

Warfarin Reversal

Based on the 2013 ASTH Consensus Guidelines



Your pocket
guide

References and further reading

- 1 Tran HA, Chunilal SD, Harper PL, et al. An update of consensus guidelines for warfarin reversal. Med J Aust 2013; 198 (4):198-199. © Copyright 2013 The Medical Journal of Australia - reproduced with permission.
- 2 H. Tran, M. Collett, S. Whitehead, H. H. Salem. Prothrombin complex concentrates used alone in urgent reversal of warfarin anticoagulation. Intern Med J 2011;41:337-343 © 2011 The Authors. Internal Medicine Journal © 2011 Royal Australasian College of Physicians - reproduced with permission
- 3 Prothrombinex-VF Medicine datasheet available from <http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp>
- 4 FFP datasheet available from <http://www.nzblood.co.nz/Clinical-information/Transfusion-medicine/Health-professionals-medicine-datasheets/Frozen-plasma-components>.

Produced by New Zealand Blood Service using an unrestricted educational grant provided by CSL Behring Australia

Leaflet prepared and provided by the New Zealand Blood Service.
Private Bag 92071, Victoria Street West, Auckland 1142.
71 Great South Road, Epsom, Auckland.
Telephone: 09 523 5733 Fax: 09 523 5754

www.nzblood.co.nz

Overview of updated guidelines

- This pocket guide provides information on the appropriate reversal of warfarin induced anticoagulation. This is based on guidelines produced by the Australasian Society of Thrombosis and Haemostasis (ASTH) in 2013.
- Warfarin remains the most commonly prescribed anti-coagulant in Australasia despite the recent introduction and funding of new anticoagulants. Warfarin is a coumarin derivative which works by blocking production of the vitamin K dependent coagulation factors (factors II, VII, IX and X).
- Warfarin has been shown to be effective in the prevention and treatment of a wide range of thrombotic disorders, it is also associated with a risk of major bleeding (requiring hospitalisation or resulting in death) of 1-3% per year for patients on long term therapy.
- Timely and appropriate management of over-anticoagulation and bleeding whilst on treatment is important. This should involve careful consideration of the balance of risks of bleeding versus further thrombotic episodes.
- A range of therapeutic options exist to reverse the anti-coagulant effect of warfarin. These comprise Vitamin K, Prothrombinex-VF and Fresh Frozen Plasma (FFP). Vitamin K₁ is essential for ensuring a sustained reversal following administration of either Prothrombinex-VF or FFP.
- Prothrombinex-VF is a three factor prothrombin complex concentrate produced by CSL Behring Australia from plasma collected from voluntary non-remunerated donors in New Zealand. It contains Factor II, IX and X with only trace levels of factor VII. Recent studies have demonstrated that in most clinical settings Prothrombinex-VF will effectively reverse the anticoagulant effect of warfarin without the need for combination treatment with FFP.
- Limited data is currently available on the effectiveness of Prothrombinex-VF in reversing warfarin in patients with life threatening or critical bleeding (including intracranial haemorrhage) and combined use of both Prothrombinex-VF and FFP (150-300ml) is therefore recommended.

Table 4: Characteristics of Prothrombinex-VF and fresh frozen plasma¹

	Prothrombinex-VF ³	Fresh frozen plasma (FFP) ⁴
Description	Prepared from plasma collected in New Zealand from unpaid voluntary donors. Sterile freeze-dried powder containing coagulation factors II, IX and X and low levels of factor VII.	Separated and frozen within 8 hours of collection from unpaid voluntary male donors in New Zealand. 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 500IU of factor II, IX and X to be reconstituted in 20ml of water for injection. Each vial also contains 25IU of antithrombin and 192IU of heparin.	Available in units of 180-300mL in New Zealand. May be stored in monitored blood refrigerator at 2-6°C for up to 5 days once thawed, and re-labelled "thawed plasma" in accordance with Australian and New Zealand Society of Blood Transfusion Guidelines. Thawed plasma has levels of factors II, VII, XI 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 group.	Available in all ABO groups, and should be ABO-group compatible with patient's red cells (or use AB plasma in situations requiring emergency issue before blood group determined)
	Known allergies to prothrombin complex concentrates.	Most common adverse events - allergic reactions and volume overload. Potential for transfusion-related lung injury and other transfusion reactions, including transmission of infections.
	Predisposition to venous thrombosis, disseminated intravascular coagulation and myocardial infarction ² .	
	Heparin- induced thrombocytopenia.	

² 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.
© The Medical Journal of Australia – reproduced with permission

Clinical setting		Therapy					
Bleeding	INR	Warfarin	Vitamin K ₁	Prothrombinex-VF	Fresh frozen plasma (FFP)	Measure INR	Comments
Bleeding absent	Above therapeutic range but <4.5	Lower or omit next dose	-	-	-	-	Consider reasons for elevated INR and patient-specific factors. Resume warfarin at lower dose when INR approaches therapeutic range. If INR <10% above therapeutic range, dose reduction may not be necessary.
	4.5-10	Cease	High risk [‡] : Consider 1-2mg (orally) or 0.5-1mg (IV)	-	-	Within 24hrs	Consider reasons for elevated INR and patient specific factors. Resume warfarin at reduced dose when INR approaches therapeutic range.
	>10	Cease	3-5mg (oral or IV)	High risk [‡] : Consider 15-30IU/kg	-	Within 12-24hrs	Resume warfarin at reduced dose when INR approaches therapeutic range.
Life threatening or critical organ bleeding ^{†*}	≥1.5	Cease	5-10mg (IV)	50IU/kg ⁺	150-300ml		If Prothrombinex-VF is unavailable, administer FFP 15mL/kg.
Clinically significant bleeding [*]	≥2.0	Cease	5-10mg (IV)	35-50IU according to INR [◇]	-		
Minor bleeding [*]	Any	Omit next dose	High risk [‡] or INR >4.5: Consider 1-2mg (oral) or 0.5-1mg (IV)	-	-	Within 24hrs	Adjust warfarin dose to maintain INR in the target therapeutic range.

‡ Risk factors include : Major bleeding within the previous 4 weeks, surgery within the previous 2 weeks, a platelet count of <50x10⁹/L, known liver disease or concurrent antiplatelet therapy.

† Includes intracranial haemorrhage.

* Indication for warfarin therapy should be reviewed; if clinically appropriate consider permanent cessation.

+ Consider a Prothrombinex-VF dose less than 50IU/kg when INR 1.5-1.9.

◇ See table 2 for details

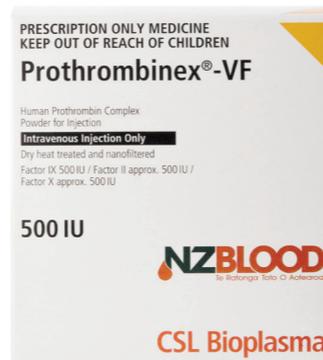
© The Medical Journal of Australia – reproduced with permission

Target INR	Initial INR			
	1.5-2.5	2.6-3.5	3.6-10.0	>10
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 61:337-343².

INR = International normalised ratio, FFP = fresh frozen plasma, LMWH = Low molecular weight heparin, UFH = Unfractionated heparin.

Adapted from: An update of consensus guidelines for warfarin reversal (2013) on behalf of the Australasian Society of Thrombosis and Haemostasis.¹



Thromboembolism risk	Therapeutic procedures before and after surgery				
	4-5 days before	2-3 days before	Night/day before	Day of Surgery	After surgery
Low	Withhold warfarin	Consider preoperative thromboprophylaxis with LMWH if immobilised	If INR 2-3 give vitamin K ₁ 3mg (IV)	If INR ≤ 1.5, proceed	<ul style="list-style-type: none"> • Recommence warfarin at the previous maintenance dose. • Employ thromboprophylaxis as per local practice.
				If INR >1.5, defer	
If surgery is urgent give Prothrombinex-VF, dose according to INR [≠]					
• For procedures with a low risk of bleeding (e.g. cataracts, dental or dermatological) continue warfarin.					
High	Option 1			<ul style="list-style-type: none"> • Recommence warfarin the night of surgery at the previous maintenance dose. • Consider bleeding risk against thrombosis. • Start LMWH (prophylactic dose) or UFH 12-24 hrs post operatively. • If using LMWH, begin with prophylactic dose; if UFH infusion is used, avoid bolus and aim to prolong the aPTT by 1.5 times. • Resume therapeutic dose LMWH 48-72 hrs after surgery in the absence of bleeding. • Continue LMWH or UFH for a minimum of 5 days, and cease 48hrs after target INR is reached. • In surgery with high bleeding risk consider using prophylactic dose LMWH or UFH only and cease after target INR is reached. 	
	Withhold warfarin	When INR <2.0 start treatment dose LMWH (1.5mg/kg od or 1mg/kg bd) or UFH	LMWH - last dose 24 hrs before surgery. UFH - cease infusion 4-6 hrs before surgery.		
	Option 2 - if INR stable at 2-3 in the 4-6 weeks preceding surgery			<ul style="list-style-type: none"> • For procedures with a low risk of bleeding (e.g. cataracts, dental or dermatological) continue warfarin. 	
		Administer vitamin K ₁ 3mg (IV)	If INR ≤ 1.5, proceed		
If INR >1.5 defer			If surgery is urgent give Prothrombinex-VF, dose dependent on INR [≠]		

◇ See table 2 for details.

≠ If Prothrombinex-VF is not available, use FFP 10-15mL/kg.

INR = International normalised ratio, FFP = Fresh frozen plasma, LMWH = Low molecular weight heparin, UFH = Unfractionated heparin
Adapted from: An update of consensus guidelines for warfarin reversal (2013) on behalf of the Australasian Society of Thrombosis and Haemostasis.
© The Medical Journal of Australia – reproduced with permission