



PRACTICE

THERAPEUTICS

Urgent reversal of vitamin K antagonists

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What you need to know

- There are three options for urgent reversal of anticoagulant effects of vitamin K antagonists such as warfarin: vitamin K, prothrombinase complex concentrate, and fresh frozen plasma
- The reversal of vitamin K antagonists can be monitored with the international normalised ratio (INR) to measure clotting time
- Prevention of bleeding is key: the patient's INR should be kept in the desired therapeutic range, and extra INR checks are needed during illness and when starting a new medication that may interfere with warfarin's effect

A 78 year old man is brought to the emergency department after collapsing. He is drowsy with signs of a left hemiparesis. Computed tomography of the brain shows an intracranial bleed. He has a history of atrial fibrillation, and he has been taking warfarin (INR target 2-3) for several years. His wife says he started a course of antibiotics for a chest infection a week before. His INR is 8.

Warfarin is a vitamin K antagonist (⚡) and a coumarin (more accurately 4-hydroxycoumarin) derivative. It is the most commonly used vitamin K antagonist in the world.¹ The main uses for vitamin K antagonists are prevention of stroke in patients with atrial fibrillation, and prevention of thrombosis in those with previous venous thromboembolism or with mechanical heart valves. In some countries, other coumarins are used with a similar action but a shorter (acenocoumarol) or longer (phenprocoumon) half-life.

In patients taking a vitamin K antagonist such as warfarin and presenting with a serious or life threatening haemorrhage, urgent anticoagulation reversal is recommended by current national guidelines (see ⚡).²⁻⁵ Each clinical situation requires a careful

assessment of the benefits and risks of reversing anticoagulants¹ by considering the indication for the antithrombotic agents and the bleeding risk.

The biochemical reversal of vitamin K antagonists can be achieved quickly. Guidelines on warfarin use, such as those produced by the British Society for Haematology,² advise rapid restoration of a normal international normalised ratio (INR), although evidence that this reduces intracranial haematoma growth or improves clinical outcome in those with an intracranial haematoma is limited to case series.^{6,7} Intracranial haematoma is the most devastating complication of vitamin K antagonist use, accounting for 90% of deaths or permanent disability (⚡).⁷ While intracranial haematoma can occur in those with INR in the target INR range, the degree of INR prolongation at the time of intracranial haematoma correlates with haematoma size, enlargement after admission, functional outcome, and mortality.⁸

What reversing agents are available?

The reversing agents available can directly replace the missing coagulation factors intravenously either by giving concentrates of the missing factors, which work immediately (prothrombinase complex concentrate), or enabling regeneration of the missing coagulation factors by giving vitamin K. The third option is fresh frozen plasma, which contains the missing coagulation factors alongside all the other plasma proteins.

Prothrombinase complex concentrate

For immediate reversal of vitamin K antagonists, the missing coagulation factors should be replaced directly with prothrombinase complex concentrate (PCC). PCCs are derived from human plasma and contain coagulation factors II, IX, and X, but the factor VII content varies considerably between

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Patricia McGettigan, clinical senior lecturer in clinical pharmacology, Queen Mary's University, London. To suggest a topic, please email us at practice@bmj.com.

different formulations. Modern PCC formulations contain substantial amounts of factor VII and can completely reverse the effect of vitamin K antagonists as it is infused. A few countries have access only to three-factor PCC, which produce poor correction of the INR and are therefore not recommended if four-factor PCCs are available.

The half-life of administered factor VII is only six hours, thus vitamin K should be given with the PCC if interruption of anticoagulation is required for longer than six hours.

Vitamin K

Reversing vitamin K antagonists for planned procedures may be achieved in hours, by giving phytonadione (vitamin K₁) to restart the production of vitamin K-dependent coagulation factors (II, VII, XI, and X). Factor VII has the shortest rate of synthesis, at six hours, whereas the other factors have synthesis times of 25-50 hours. As the INR is most affected by factor VII levels, the INR should return to normal in six hours after vitamin K administration.

Fresh frozen plasma

The alternative to PCC is fresh frozen plasma (FFP) which contains the missing coagulation factors diluted among all the other constituents of plasma.

How well do they work?

Prothrombinase complex concentrate

↓ gives details of two randomised trials comparing PCC versus FFP in reversing warfarin with clinical endpoints of mortality and safety. PCC was significantly superior to FFP in terms of speed of effect and risk of fluid overload.^{9,10} A recent systematic review and meta-analysis (19 studies, 18 cohort and 1 randomised controlled trials (n=2878)) suggests that PCC provides more rapid and complete factor replacement than FFP (odds ratio 0.64, 95% confidence interval 0.27 to 1.5).¹¹

Vitamin K

Immediately after administration of vitamin K, the synthesis of active vitamin K-dependent coagulation factors will recommence, with restoration of adequate factor VII levels in about six hours after intravenous vitamin K and 12 hours after oral vitamin K.^{12,13} An intravenous dose of 2 mg or an oral dose of 5 mg is usually adequate. The reversal of vitamin K antagonists can be monitored with the INR, which is very sensitive to factor VII levels. A recent meta-analysis of 21 studies (n=983) suggested that oral and intravenous vitamin K had similar efficacy, but that subcutaneous vitamin K was inferior and similar to placebo.¹⁴ In the four trials using oral vitamin K (n=75), the proportion of patients with a target INR at 24 hours was 82% (95% confidence interval 70% to 93%), which was similar to that with intravenous vitamin K (six trials, n=69; target INR 77%, 95% CI 60% to 95%).¹⁴

Fresh frozen plasma

If FFP is used, the amount required to replace the missing coagulation factors in an adult is about 1500 mL (six units) and is not as rapid acting as PCC and will not necessarily fully correct the INR.¹¹ It also takes time to thaw and transport, whereas PCC can be stored locally and therefore be reconstituted in minutes. For all these reasons guidelines recommend PCC over FFP in life threatening bleeding,²⁻⁵ although we suggest that if FFP is immediately available pre-thawed (as is

recommended in trauma centres) it can be used for a patient needing volume restoration as well as warfarin reversal.

What are the harms of reversing agents?

It is important to consider the risk and benefit of reversing anticoagulation in each case individually, and to consult specialist haematologists for advice. For example, in a patient with prosthetic mitral and aortic valves who presents with moderately severe gastrointestinal bleeding (that can probably be managed endoscopically), interruption of vitamin K antagonist may increase the risk of valve thrombosis and cerebral or systemic embolism, and this should be offset against the risk of sustained anticoagulation.

Prothrombinase complex concentrate

Early forms of PCCs were associated with thromboembolism, which was ascribed to the presence of activated coagulation factors in the concentrate. With modern manufacturing processes, this risk has been greatly reduced.¹¹ Currently thromboembolic complications such as stroke in those with atrial fibrillation after reversal of anticoagulant treatment are mainly ascribed to a patient's pre-existing thromboembolic risk in the absence of anticoagulation.¹⁵ This risk may be amplified by the prothrombotic state induced by the specific clinical settings that require reversal (such as trauma). A meta-analysis of 18 cohort studies and one randomised controlled trial (n=2878)—of which six were judged as good methodological quality, nine were moderate, and four were poor—found that thromboembolic complications were observed in an average of 2.5% of PCC recipients and in 6.4% of FFP recipients. The same meta-analysis found no significant difference in mortality between PCC versus FFP (odds ratio 0.64, 95% CI 0.27 to 1.3) or between PCC versus no treatment (odds ratio 0.41, 0.13 to 1.3), suggesting that, even with treatment, clinical outcome was poor.¹¹

Vitamin K

The most important side effect of intravenous vitamin K is an unpredictable anaphylactoid reaction (characterised by dyspnoea, hypotension, shock, and in some cases cardiac arrest), which has an incidence of 3 per 100 000 doses via a non-IgE mechanism, possibly due to the solubiliser.¹⁶ There is a danger of overdose, as large doses of vitamin K (such as 10 mg) will prevent vitamin K antagonists from working for days.

Fresh frozen plasma

FFP, like any other unpasteurised blood product, carries a risk of rare adverse events of about 1:1700 units.¹⁷ These risks include transfusion related lung injury, circulatory overload, allergic reactions, and, less commonly, transfusion associated infection.

How are they administered and monitored?

A life threatening bleed in a patient receiving vitamin K antagonists requires urgent reversal of the vitamin K antagonist effect. Either PCC or prethawed FFP is given to immediately reverse the anticoagulant effects, and, as indicated above, four-factor PCCs provide more rapid and complete reversal than FFP, and without the possible side effects of transfusing large volumes of plasma. Vitamin K should be given simultaneously to cover the period after the effects of PCC have worn off:

vitamin K will allow an endogenous regeneration of the missing factors.

Prothrombinase complex concentrate

Give four-factor PCC (examples are Octaplex, Beriplex, Cofact, KCentra) intravenously. The dose of PCC is 25-50 units/kg, and algorithms are available to calculate the most appropriate dose based on body weight and INR level (such as <http://beriplex.co.uk/home/dosing-and-administration/>). A stepwise increase in dose is recommended with INR prolongation (for example, 25 units/kg if INR is 2-4.0, 35 units/kg if INR 4-6.0, and 50 units/kg if INR >6.0). Thus, in an adult weighing 80 kg with an INR of 8, you should give 4000 units PCC. Overuse of PCC (giving further PCC when INR is in normal range) will produce a prothrombotic state which may lead to further thrombosis.

Vitamin K

Give vitamin K intravenously and not intramuscularly in an anticoagulated patient because of the risk of muscle bleeding. After reversal of the vitamin K antagonist effect, check INR regularly for at least the next week, as a minority of patients take over a week to clear warfarin. It may be necessary to give further vitamin K. Do not “overcorrect” reversal with more than 10 mg vitamin K as it can prevent “rewarfarinisation” for days.

Fresh frozen plasma

FFP is given intravenously, and a blood transfusion bedside checklist must be followed to ensure positive patient identification and that the blood unit is compatible, and the blood unit number is recorded. The blood unit must also be checked for leaks, discolouration, and expiry date

Generally, restarting anticoagulation needs daily monitoring—especially for patients at high risk of thrombosis. For each individual, the risk of bleeding must be weighed against the benefits of reducing the risk of thrombosis.

How cost effective are they?

In a cost effectiveness analysis of UK practice in 2010,¹⁸ the cost of warfarin reversal with either PCC or FFP was estimated to be ≤15% of the total cost of managing a patient after a life threatening intracranial, gastrointestinal, or retroperitoneal haemorrhage, and PCC was more cost effective than FFP. The cost per life-year gained with PCC was estimated to range from £1000 to £2000, depending on haemorrhage type (intracranial, gastrointestinal, or retroperitoneal). The cost per quality adjusted life-year gained with PCC was estimated at £3000 or less depending on haemorrhage type. The current price of FFP in the UK is £28.46 per unit (<http://hospital.blood.co.uk/media/28230/component-price-list-2016-2017.pdf>) and in the US is on average \$60.70, and at least six units are required for a 70 kg adult.

Preventing bleeding in patients receiving vitamin K antagonists

- Prevention is key: keeping the patient's INR in the desired therapeutic range is important
- Dietary intake of vitamin K should be consistent
- It is particularly important to perform extra INR checks during intercurrent illness
- Since many drugs interfere with the action of warfarin, recheck INR after changes in other medication (in particular antibiotics)
- Management by dedicated anticoagulation clinics or patient self management with access to medical advice is recommended
- NICE guidance¹⁹ recommends reassessment of anticoagulation for patients with poor anticoagulation control, shown by any of the following:
 - Two INR values >5 or one INR value >8 within the past six months
 - Two INR values <1.5 within the past six months
 - Time in therapeutic range (duration of time in which patient's INR values were within the desired range) <65%

Tips for patients

1. Warfarin depletes the blood of effective coagulation factors II, VII, IX, and X
2. In life threatening bleeding we need to replace the missing coagulation factors in the quickest and most effective way
3. There are three options to do this:
 - Injection of vitamin K will stimulate the regeneration of missing factors. However, this takes around six hours to achieve and so is not suitable to use alone when bleeding is life threatening and ongoing
 - Fresh frozen plasma has the missing coagulation factors in a dilute form. However, defrosting the plasma and then infusing it in the patient quickly is difficult, and the amount required can risk causing fluid overload, and, even if the correct amount is given, it does not fully correct the deficit
 - Prothrombin complex concentrate (PCC) contains the missing coagulation factors in a small volume and, when given intravenously, immediately replaces the missing factors
4. Therefore when there is a life threatening bleed, we prefer to use PCC
5. Once normal blood clotting is achieved and the bleeding has stopped, the decision and timing to restart anticoagulation depends on the patient, their personal thrombotic risk, type of bleed, and risk of rebleeding

Education into practice

- How would you explain to a patient taking warfarin the benefits and harms of the three agents used to reverse vitamin K antagonists?
- Which agents are used in your department or organisation to reverse warfarin? Does their use adhere to the guidelines presented in this article?
- How can you ensure all patients you see taking warfarin are being assessed regularly for their time in therapeutic range of INR?

How patients were involved in the creation of this article

The executive team of Thrombosis UK (some of whom have taken or are taking warfarin) advised on a summary of the article for patients. Thrombosis UK is a charity aiming to increase awareness of, and improve care and research in, thrombosis.

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Tables

Table 1 | Recommendations from national and international guidelines on urgent reversal of vitamin K antagonists

Guideline and date produced	Stop anticoagulation and check INR	Reversing agent			Comments
		Vitamin K	Prothrombinase complex concentrate (PCC)	Fresh frozen plasma (FFP)	
British Society for Haematology 2012 ²	Yes	5 mg IV	25-50 units/kg of four-factor PCC	FFP produces suboptimal anticoagulation reversal and should only be used if PCC not available	Recombinant factor VIIa is not recommended for emergency anticoagulation reversal
Thrombosis Canada ³	Yes	10 mg in 50 mL of saline IV	Dose of PCC worked out by an algorithm on their website	If PCC unavailable or contraindicated, transfuse FFP 10-15 mL/kg (~3-4 units for adults)	If INR not reported or weight unknown and cannot delay PCC administration, give PCC 2000 units IV and vitamin K 10 mg IV Repeat INR 15 min after PCC infusion. If INR ≤1.5, warfarin reversed. If INR >1.5, consider extra dose of PCC, consider other causes
American College of Chest Physicians antithrombotic guidelines 9th ed 2012 ⁴	Yes	Additional use of vitamin K 5-10 mg by slow IV injection rather than reversal with coagulation factors alone	For patients with major bleeding, rapid reversal of anticoagulation with four-factor PCC rather than with plasma	—	—
Australasian Soc of Thrombosis and Haemostasis guidelines 2013 ⁵	Yes	Vitamin K ₁ 5-10 mg IV	PCC 50 units/kg IV	Plus FFP 150-300 mL. IF PCC unavailable, give FFP 15 mL/kg	In Australia and New Zealand only three-factor PCC is available

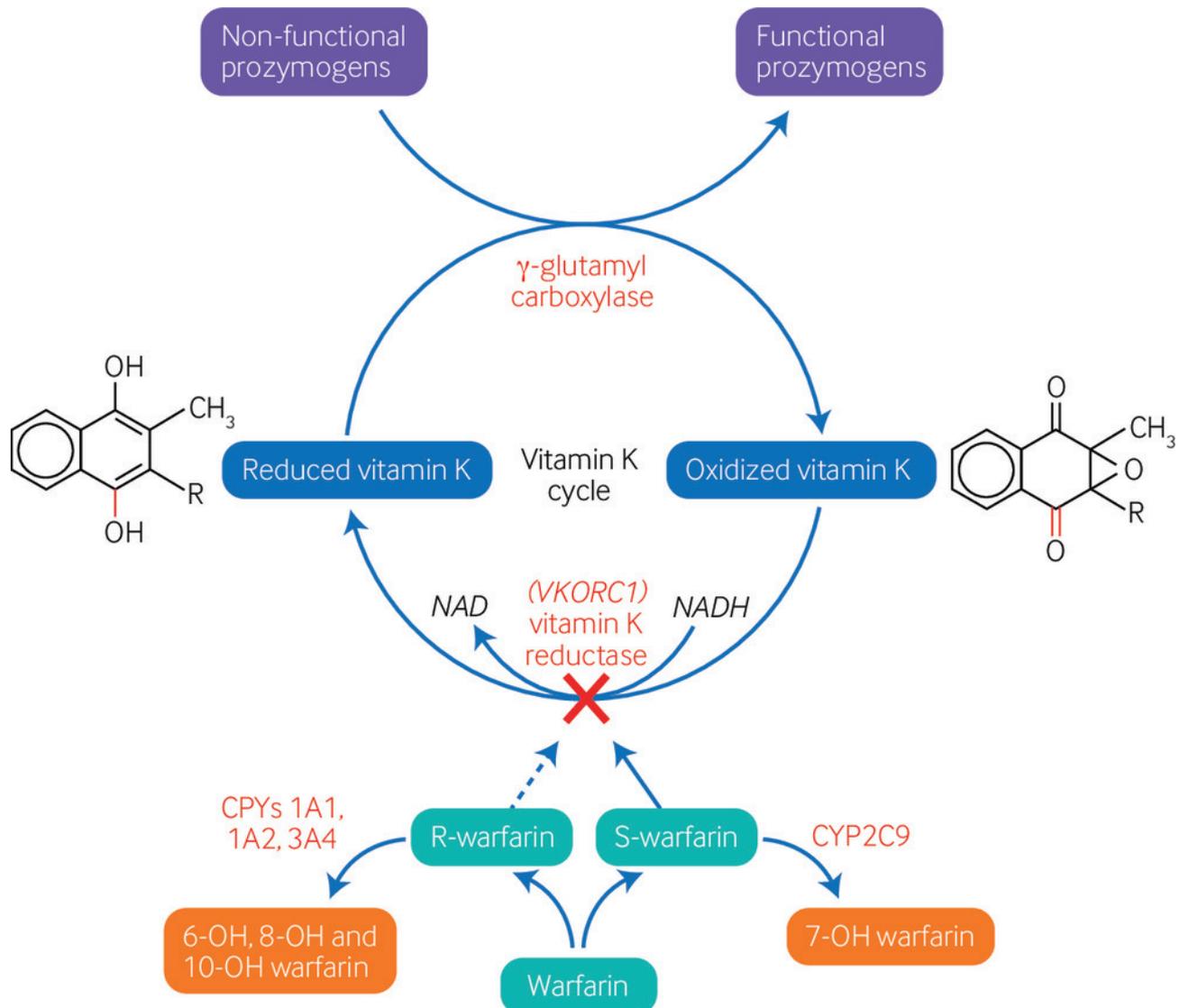
IV = intravenous; INR = international normalised ratio.

Table 2| Details of clinical trials of prothrombin complex concentrate (PCC) versus fresh frozen plasma (FFP) for rapid reversal of vitamin K antagonists

	Sarode et al 2013 ⁹	Goldstein et al 2015 ¹⁰
Trial design	Randomised trial comparing PCC with FFP in patients presenting with major bleeding. Phase IIIb, multicentre, open-label, non-inferiority trial funded by manufacturer	Randomised trial comparing PCC with FFP in patients requiring urgent invasive procedures. Phase IIIb, multicentre, open label, non-inferiority trial funded by manufacturer
Population	202 adult patients (mean age 69 (range 29-96) years) taking warfarin (mean INR 3.9 (range 1.8-39)) with major bleeding (gastrointestinal, intracranial, musculoskeletal, or visible)	168 adult patients (mean age 68 (42-88) years) taking warfarin (mean INR 2.9 (2.0-27)) needing neurosurgical (1%), cardiothoracic (4%), major orthopaedic (21%), or other surgery (57%) or an invasive procedure (17%)
Efficacy		
Effective haemostasis (rated excellent or good)	71 (72%) PCC v 68 (65%) FFP (difference 7.1%, 95% CI -5.8 to 19.9)	78 (90%) PCC v 61 (75%) FFP (difference 14.3%, 2.8 to 25.8)
Rapid INR reduction (INR <1.3 at 30 min after infusion)	61 (62%) PCC v 10 (10%) FFP (difference 52.6%, 95% CI 39.4 to 65.9)	48 (55%) PCC v 8 (10%) FFP (difference 45.3%, 31.9 to 56.4)
Outcome		
Deaths after 45 days	10 (10%) PCC v 5 (5%) FFP (difference 5%, 95% CI -2.4 to 10.4)	3 (3%) PCC v 8 (9%) FFP (difference -5.7%, -14.6 to 2.7)
Safety		
Thromboembolic events	8 (8%) PCC v 7 (6%) FFP (difference 1%, 95% CI -6.1 to 8.2)	6 (7%) PCC v 7 (8%) FFP (difference -1.1%, -10.3 to 8.0)
Fluid overload	5 (5%) PCC v 14 (13%) FFP (difference -8%, 95% CI -16.0 to -0.5)	3 (3%) PCC v 11 (13%) FFP (difference -9.1%, -18.6 to -0.1)

PCC = prothrombin complex concentrate; FFP = fresh frozen plasma; INR = international normalised ratio; CI = confidence interval.

Figures



Coagulation factors II (prothrombin), VII, IX, and X, and the physiological anticoagulant proteins C and S, undergo vitamin K-dependent post-translational carboxylation in the liver before secretion into plasma. This step activates the coagulation factors, giving them the ability to bind to calcium. During carboxylation, vitamin K is oxidised to its inactive form vitamin K epoxide, which is regenerated by the enzyme vitamin K epoxide reductase. Vitamin K antagonists act as competitive inhibitors of the enzyme vitamin K epoxide reductase. Thus “vitamin K antagonists” do not directly antagonise the action of vitamin K but rather the recycling of vitamin K.



Computed tomography of an intracranial haematoma