Updated recommendations for warfarin reversal in the setting of four-factor prothrombin complex concentrate

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Abstract

Introduction: Warfarin (vitamin K antagonist) remains an established anticoagulant for patients at high risk of arterial and venous thromboembolism. The prompt reversal of the anticoagulant effect of warfarin is necessary in the context of major bleeding or emergency surgery because of its extended inhibition of vitamin K-dependent coagulation factors for days. The mainstay of urgent warfarin reversal has been vitamin K administration, and infusion of a three-factor prothrombin complex concentrate (3FPCC) and the option for the addition of fresh frozen plasma as a source of factor VII. With the upcoming introduction in Australia and New Zealand of a four-factor prothrombin complex concentrate (4FPCC), which replaces all the vitamin K-dependent clotting factors, this article updates the previously published warfarin reversal guidelines.

Main recommendations: For urgent warfarin reversal, 4FPCC should be used instead of 3FPCC, using the same suggested dose. Vitamin K co-administration is still recommended for more sustained reversal.

Changes in management as a result of this statement: The use of 4FPCC for urgent warfarin reversal obviates the need for co-administration of fresh frozen plasma.

Warfarin, a vitamin K antagonist, is an effective and widely used oral anticoagulant for primary and secondary prevention of thromboembolic disorders. Common indications for the use of warfarin in the community include prevention of systemic embolism in atrial fibrillation, preventing thrombus formation in patients with mechanical heart valves and the treatment of venous thromboembolism disease, particularly in the setting of antiphospholipid syndrome.

The most common complication of warfarin therapy is bleeding, with a 1–3% annual incidence of warfarin-associated major bleeding.[1] Although increased international normalised ratio (INR) is associated with increased bleeding risk, patient factors such as age, prior bleeding history, concomitant medications (especially aspirin and non-steroidal anti-inflammatory drugs) and medical comorbid conditions (eg, deranged renal and liver function) are all well recognised risk factors that increase the risk of vitamin K antagonist-associated bleeding.[2] Consensus recommendations for reducing the occurrence of supratherapeutic INR levels (INR > 4.5) that lead to bleeding in patients on warfarin include regular INR monitoring, especially during episodes of illness or hospitalisation, and avoidance of concomitant medications that can result in INR lability.[3]

Nonetheless, there are commonly encountered scenarios, such as major bleeding or urgent surgery, that warrant prompt reversal of warfarin anticoagulation. Australia and New Zealand will soon transition from three-factor prothrombin complex concentrate (3FPCC; Prothrombinex-VF, CSL Behring) to four-factor prothrombin complex concentrate (4FPCC; Beriplex, CSL Behring). This article will therefore provide an update to the previously published consensus guidelines on warfarin reversal.[4] CSL Behring has had no role in the development or revision of this guideline. A summary of key changes is highlighted in Box 1.

Methods

The National Blood Authority of Australia announced in January 2024 that Australia's prothrombin complex concentrate, 3FPCC Prothrombinex-VF would be changing to 4FPCC Beriplex.[5]

To update the existing guideline, we reviewed up-to-date evidence and existing high quality evidence-based international guidelines for warfarin reversal using PubMed and Embase.[4] As international guidelines have already made evidence-based recommendations on the use of 4FPCC for warfarin reversal (coupled with no available alternatives), we did not perform a formal appraisal of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment tool.[6,7] This change will bring the practice in Australia and New Zealand in line with current international recommendations.

3FPCC versus 4FPCC

For many years, prothrombin complex concentrate, in the form of 3FPCC, has been the mainstay of vitamin K antagonist reversal in

1 Comparison of warfarin reversal in the use of 3FPCC (Prothrombinex-VF*)[4] versus 4FPCC (Beriplex*)

	Previously published guidelines: 3FPCC (Prothrombinex-VF)	New guidelines: 4FPCC (Beriplex)
Management of patients on warfarin therapy with bleeding	• Co-administration of FFP in addition to Prothrombinex-VF • INR ≥ 2 with clinically significant bleeding: 35–50 IU/kg IV Prothrombinex-VF	• No requirement for additional administration of FFP • INR ≥ 2 with clinically significant bleeding: 25–50 IU/kg IV Beriplex
Management of non-bleeding patients on warfarin (eg, before urgent surgery)	Unchanged	Unchanged

3FPCC = three-factor prothrombin complex concentrate; 4FPCC = four-factor prothrombin complex concentrate; FFP = fresh frozen plasma; INR = international normalised ratio; IV = intravenous. * CSL Behring. ◆

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Australia and New Zealand. Prothrombinex-VF, a non-activated prothrombin complex concentrate product, contains factors II, IX and X, and only small amounts of factor VII. It is often combined with fresh frozen plasma (FFP) as a more substantial source of factor VII, and has been shown to effectively and rapidly reduce an excessive INR to within target range.[8] As such, it is widely used in Australia and New Zealand for warfarin reversal.

Both 3FPCC and 4FPCC have significant increases of vitamin K-dependent clotting factors within five minutes of infusion;[9] however, due to the higher concentrations of factor VII in 4FPCC compared with 3FPCC, administration of FFP is not required with 4FPCC. This has patient-level benefits, including avoiding delay of administration because of thawing FFP, minimising exposure to FFP-related side effects such as fluid overload, febrile reactions, anaphylaxis, transfusion-related acute lung injury, infection risk or alloimmunisation, as well as population-level benefits, including reduced use of rare blood products.

Both 3FPCC and 4FPCC result in a more rapid INR reduction than FFP in patients requiring urgent warfarin reversal. A systematic review and meta-analysis published in 2022 evaluated twelve studies that compared 3FPCC and 4FPCC in warfarin reversal for patients with bleeding, undergoing surgery or in a trauma.[10] In patients requiring emergency warfarin reversal, patients who received 4FPCC had greater than three times the odds of achieving their goal INR compared with those individuals who received 3FPCC (often with concomitant FFP). Reassuringly, there was no statistical difference in the odds of thromboembolic complications between the two prothrombin complex concentrate formulations.[10] 4FPCC also has significant concentrations of antithrombotic factors protein C and protein S, which are absent in 3FPCC.

Warfarin reversal and 4FPCC: the bleeding patient

Many aspects of warfarin reversal in the bleeding patient will remain the same when 4FPCC is introduced. This includes withholding warfarin, and providing rapid and adequate local haemostatic measures. Consistent with previously published guidance on warfarin reversal, concomitant administration of 5–10 mg intravenous vitamin K for patients with major bleeding is recommended but the effect is delayed by 12–24 hours.[4]

Sarode and colleagues,[11] demonstrated that 4FPCC was superior to FFP in achieving INR correction in patients with acute and major warfarin-associated bleeding. INR reduction to less than 1.3 at 30 minutes after the end of product infusion was achieved in 62% of patients who received 4FPCC, compared with only 10% in the FFP cohort. Achieving haemostasis, which included assessment of cessation of bleeding and need for transfusion of blood products, of over 72% were observed for the 4FPCC arm compared with 65% with FFP. The dosing regimen used in this trial, which has formed the basis of the dosing guidelines in the manufacturer's product information, ranged from 25 IU/kg to 50 IU/kg body weight according to the patient's INR.[11]

Box 2 outlines our recommendations for urgent warfarin reversal in the setting of warfarin-associated bleeding. These suggestions are based on previously published consensus guidelines,[4] as well as the 4FPCC dosing schedule published by Sarode and colleagues[11] and used in subsequent trials[12] and clinical practice. Nonetheless, all real-life 4FPCC dosing decisions should be made with consideration of the individual patient, including their degree of bleeding, the ability to perform timely and adequate haemostatic interventions and their underlying thrombotic risk that warranted anticoagulation with warfarin in the first place.

2 Management of patients on warfarin therapy with bleeding

Clinical setting	Recommendations
INR ≥ 1.5 with life-threatening or critical organ bleeding	Omit warfarin therapy and administer: • vitamin K 5.0–10.0 mg IV; and • 4FPCC 50 IU/kg*
INR ≥ 2.0 with clinically significant bleeding (not life-threatening)	Omit warfarin therapy and administer: • vitamin K 5.0–10.0 mg IV; and • 4FPCC 25–50 IU/kg based on INR and patient level factors (eg, type of bleeding, need and ability to undergo intervention)
Any INR with minor bleeding	• Omit warfarin • Repeat INR and adjust warfarin dose to maintain INR in the target therapeutic range • If bleeding risk is high or INR > 4.5, consider vitamin K (1.0–2.0 mg orally, or 0.5–1.0 mg IV)

4FPCC = four-factor prothrombin complex concentrate; INR = international normalised ratio; IV = intravenous. * Consider administering a 4FPCC dose < 50.0 IU/kg when INR 1.5–1.9. ◆

Warfarin reversal and 4FPCC: before urgent surgery

Cessation of warfarin therapy before surgery needs to balance the risk of thrombosis if warfarin is temporarily stopped against the risk of bleeding related to the ongoing systemic anticoagulation. The periprocedural bleeding risk in patients on warfarin can be significant, occurring in up to nearly 25% of cases.[13] Oral or intravenous vitamin K alone has been shown to be effective in reversing warfarin,[3] but the full effect of vitamin K typically takes 12–24 hours.[4] Therefore, in cases where rapid reversal of INR is required (ie, emergency surgery, major bleeding), 4FPCC is recommended.[11] In elective surgery, either omission of warfarin alone or with co-administration of vitamin K is the recommended pathway for warfarin reversal.[14]

A previously published randomised controlled trial compared 4FPCC with FFP, in conjunction with vitamin K, for warfarin reversal for patients who required urgent surgery or invasive procedures.[15] The surgeries and procedures were wide-ranging and included individuals with active bleeding and those requiring surgeries that carried lower bleeding risk. The study, which enrolled over 180 patients, showed the superiority of 4FPCC compared with FFP in achieving haemostasis, with up to 90% haemostasis rates achieved in emergency surgery compared with 75% with FFP. In this trial, haemostatic efficacy was determined based on surgical or procedural blood loss not exceeding predicted blood loss by 30% (or 50 mL), surgeon-assessed haemostasis adequacy, and no requirement for additional coagulation products. Superiority was also observed regarding rapid reductions in INR. Reassuringly, there were no differences in the rates of adverse and serious adverse events, including thromboembolic events.[15]

Box 3 shows our suggestion for dosing of 4FPCC to reverse warfarin anticoagulation in the non-bleeding patient, using the patient's initial INR and desired INR. This approach needs to be individualised, taking into account the patient's underlying

3 Suggested dose of four-factor prothrombin complex concentrate (4FPCC) to reverse warfarin anticoagulation in a non-bleeding patient (eg, before surgery)[4]*

	Initial international normalised ratio (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

* Outside of the peri-operative setting, 4FPCC use should only be considered if INR > 10 and there is high risk of bleeding. ◆

thrombotic risks as well as the indication for warfarin reversal (eg, urgent surgery) and potential for high risk bleeding associated with invasive procedures. For patients weighing more than 100 kg, the dose of 4FPCC should be calculated based on a capped 100 kg body weight and maximum dose of 50 IU/kg (ie, maximum 4FPCC dose of 5000 IU).

Conclusions

The upcoming introduction of 4FPCC to Australia and New Zealand for warfarin reversal will allow for comprehensive replacement of vitamin K-dependent clotting factors and improved and safter rapid INR correction compared with 3FPCC and FFP. Concomitant vitamin K administration is still recommended for patients with major bleeding for more sustained warfarin reversal, and the suggested dose is unaltered with the 4FPCC. 4FPCC has higher factor VII concentrations and, therefore, co-administration with FFP is no longer required.

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1 Schulman S, Beyth RJ, Kearon C, Levine MN; American College of Chest Physicians. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (Suppl): 257S-298S.

2 Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. *Am J Med* 1993; 95: 315-328.

3 Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141: e152S-e184S.

4 Tran HA, Chunilal SD, Harper PL, et al; Australasian Society of Thrombosis and Haemostasis. An update of consensus guidelines for warfarin reversal. *Med J Aust* 2013; 198: 198-199. https://www.mja.com.au/journal/2013/198/4/update-consensus-guidelines-warfarin-reversal

5 National Blood Authority of Australia. Update on the transition of Prothrombinex-VF. 3 January 2024. https://www.blood.gov.au/update-transition-prothrombinex-vf (viewed Sept 2024).

6 Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2020; 76: 594-622.

7 Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2022; 53: e282-e361.

8 Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. *Am J Hematol* 2008; 83: 137-143.

9 Ostermann H, Haertel S, Knaub S, et al. Pharmacokinetics of Beriplex P/N prothrombin complex concentrate in healthy volunteers. *Thromb Haemost* 2007; 98: 790-797.

10 Margraf DJ, Brown SJ, Blue HL, et al. Comparison of 3-factor versus 4-factor prothrombin complex concentrate for emergent warfarin reversal: a systematic review and meta-analysis. *BMC Emerg Med* 2022; 22: 14.

11 Sarode R, Milling TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013; 128: 1234-1243.

12 Voils SA, Holder MC, Premraj S, et al. Comparative effectiveness of 3- versus 4-factor prothrombin complex concentrate for emergent warfarin reversal. *Thromb Res* 2015; 136: 595-598.

13 Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation* 2012; 126: 343-348.

14 Thigpen JL, Limdi NA. Reversal of oral anticoagulation. *Pharmacotherapy* 2013; 33: 1199-1213.

15 Goldstein JN, Refaai MA, Milling TJ, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet* 2015; 385: 2077-2087. ■