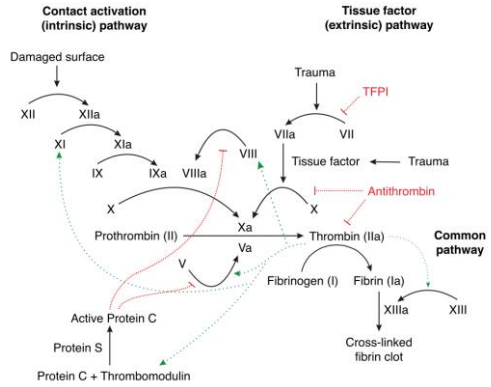
Clinical update no. 525
7 November 2018

Case scenario: 78yr-man falls off ladder at home hitting his head on concrete. He has a headache but obeys commands, though is a little vague. He has an occipital haematoma. He has AF, and had a coronary artery stent 3 months ago for NSTEMI. He takes warfarin/ apixaban/ rivaroxaban/dabigatran (select 1) and aspirin/clopidogrel in combination.

What do you do?

NOACs are no longer novel; DOAC is the current terminology, i.e. **direct** acting.

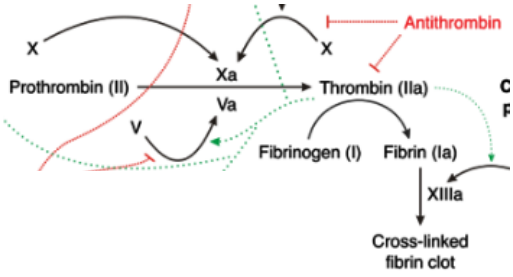


Drug	Mechanism Of Action	Dose
Warfarin *Coumadin®*	Vitamin K antagonist	2-10 mg QDay
Dabigatran *Pradaxa®*	Direct thrombin inhibitor	150 mg BID
Apixaban *Eliquis®*	Direct factor Xa inhibitor	5 mg BID
Rivaroxaban *Xarelto®*	Direct factor Xa inhibitor	20 mg QDay

Warfarin: inactivates factors II, VII, IX, X.

Unfractionated heparin: binds to antithrombin III, and inactivates f. IIa (thrombin) and Xa.

Low MW heparins inhibit predominantly Xa.



The critical steps are focussed on prothrombin (II) and Xa which regulates thrombin (IIa) and fibrinogen -> fibrin, i.e. forming a clot.

Scientific Assembly SAN DIEGO, CA 18

Overall DOACs have a marginally lower rate of major bleeding (annual risk shown):

Drug	Risk[1,2]
Vitamin K Antagonists	**1.5% – 5.2%**
Direct Oral Anticoagulants	**2% - 3%**

The time to spontaneous inactivation without intervention varies, and is longer with reduced eGFR, but approximates as follows:

	Mechanism Of Action	Time To Hemostasis After Stopping
Vitamin K Antagonists (Warfarin)	Inhibition of coagulation Factors II, VII, IX, X	**60-80 hours**
Direct Thrombin Inhibitors (Dabigatran[1])	Direct inhibition of thrombin	**12 hour**
Factor Xa Inhibitors (Apixaban, Rivaroxaban[1], Edoxaban)	Direct inhibition of Factor Xa	**5-10 hour**
Platelet Inhibitors	COX Inhibition ADP Inhibition	**Days**
Unfractionated Heparin (15 KDa)|	Accelerates ATIII inactivation of Factors IIa, Xa	**3-4 hours**
LMW Heparin[1] (4.5 KDa)	Accelerates ATIII inactivation of Factors IIa, Xa	**12-24 hour**
Thrombolytics (Altepase, Tenecteplase)	Plasminogen activation that induces fibrinolysis	**24 hour**

Reversal with intervention is as follows:

	Antidote(s)	Time To Reversal
Vitamin K antagonists (Warfarin)	Vitamin K	**12-16 hours**
	FFP	**2-6 hours**
	4-Factor PCC	**Immediate**
Direct Thrombin Inhibitors (Dabigatran)	Idarucizamab	**Immediate**
Factor Xa inhibitors (Apixaban, Rivaroxaban, Edoxaban)	Andexanet alfa	**Immediate**
	4-Factor PCC?	**Conflicting Data**
Platelet Inhibitors	Platelets, *dd*AVP	**2-4 hours**
Unfractionated Heparin	Protamine	**Immediate**
LMW Heparin	Protamine	**Fast but only partial reversal**
Thrombolytic Therapy (Alteplase, Tenecteplase)	Cryoprecipitate	**2-4 Hours**

Of note, a recently FDA approved reversal for oral Xa inhibitors is effective but hugely expensive, and not available in Australia.

Consensus Guidelines as follows:

"Guidelines for Reversal of Antithrombotics in Intracranial Hemorrhage."

A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine.

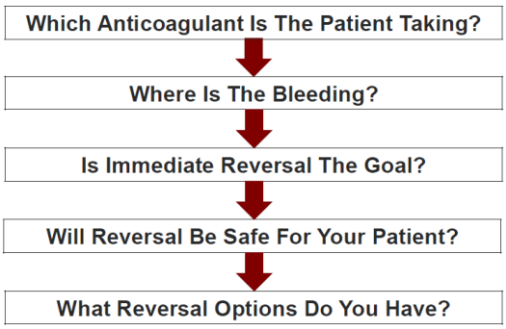
Frontera JA. ***Neurocritical Care*** 2016; 24:6-46.

EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

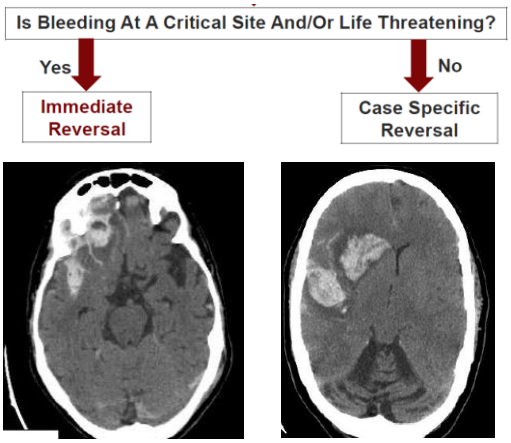
Tomaselli GF. ***J Am College Cardiology*** 2017; 70:3042-63.

Key considerations in reversal are as follows:



An unconscious patient with a head bleed won't be able to say if they are taking warfarin or a DOAC. Check INR (warfarin) and APTT (elevated if taking DOACs) if any doubt.

CNS bleeds can progress and require immediate reversal. If taking warfarin, don't wait for the INR before reversing if otherwise indicated. Similarly for other major bleeds or haemodynamic instability. Otherwise can pause to think.



Initial CT 3hr later without reversal

Rapid reversal reduces haematoma expansion and improves outcome.

Guidelines

An update of consensus guidelines for warfarin reversal

1 MJA 198 (4) · 4 March 2013

Warfarin reversal is not controversial. Note that he US has 4 factor PCCs, whereas in Australia it just replaces f II, IX, X.

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

The NEW ENGLAND JOURNAL of MEDICINE

Dabigatran can be effectively reversed.

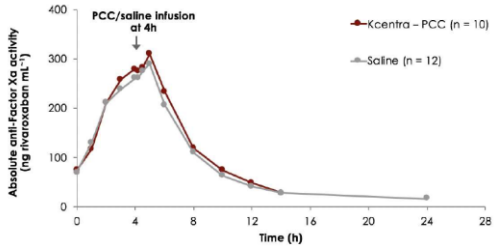
Recommendations For Factor Xa Inhibitor Reversal
Discontinue Factor Xa inhibitor
Pharmacologic reversal should be guided by bleeding (major or intracranial) and not laboratory findings
Administer **50 grams of activated charcoal** to intubated ICH patients who present within 2 hours of the last dose
Administer **4-Factor PCC** (50 U/kg) if the patient presents within 3-5 terminal half-lives of the drug exposure

Journal of Thrombosis and Haemostasis, 13 (Suppl. 1): S187–S194 DOI: 10.1111/jth.12949

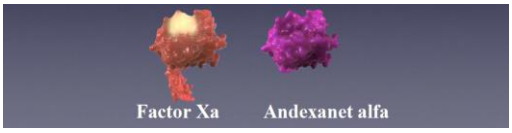
INVITED REVIEW

Reversal of oral factor Xa inhibitors by prothrombin complex concentrates: a re-appraisal

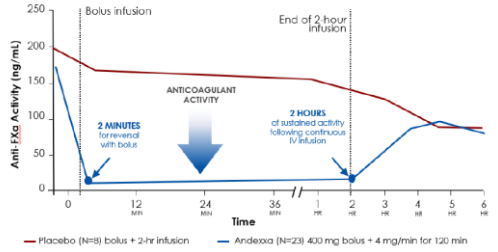
Reversal of apixaban and rivaroxaban is problematic. PCCs are recommended. The question is whether it is effective.



No point spoiling good Guidelines with evidence, but PCCs do not alter Xa activity.



Andexanet alfa is a specific reversal agent – Xa DOACs bind to it rather than to f. Xa, but only for as long as the infusion is running.



NEJM 2015; 373:2413-

Recommendations For Antiplatelet Reversal
Discontinue antiplatelet agent
Recommend against platelet transfusion for patient who will not undergo a neurosurgical procedure
Recommend **platelet transfusion** for patients who will undergo a neurosurgical procedure

Giving platelets for ICH if on aspirin/ clopidogrel/other gives *worse outcomes.* Be guided by neurosurgery if need a procedure.

A single dose of desmopressin (**DDAVP** 0.4 mcg/kg IV) is recommended

Desmopressin (DDAVP) augments platelet adhesion– discuss with haematology.

These updates are a review of current literature at the time of writing. They do not replace local treatment protocols and policy. Treating doctors are individually responsible for following standard of care.