrombinex-VF†	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
Contraindications	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_1, cryoprecipitate or other specific factor concentrates
Specifications	Available in vials containing 500 IU of factor II, IX and X to be reconstituted in 20 mL of water for injections. Each vial also contains 25 IU of antithrombin and 192 IU of heparin	Available in Australia in units of 250–334 mL and in New Zealand as 180–300 mL (typically 240–275 mL). May be stored in monitored blood refrigerator at 2–6°C for up to 5 days once thawed, and relabelled "thawed plasma" in accordance with Australian and New Zealand Society of Blood Transfusion Guidelines. Thawed plasma has levels of factors II, VII, IX and X adequate for warfarin reversal
Availability	From relevant blood service or hospital blood bank	From relevant blood service or hospital blood bank
Considerations for use	No need to consider ABO blood group	Available in all ABO blood groups and should be ABO-group compatible with patient's red cells (or use AB plasma)
	Known allergies to prothrombin complex concentrates	Most common adverse events — allergic reactions and volume overload. Potential for transfusion-related acute lung injury and other transfusion reactions, including transmission of infections
	Predisposition to venous thrombosis, disseminated intravascular coagulation and myocardial infarction‡	
	Heparin-induced thrombocytopenia	

* CSL Bioplasma. † For more comprehensive information on these products, refer to approved product information[27] and blood service data.[28,29] ‡ Thrombotic complications of prothrombin complex concentrates appear to be rare. Since 1993 thrombotic episodes with Prothrombinex-VF or its predecessor, Prothrombinex-HT, have been rarely reported to CSL Bioplasma.[27,28] ◆

matoma and bleeding, and its effect on reversal is unpredictable owing to variable absorption — it can be associated with a prolonged increase of vitamin K_1 plasma levels, which may hinder re-anticoagulation.[24,25] The major concern about intravenous vitamin K_1 has been anaphylaxis. Although the absolute incidence is unknown, it is most likely rare. There is no convincing association between anaphylaxis and dose, concentration or rate of administration of vitamin K_1 but the literature suggests that current formulations with mixed micelles of lecithin and glycol are safer than the previous preparations containing polyethylated castor oil.[26]

Prothrombin complex concentrate and fresh frozen plasma

Replacement is necessary to correct the low levels of factors II, VII, IX and X induced by warfarin. This can be achieved by using a prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) (Box 3).

PCC are formulated with three factors (II, IX and X) or four factors (II, VII, IX and X). Advantages of PCC over FFP include rapid reconstitution into a small volume for infusion over 20–30 minutes, fast onset of action, no requirement to check a patient's blood group, minimal risk of viral transmission due to pathogen reduction and inactivation steps during manufacturing,[27] and reduced risk of other clinical adverse reactions such as transfusion-associated circulatory overload or transfusion-associated acute lung injury. The latter is due to circulating antihuman leukocyte antigen or antigranulocyte antibodies in plasma.[28,29] However, PCC does contain small amounts of heparin and its use to reverse warfarin anticoagulation should be carefully considered in patients with heparin-induced thrombocytopenia.[27]

Prothrombinex-VF, a three-factor PCC, is the only product currently in routine use in Australia and New Zealand for warfarin reversal. Due to its low levels of factor VII, the Warfarin Reversal Consensus Guidelines published in 2004 recommended that it be supplemented with FFP.[11] Since that time, there have been several reports of the successful use of a three-factor concentrate without addition of FFP.[30-33] Prothrombinex-VF has been used successfully to electively reverse anticoagulation in patients on warfarin therapy with a stable INR, and achieved the target INR in over 90% of patients.[30] However, this study included few patients (14%) with INR > 3.5 requiring normalisation of the INR. Patients with major or life-threatening bleeding or INR > 10.0 accompanied by high risk of bleeding are of great concern to clinicians, and the efficacy of Prothrombinex-VF when used alone in these patients has not been extensively evaluated. In such patients, supplementing factor VII by administering FFP should ensure optimal reversal of the anticoagulant effect of warfarin.

The previous Warfarin Reversal Consensus Guidelines recommended three-factor PCC (Prothrombinex-HT) be administered at a dose range of 25–50 IU/kg.[11] The revised dosing recommendations for various clinical scenarios included in this update are based on panel consensus alone (ie, rather than gradable evidence). The suggested dose of Prothrombinex-VF for reversal of the anticoagulant effect of warfarin is based on initial and target INRs (Box 4).[30]

Prothrombinex-VF is able to completely reverse an excessive INR within 15 minutes, but the infused clotting factors have half-lives similar to endogenous clotting factors. Therefore, vitamin K_1 5–10 mg should be given intravenously with the PCC to sustain the reversal effect.

4 Suggested dose of Prothrombinex-VF to reverse the anticoagulant effect of warfarin according to initial and target international normalised ratio (INR)*

	Initial INR			
Target INR	**1.5–2.5**	**2.6–3.5**	**3.6–10.0**	**> 10.0**
0.9–1.3	30 IU/kg	35 IU/kg	50 IU/kg	50 IU/kg
1.4–2.0	15 IU/kg	25 IU/kg	30 IU/kg	40 IU/kg

* Table reproduced with permission from *Intern Med J* 2011; 41: 337-343.[30] ◆

FFP contains all coagulation factors present in whole blood but it is not a factor concentrate, and multiple units may be needed if FFP alone is used for warfarin reversal. In addition to the inherent risks of plasma use mentioned already, requirements for its use include the need to determine the patient's blood group (or to use group AB plasma), appropriate facilities for frozen plasma storage and thawing, and the time taken for infusion. Therefore, FFP should not be used routinely to reverse warfarin anticoagulation; however, where PCC is unavailable and emergency reversal is required, FFP should be used, along with vitamin K_1 to sustain the reversal effect.

Treating a patient with bleeding, regardless of INR

For patients on warfarin therapy with bleeding in whom the aim is to normalise the INR, vitamin K_1 given intravenously is the preferred treatment because of its faster and predictable onset of action. For this indication, doses ⩽ 3 mg are ineffective. Consistent with other guidelines, we recommend a dose of 5–10 mg.[25,34,35] Our recommendations for managing patients on warfarin therapy with bleeding are summarised in Box 5. For life-threatening (critical organ) and clinically significant bleeds, the consensus is to use the maximum dose of Prothrombinex-VF (with vitamin K_1 and FFP) and the maximum amount of FFP when Prothrombinex-VF is unavailable.

Treating patients with high INR and no bleeding

Among patients with an elevated INR up to 10.0 who do not have bleeding or risk factors for major bleeding, it has been shown that oral administration of low-dose vitamin K_1 does not lower the risk of bleeding compared with placebo and should not be used routinely.[36] However, for patients with risk factors for bleeding, vitamin K_1 1–2 mg orally or 0.5–1.0 mg intravenously should be considered. Risk factors for major bleeding include a major bleed within the previous 4 weeks, surgery within the previous 2 weeks, a platelet count less than 50×10^9/L, known liver disease or concurrent antiplatelet therapy. There are no randomised studies to guide management of patients whose INR exceeds 10.0 and who are not bleeding. A recent single-arm study involving outpatients with an INR greater than 10.0 reported a low rate of major bleeding when these patients received 2.5 mg of oral vitamin K_1.[37] Our recommendations for managing patients with high INR and no bleeding are summarised in Box 6. Many patients on warfarin are outpatients and information on individual patient bleeding risk is frequently not available to laboratory staff who are involved in reporting elevated INR results and attempting to communicate results to patients. In these settings, good communication between clinical and laboratory staff is essential.

5 Management of patients on warfarin therapy with bleeding*

Clinical setting	Recommendations and levels of evidence†
INR ⩾ 1.5 with life-threatening‡ (critical organ) bleeding	**Cease warfarin therapy and administer:** • vitamin K_1 5.0–10.0 mg IV **(2C)** • *and* Prothrombinex-VF 50.0 IU/kg§ IV **(GPP)** • *and* fresh frozen plasma 150–300 mL **(GPP)** • If Prothrombinex-VF is unavailable, administer fresh frozen plasma 15 mL/kg **(GPP)**
INR ⩾ 2.0 with clinically significant bleeding (not life-threatening)	• Cease warfarin therapy and administer: • vitamin K_1 5.0–10.0 mg IV **(2C)** • *and* Prothrombinex-VF 35.0–50.0 IU/kg IV **(GPP)** according to INR (see Box 6) • If Prothrombinex-VF is unavailable, administer fresh frozen plasma 15 mL/kg **(GPP)**
Any INR with minor bleeding	• Omit warfarin, repeat INR the following day and adjust warfarin dose to maintain INR in the target therapeutic range **(2C)** • If bleeding risk is high¶ or INR > 4.5, consider vitamin K_1, 1.0–2.0 mg orally or 0.5–1.0 mg IV **(GPP)**

INR = international normalised ratio. IV = intravenously. * Indication for warfarin therapy should be reviewed; if clinically appropriate, consider permanent cessation. † Level of evidence in parentheses in **bold**. Details, Box 1. ‡ Includes intracranial bleeding. § Consider administering a Prothrombinex-VF dose less than 50.0 IU/kg when INR 1.5–1.9. ¶ Recent major bleed (within previous 4 weeks) or major surgery (within previous 2 weeks), thrombocytopenia (platelet count, $< 50 \times 10^9$/L), known liver disease or concurrent antiplatelet therapy. ◆

6 Management of patients on warfarin therapy with high INR and no bleeding

Clinical setting	Recommendations and levels of evidence*
INR higher than the therapeutic range but < 4.5 and no bleeding	Lower or omit the next dose of warfarin Resume therapy at a lower warfarin dose when the INR approaches therapeutic range • If the INR is only minimally above therapeutic range (up to 10%) dose reduction is generally not necessary **(2C)**
INR 4.5–10.0 and no bleeding	• Cease warfarin therapy; consider reasons for elevated INR and patient-specific factors. Vitamin K_1 is usually unnecessary **(2C)** • If bleeding risk is high:† • consider vitamin K_1 1.0–2.0 mg orally or 0.5–1.0 mg IV **(GPP)** • measure INR within 24 h • resume warfarin at a reduced dose once INR approaches therapeutic range
INR > 10.0 and no bleeding	• Cease warfarin therapy, administer 3.0–5.0 mg vitamin K_1 orally or IV‡ **(2C)** • Measure INR in 12–24 h. Close monitoring of INR daily to second daily over the following week **(GPP)** • Resume warfarin therapy at a reduced dose once INR approaches therapeutic range • If bleeding risk is high:† • consider Prothrombinex-VF, 15–30 IU/kg **(GPP)** • measure INR in 12–24 h. Close monitoring over the following week • resume warfarin therapy at a reduced dose once INR approaches therapeutic range

INR = international normalised ratio. IV = intravenously. * Level of evidence in parentheses in **bold**; details, Box 1. Recommendations with no evidence level are standard practice and not based on gradable evidence. † Recent major bleed (within previous 4 weeks) or major surgery (within previous 2 weeks), thrombocytopenia (platelet count, $< 50 \times 10^9$/L), known liver disease or concurrent antiplatelet therapy. ‡ Extrapolated from oral vitamin K data in absence of IV data. ◆

7 Suggested perioperative arterial and venous thromboembolism risk stratification*

Risk group	Atrial fibrillation	Venous thromboembolism	Mechanical heart valves
High	$CHADS_2$ score 5–6	Recent VTE (< 3 months previously)	Any mechanical mitral valve or older aortic heart valves (eg, caged-call)
	Recent stroke or TIA (< 3 months previously)	High-risk thrombophilia†	Recent stroke or TIA (< 3 months previously)
	Rheumatic valvular heart disease		
Moderate	$CHADS_2$ score 3–4	Recurrent VTE	Bileaflet aortic valve prosthesis with one or more risk factors‡
		VTE within last 3–12 months	
Low	$CHADS_2$ score 0–2 (no previous TIA or stroke)	VTE > 12 months previously	Bileaflet aortic heart valve without any risk factors

TIA = transient ischaemic attack. VTE = venous thromboembolism. * Adapted with permission from Table 1 in *Blood* 2011; 117: 5044-5049.[38] $CHADS_2$ = congestive heart failure, hypertension, age ⩾75 years, diabetes, 1 point each; prior stroke or transient ischaemic attack, 2 points. ‡ Risk factors: atrial fibrillation, cardiac failure, hypertension, age ⩾ 75 years, diabetes, prior stroke or TIA. † Deficiency of antithrombin, protein C or protein S, antiphospholipid syndrome, or homozygous or double-heterozygous factor V Leiden and prothrombin variant. ◆

Pre- and postoperative management of warfarin anticoagulation

When considering how to manage patients receiving warfarin who need surgery, it is important to consider the risk of thrombosis if warfarin is temporarily stopped, relative to the risk of bleeding if it is continued or modified. The perioperative thrombosis risk is determined by the indication for warfarin and the type of surgery, particularly with respect to postoperative VTE. Patients with MHV, AF with a history of stroke or transient ischaemic attack (TIA) or with multiple risk factors ($CHADS_2$ score [congestive heart failure, hypertension, age ⩾ 75 years, diabetes, 1 point each; prior stroke or transient ischaemic attack, 2 points] > 2, including a history of stroke or TIA), or an episode of VTE within the previous 3 months can be considered as high risk. Box 7 shows our adapted version of a recently published empirical risk stratification scheme for arterial and venous thromboembolism.[38]

Bleeding risk is high with cardiac, neurosurgical, cancer-related, orthopaedic or urological operations, and also with certain otherwise minor procedures like colonic polypectomy.

8 Management of patients on long-term warfarin therapy undergoing invasive procedures

	Recommendations*	
Thrombosis risk	Before surgery	After surgery
Low	Withhold warfarin 4–5 days before surgery **(1C)** Check INR day before surgery: If INR 2–3, administer 3 mg vitamin K_1 IV Day of surgery: • If INR ⩽ 1.5, surgery can proceed **(GPP)**; • If INR > 1.5, defer surgery or if urgent, dose Prothrombinex-VF according to Box 6; *or* • If Prothrombinex-VF is not available, use FFP 10–15 mL/kg (**GPP**) • Consider preoperative thromboprophylaxis with LMWH if immobilised (**GPP**) • For procedures with a low risk of bleeding (eg, cataracts, dental or dermatological), continue warfarin **(2C)**	• Recommence warfarin on the night of surgery at the previous maintenance dose **(2C)** • Employ thromboprophylaxis as per local practice
High	Option 1 • Withhold warfarin 4–5 days before surgery **(1C)** • Once INR < 2.0, start LMWH, eg, enoxaparin 1.5 mg/kg once daily or 1.0 mg/kg twice daily, or UFH infusion at treatment doses **(2C)** ➢ If LMWH is used, the last dose should be 24 h before surgery **(2C)**. ➢ If UFH infusion is used, cease 4–6 h before surgery **(2C)** ➢ Option 2 • If INR stable at 2–3 in the preceding 2–4 weeks, administer vitamin K_1 3 mg IV the day before surgery **(2C)** • Day of surgery: ➢ If INR ⩽ 1.5, surgery can proceed **(GPP)** ➢ If INR > 1.5, defer surgery or, if urgent, administer Prothrombinex-VF according to Box 6, *or* ➢ If Prothrombinex-VF is not available, use FFP 10–15 mL/kg **(GPP)** ➢ Option 3 • For urgent surgery, check INR before surgery and administer Prothrombinex-VF according to Box 4 **(2C)** • For procedures with a low risk of bleeding (eg, cataracts, dental or dermatological), continue warfarin **(2C)**	• Recommence warfarin the night of surgery at the previous maintenance dose **(2C)** • Consider bleeding risk against thrombosis • Start LMWH or UFH 12–24 h postoperatively • If using LMWH, begin with prophylactic dose; if UFH infusion is used, avoid bolus and aim to prolong the aPTT by 1.5 times • Delay resumption of therapeutic dose LMWH for 48–72 h after surgery in absence of bleeding **(2C)** • Continue LMWH or UFH for minimum of 5 days and cease 48 h after target INR is reached • In surgery with high bleeding risk, consider using prophylactic dose LMWH or UFH only and cease 48 h after target INR is reached

aPTT = activated partial thromboplastin time. FFP = fresh frozen plasma. INR = international normalised ratio. LMWH = low molecular weight heparin. UFH = unfractionated heparin. * Level of evidence given in parentheses in **bold**. For details, see Box 1. Recommendations with no evidence level are standard practice and not based on gradable evidence. ◆

Patients at high risk for arterial and venous thromboembolism should be considered for bridging anticoagulation with therapeutic low molecular weight heparin (LMWH) or an infusion of unfractionated heparin.[39] Bridging may include a heparin before and/or after surgery. It should be noted that quality evidence is lacking to show that bridging with heparin reduces arterial thromboembolism in patients with AF but is associated with increased bleeding (see below). Bridging is usually not needed in patients with low-risk AF ($CHADS_2$ score 0–1 and no history of TIA or stroke), or VTE occurring more than 3 months before surgery.

Bridging with a heparin is associated with an added risk of surgical bleeding that varies depending on the type of surgery (20% with major surgery, compared with 0.7% with minor surgery).[40] The risk of bleeding should be considered in the context of the severe consequences of thromboembolic stroke (death in 40% and severe disability in 30% of patients).

Traditionally, warfarin has been stopped 5 days before a major operation. Surgery can proceed safely if the INR is < 1.5 on the day of surgery. To avoid cancellations because the INR is above this level, the INR can be checked on the day before surgery and vitamin K_1 can be administered if needed. In patients who are given heparin before surgery, an LMWH is usually started when the INR is < 2.0 (typically on the third morning after the last warfarin dose) and continued until 24 hours before surgery; some guidelines recommend halving the last dose of LMWH before surgical procedures associated with a high bleeding risk.[41]

The above method can be labour intensive. In patients with a stable INR of 2.0–3.0 during the preceding 4 weeks, vitamin K_1 3 mg given intravenously on the evening (12–18 hours) before surgery has been shown to be effective in achieving a preoperative INR of < 1.5 in 94%, with few episodes of major bleeding related to surgery and low rates of warfarin resistance when restarting the drug.[42] Both methods using vitamin K_1 to reverse warfarin anticoagulation often require hospital in the home services or a general practitioner to administer the subcutaneous LMWH or intravenous vitamin K_1, and can result in higher rates of cancellation of surgery if the INR is > 1.5 on the day of surgery.

For patients who need urgent surgery while receiving warfarin therapy, three-factor PCC can effectively reverse the anticoagulant effect.[30,31] PCC should not be used routinely to enable elective surgery however, as vitamin K_1 is effective and less costly.

Many dental, dermatological or ophthalmological procedures are associated with a low bleeding risk. Patients with a low bleeding risk need not stop warfarin.

Bleeding risk can be minimised after major surgery by adjusting the time when anticoagulant is resumed, according to the anticipated surgical bleeding risk and the extent of intraoperative or immediate postoperative bleeding. This means that therapeutic LMWH is delayed for 48–72 hours or substituted with prophylactic LMWH in patients having major surgery with a high bleeding risk.[43] Bleeding risk is low after minor procedures if therapeutic LMWH is started about 24 hours after surgery. Warfarin can be restarted on the evening of surgery at the previous maintenance dose if there is adequate surgical haemostasis.

The strategies that can be used to manage patients on long-term warfarin therapy during surgery and other invasive procedures are summarised in Box 8. These strategies are not associated with a delay in re-establishing a therapeutic INR when resuming warfarin after surgery.

Competing interests: A restricted educational grant from CSL Bioplasma that was administered by the ASTH enabled the Warfarin Reversal Consensus Group (WRCG) to travel to meet, develop and write these guidelines. No members of the WRCG received honoraria. Paul Harper is a Director of INR Online, an online warfarin management system, and a member of the Bayer HealthCare rivaroxaban New Zealand advisory committee. Erica Wood is a member of the Transfusion Outcomes Research Collaborative, which operates the Massive Transfusion and Critical Bleeding Registry through Monash University. CSL Limited, the manufacturers of Prothrombinex-VF, have provided financial support to this registry.

Provenance: Not commissioned; externally peer reviewed.

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