

Anticoagulation reversal

Vitamin K antagonists and New Oral Anticoagulants

Robert Orman, MD

Warfarin

How does warfarin work?

We know it's a vitamin K antagonist, but what does that mean? What's really getting antagonized?

Let's start with the vitamin K dependent clotting proteins II, VII, IX and X.. They're almost ready to face the world and start clotting blood, but not quite yet. They need vitamin K to reach maturity. Vitamin K is involved in the carboxylation of these proteins, or you can think of it as building them. Vitamin K is then oxidized and becomes inactive, but the body is able to recycle vitamin K. The enzyme *vitamin K epoxide reductase* reactivates vitamin K so it can carboxylate (build) more clotting proteins. Warfarin inhibits this recycling enzyme. Warfarin is called a vitamin K antagonist but it's really not antagonizing vitamin K at all, it just keeps the body from recycling vitamin K and creates a state of **vitamin K depletion**, which leads to factor II, VII, IX, X, protein C and S depletion.

How is warfarin reversed?

Days to reversal: Stop the drug

Of all the options of warfarin reversal, this has the least side effects but is also the slowest.

If no more warfarin is ingested, how long does it take for things to come back to normal?

- 1) The half life of warfarin is 40 hours, so its effect is going to linger even after it's stopped.
- 2) Different clotting factors are going to come back on line at a different rate. Some recover quickly and some at a glacial pace. If your patient is therapeutic, it will probably take a few days for the INR to drop below two and almost a week for it to get to 1. Just as the anticoagulation response to warfarin is variable, so is the response to cessation. It can take days and days and days.

A day to reversal: Give vitamin K

Exogenous vitamin K will bring clotting factors back faster than simply waiting for warfarin effect to wear off. There are misconceptions about vitamin K so let's look at some vitamin K fact and fiction:

1) Subcutaneous vitamin is a reasonable option. Fact or Fiction?

Fiction. Sub Q vitamin K is slower than oral and IV vitamin K and, in some studies, no better than placebo.

The 2012 ACCP guidelines recommend PO or IV vitamin K. Nowhere is sub Q recommended.

2) IV vitamin k can cause an anaphylactoid reaction. Fact or Fiction?

Fact, but it's not really the vitamin K, it's the diluent.

It's not the vitamin K but the diluent (castor oil) that causes the reaction. There is some vagary as to how frequently vitamin K associated anaphylactoid reaction occurs. What we know comes mostly from case reports, but a 2002 retrospective study found an incidence of 3 in 10,000. Giving the IV vitamin K slowly may decrease the likelihood of reaction. There's no evidence that the dose of IV vitamin K dose changes the likelihood of anaphylaxis

To put the 3 in 10,000 number in perspective, that's a similar reaction rate to something we give much more commonly than IV vitamin K: IV contrast.

3) Giving vitamin k can cause warfarin resistance. Fact or Fiction?

Fact. Higher doses of vitamin K may lead to transient warfarin resistance. The low doses used to correct a high INR in a non-bleeding patient, such as 1-2mg, are unlikely to cause resistance. Higher doses, such as 5 or 10 mg that we use in life threatening bleeding to completely reverse INR, are more likely to cause resistance that can last up to 1 - 2 weeks.

4) Vitamin K dosing is a precise science. Fact or Fiction

Fiction. The dosing of vitamin K is an imperfect science at best. There are recommendations from the ACCP regarding how much vitamin K to give for what INR but, even using these guidelines, we will undershoot, overshoot, and sometimes land on the target INR.

Should you use IV or PO vitamin K?

In the bleeding patient, we want to completely reverse the INR and do it quickly. This means high dose IV vitamin K (5-10 mg). There is no evidence to say one dose is more effective than another. I personally use 10 mg because, in the actively bleeding patient, I want to blast the clotting system back into action. There may be more sustained warfarin resistance down the road, but our concern in this patient is dead versus not dead.

If you're not in a hurry, PO is an excellent option. By 24 hours, INR will be the same after administration of low dose IV or PO vitamin K, but IV vitamin K starts working much faster than PO. Oral vitamin K is going to have a slow, steady effect over 24 hours while IV has a more significant impact on INR in the first few hours.

ACCP guidelines What type of vitamin K to give and when to give it

For an elevated INR with no bleeding,

INR just over 3, do nothing and continue regular dosing

INR <10 hold warfarin and restart when INR therapeutic

INR >10 hold warfarin give 1-2.5 mg PO vitamin K

These doses depend on your individual patient's risk factors and can be adjusted accordingly

At our shop, we have a middle ground. For patients with INR of 6 to <10 but high bleeding risk, we give 1-2.5 mg PO vitamin K.

Actively bleeding or potential life threatening bleeding

5-10 mg IV vitamin K and replace clotting factors.

Reversal in minutes: replace clotting factors

A caveat here, and one that gets forgotten from time to time, is that the moment you start replacing clotting factors, either by FFP or PCC, the body starts breaking them down. If you are going to replace clotting factors, you also need to give vitamin K so that the body can resume clotting factor production. Factor replacement is just a bridge until vitamin K starts working.

When we talk about factor replacement, we're generally talking about plasma (FFP) and Prothrombin Complex Concentrate (PCC). FEIBA and rVIIa are also out there, but FFP and PCC are the main players.

FFP versus PCC

FFP comes in 250cc bags and contains all the clotting proteins. It is type specific (must be ABO compatible) and AB is the universal donor. One unit of FFP corrects clotting factors by 2.5-5% in a 70 kg person. Why is 4 units of FFP the usual starting dose? To have a significant change on clotting status, you need to get at least 10% increase in clotting factor levels. Taking the low end of the 2.5% correction per unit of FFP, that's 4 units to get 10%. For extremely high INRs, you will likely need to give more than 4 units, but it's a good starting point.

How can FFP correct the INR or, in other words, *what is the INR of FFP?*

I hear many numbers bandied around: 1.3, 1.5, 1.6 and the answer is it can be any of these. Different donors are going to have different clotting factor levels and their plasma will have varying INRs. There have been a few small studies on this and, at least going by the literature, the lowest you will get an INR from FFP infusion alone is 1.6. The INR of thawed FFP is going to be higher because of clotting factor degradation.

Random fact INR of 1.6 - clotting activity is 30-50% of normal

Prothrombin Complex Concentrate

Four factor PCC (Kcentra) is dosed on the amount of factor IX. Each vial has about 500 units of factor IX.

One vial of PCC also contains factors II, VII, IX, X, Proteins C and S, Antithrombin III and a small amount of heparin.

How much factor is in a vial of PCC versus a unit of FFP?

There is a some variability in how much factor is in each PCC vial but, if you go by factor IX, which is the standard measurement of PCC, each 500 unit vial of 4 factor PCC is the equivalent of 2 units of FFP.

Say you've got an 80 kg sick bleeding patient with an INR of 10.
Recommended reversal doses: 50 IU/kg of PCC and 15cc/kg of FFP

Let's take a look at how much factor each one of those gives us:
15cc/kg FFP = 1200cc which is 1200 units of factor
50 IU/kg of PCC = 4000 units = 8 vials (equivalent of *4 liters of FFP*)

Going by current dosing, to achieve the equivalent amount of factor in 8 vials of PCC, it would take 4 liters, that's 16 bags, of FFP.

FFP is the old standard and PCC is the newer stuff. So which is better?

There has been one trial to date (Circulation 2013) directly comparing PCC and FFP.

Patients: 202 on VKA patients with major bleeding. Half got FFP and half got PCC. Each treatment arm got vitamin K.

Results:

1) PCC corrected INR much faster than FFP. FFP is a slow drip over hours, PCC is a fast drip usually infused over less than an hour, sometimes minutes. Since both FFP and PCC are methods of delivering clotting proteins, it follows that getting in a massive amount of factor in 30 minutes will correct the INR faster than a slow drip of unconcentrated factor over several hours.

2) At 24 hours, INR was similar in both groups. This was probably from the vitamin K effect.

3) No difference in 24 hour hemostasis, except in musculoskeletal bleeds.

4) Death rate the same in both groups

5) Patient oriented outcomes, except death, not studied.

6) Thromboembolic events, which have been a concern with pumping in a hefty dose of clotting factors, were statistically the *same for both groups*: 7.8% PCC and 6.4% FFP. These are sick patients with a predilection for TE events (otherwise, they wouldn't be on VKA) so thromboembolic event is an outcome that is always going to be a grey area.

What we know from the ***PCC safety studies*** is....

Meta-analysis from *Thrombosis and Hemostasis* 2011

Risk of Thromboembolic events (stroke, DVT, MI, PE)

3 factor 0.7%

4 factor 1.8%

Patient outcome with PCC

The INR corrects much faster with PCC compared with FFP, but does this affect patient outcome? The above 2013 Circulation study would suggest not, but our knowledge and research on this is still in its infancy. A recent abstract out of France by Vigue, et al. found that in ICH patients, it makes a difference how fast you reverse. Mortality was cut in half when PCC and Vitamin K reversal were started within 8 hours compared to after 8 hours.

Circulation 2013 Hickey Et al

In a retrospective study of patients given FFP and 4 factor PCC, the PCC group had a *lower rate of transfusion*. Mortality was half in the PCC group but it didn't reach statistical significance.

Comparison of PCC and FFP

1) Rate of administration. **PCC**. Minutes with vs hours with FFP

2) Rate of INR correction. **PCC**. Minutes vs hours. Complete correction versus a best case INR correction of 1.6

3) Time of preparation. **PCC** (not blood group specific and does not need to thaw)

4) Hemostasis. **Tie** so far, but there is growing evidence that PCC may be superior in certain scenarios

5) Risk of pathogenic transmission. **PCC**

6) Risk of TRALI and TACO. **PCC**

7) Cost. Gross cost of PCC is higher than FFP. There was a very strange cost effectiveness study done in the UK that found medical costs were higher for

PCC than FFP, although not by much. The authors concluded that patients given PCC over FFP will live longer and that the extra initial cash payout is worth it. I don't understand how they can say PCC patients will live longer, but they say it. Initial monetary cost is higher for PCC. Kcentra costs \$500 per vial, which comes out to \$4000 to fully reverse an 80 kg patient at 50IU/kg

- 8) Efficacy/Outcome: **Question mark.** There is some observational data that PCC improves some outcome measurements over FFP and an abstract of a large unpublished trial that shows rapid PCC infusion can reduce mortality in ICH patients.

My recommendations in VKA associated life threatening bleeding

Give PCC and vitamin K

If you have no PCC, give FFP

If you have no PCC or FFP, it's all up to vitamin K. Some military physicians asked me what kind of workaround there was for a warfarin bleed in a remote setting. There is no workaround, but if you have IV vitamin K, that starts working within hours, so it's an option. If there's no IV, then give a hefty dose of PO vitamin K, 10 mg, maybe 15 mg, nobody really knows.

Is there still a role for FFP? Yes, if immediate hemostasis isn't needed to save life or brain, or if volume expansion trumps immediate reversal.

What dose of 4 factor PCC to use?

The 2013 FFP vs PCC trial used an INR guided PCC dosing

INR	2 to <4	4-6	>6
IU/KG PCC	25	35	50
mL/kg FFP	10	12	15

There was another trial that looked at low dose (25U/kg) vs higher dose (40U/KG) that found that the more PCC you use (the more factor you replace) the lower the INR corrects and the longer the correction from PCC lasts, but no difference in ICH hematoma volume or outcome.

Other factor replacement options

FEIBA (Factor eight inhibitor bypass activity)

Gets the INR down fast, contains less factor than 4 factor PCC

What's in FEIBA: II, IX, X (inactive) and VII (active form), factor VII coagulation antigen. FEIBA gets a bad rap because of increased incidence of thromboembolic events. I've read up to 5% TE risk, but it may not be so high.

Factor VIIa

rVIIa has rapidly corrected INR in a few small case series. It is very expensive, has a short half life, increased incidence of thrombotic events and, the kicker is, it hasn't been shown to have an impact on bleeding. The American Society of Hematology recommends against using rFVIIa for acute warfarin reversal.

New Oral Anticoagulants

Dabigatran

How it works: Inhibits thrombin.

What we know about reversing dabigatran

1. There is no direct reversal agent
2. In animal studies, PCC given at higher doses improves bleeding time (with the effect lasting at least 2 hours). PCC may not improve laboratory clotting tests (TT, PTT, ECT)
3. Different studies have used different doses 40 IU/kg and 100 IU/kg.
4. Three factor PCC also works but with short lived effect (30 min)
5. FFP is replete with clotting factors, but at nowhere near the concentration of PCC. FFP is probably not going to be effective.
6. There is some animal data supporting the use of Factor VIIa

What we wish we knew

Does giving PCC make a difference in human bleeding or clinical outcome?
If PCC works, what is the optimal dose?

What about dialysis?

You hear that mentioned in hushed whispers, "You can always dialyze it." The cold hard facts on dabigatran dialysis...

Dabigatran is mostly renally cleared and has low protein binding, making it a good candidate for removal by dialysis.

Half life is about 12 hours but will be increased in renal insufficiency

There are case reports of successful removal of dabigatran through hemodialysis in renal insufficiency patients with: an expansile hematoma that required surgical evacuation, post cardiac surgical bleeding, ICH.

Dialyzing dabigatran has been described in case reports but it's logistically challenging and time is of the essence is an exsanguinating patient. Also, placing

a large bore catheter can be risky in an anticoagulated patient. It is also unknown whether it's worthwhile to dialyze a patient with normal renal function and dabigatran associated hemorrhage.

My take on reviewing the literature

1. There are limited options and no direct reversal agents
2. PCC is the most studied but there is no outcome data or published trials on bleeding humans. It probably takes a good wallop to have any effect, so aim high with dosing.
3. In the setting of potentially life threatening bleeding, give 50 IU/kg 4 factor PCC
4. There are case reports of dialyzing patients with renal insufficiency and dabigatran associated bleeding

Under development

Humanized mouse monoclonal antibody fragment

Factor Xa inhibitors Rivaroxaban, Apixaban, Edoxaban

How they work: Bind to and inhibit factor 10a. This prevents factor II (prothrombin) from activating and becoming thrombin

What we know

1. There is no direct reversal agent
2. Rivaroxaban is the most studied oral Xa inhibitor
3. PCC reverses rivaroxaban PT prolongation (unlike dabigatran where PCC has minimal to no effect on coagulation lab tests)
4. Reversal in Animal models
 - a) Higher doses of PCC (50 and 100 IU/kg) reduced ICH expansion in mice. Low dose (25IU/kg) did not change ICH expansion but did improve post ICH neurologic deficits
 - b) In rats, 50 IU/kg but not 25 IU/kg, reduced mesenteric bleeding. FEIBA also effective
 - c) Rabbit study, no PCC effect in reversing very high dose rivaroxaban

It's unknown *which components of PCC* are important in reversing the new anticoagulants. Factor VII is probably involved because when you look at the effect of 3 factor PCC (which has very little factor 7) versus 4 factor PCC (which has a good dose of factor 7) hemostasis is much longer in the 4 factor PCC

group. Administration of Factor 7 has variable effects on new oral anticoagulant bleeding but carries a higher thrombotic risk, is *extremely* expensive and has not had as consistent results as PCC. FEIBA, which is essentially an activated PCC, has also been effective in animal models. (Dose 50 U/kg)

What we wish we knew

Does giving PCC make a difference in human bleeding or clinical outcome?
If PCC works, what is the optimal dose?

Under development

r-antidote (recombinant factor Xa variant) is currently in clinical trials. It has no anticoagulant activity, only a receptor site that can bind the oral Xa inhibitor. What we know so far is that it improves clotting tests and controls bleeding in animals given oral Xa inhibitors (as well as indirect Xa inhibitors like LMWH). What we don't know: dosing, efficacy and safety in humans. This is a potential antidote for oral Xa inhibitors and LMWH.

My take on oral Xa reversal in potentially life threatening bleeding

50 IU/kg four factor PCC.

If you only have FEIBA, then 50 U/kg FEIBA

Caveats on NOAC reversal

1. Do you need to give vitamin K as you would in warfarin reversal? No, vitamin K has no involvement in the mechanism of action of thrombin inhibitors or oral Xa inhibitors
2. PTT can give a qualitative indication of dabigatran activity. A PTT over 40 indicates dabigatran activity but does not give a quantitative measurement of activity as does the INR for warfarin.
3. PT (INR) can give a qualitative indication of oral Xa inhibitor activity. An INR over 1.5 indicates oral Xa activity but does not give a quantitative measurement of activity as INR does for warfarin.

All references for this lecture can be found at www.ercast.org