

Anticoagulant reversal in ICH

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Presenter



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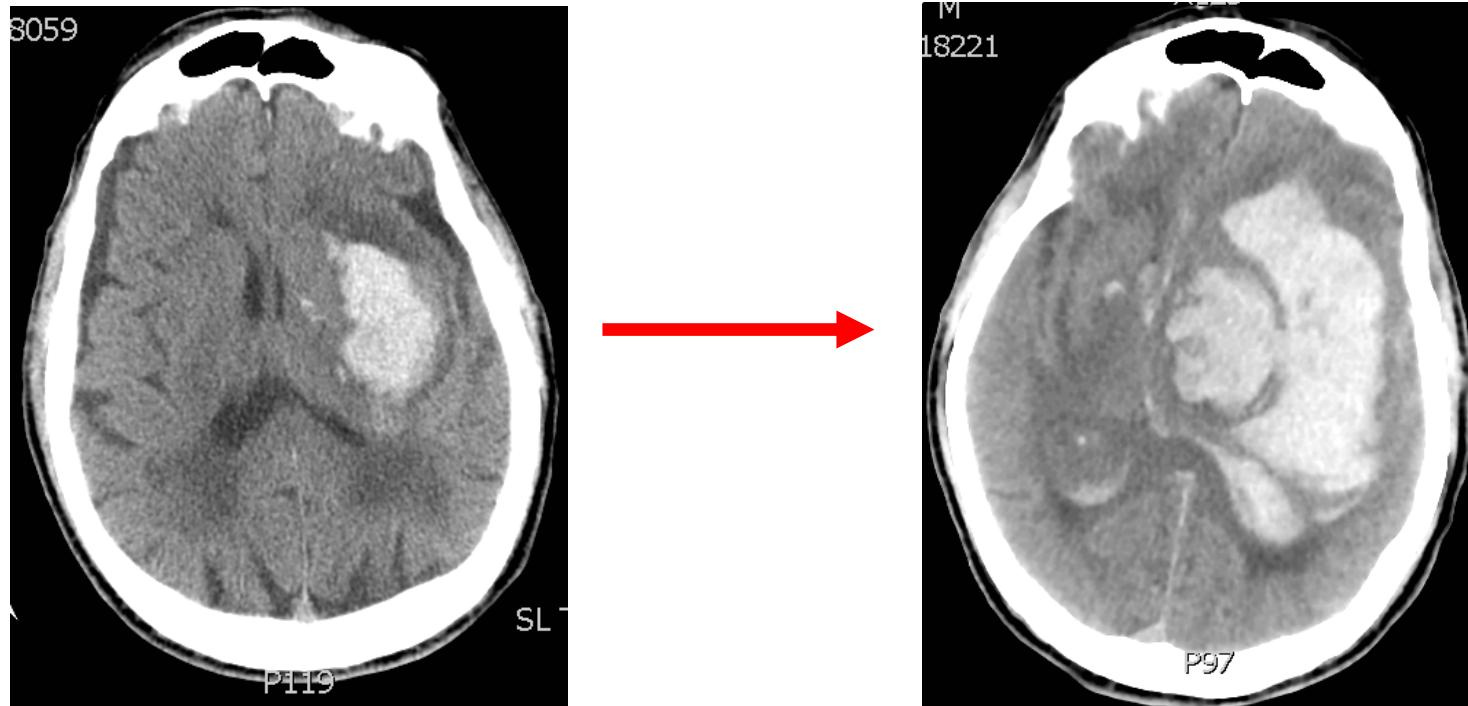
Outline

- Warfarin Reversal
- Dabigatran Reversal
- Factor Xa Inhibitor Reversal (including Rivaroxaban and Apixaban)
- Antiplatelet Reversal

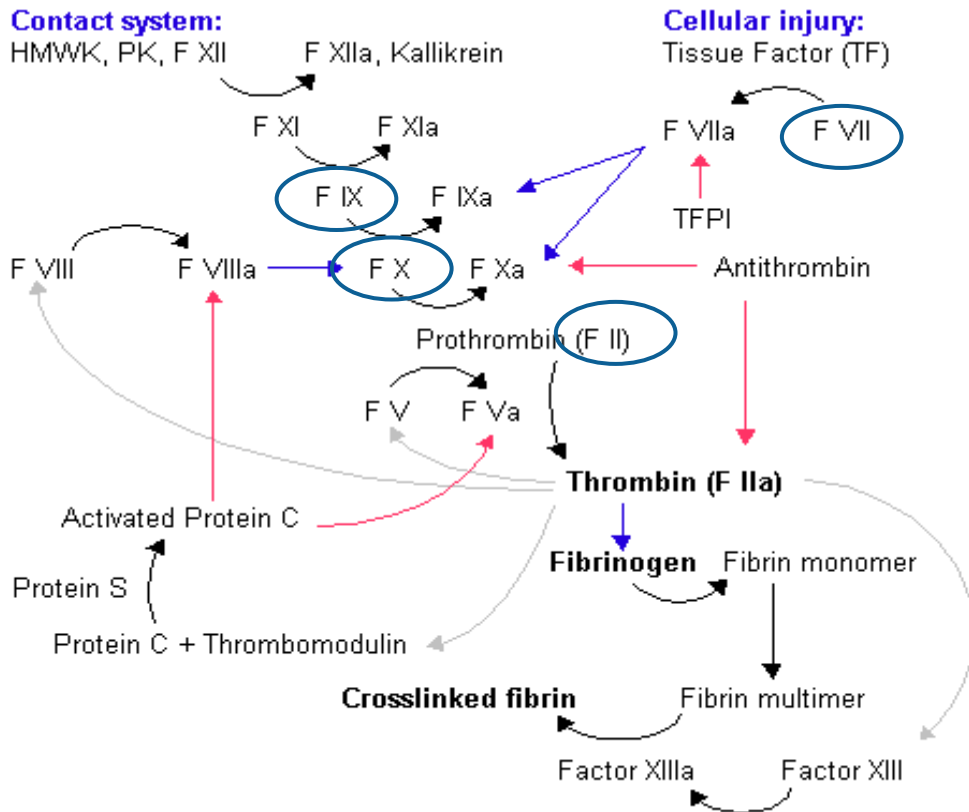


Introduction

- Goal of anticoagulation reversal: Lower the risk of ICH expansion



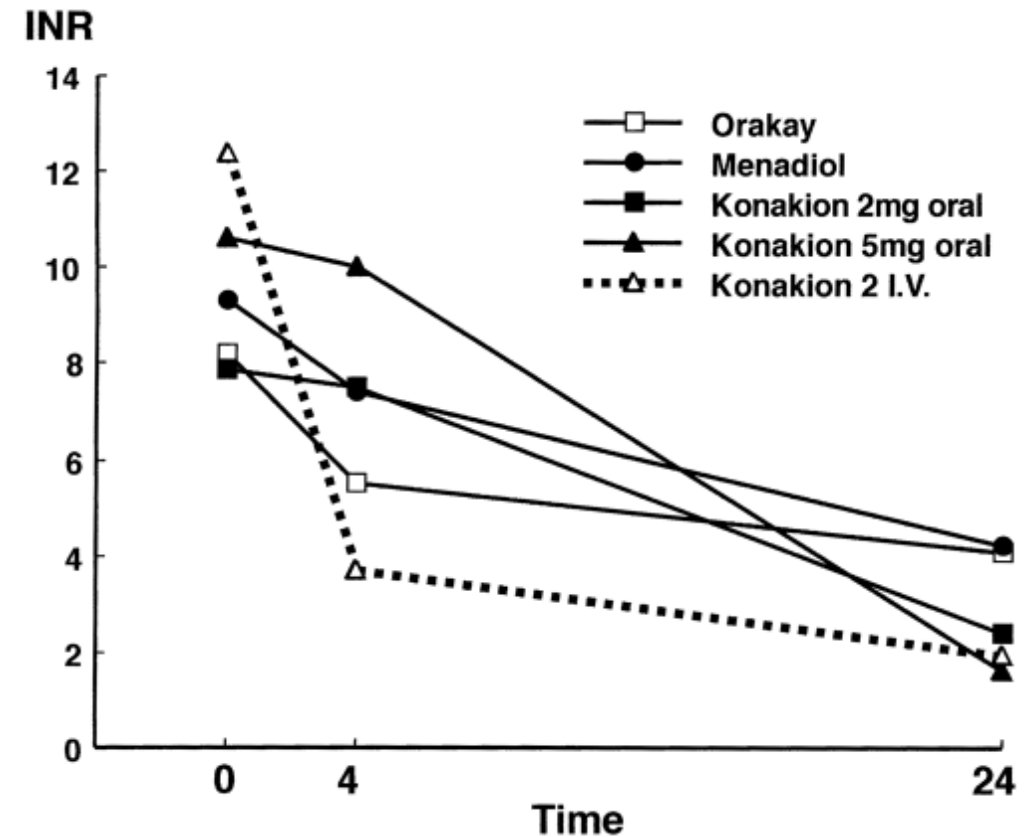
Warfarin



- Vitamin K antagonist
- Vitamin K is required for carboxylation of factors II, VII, IX, and X
- Warfarin therefore prevents the *synthesis* of biologically active factors

Warfarin (Coumadin)

- Patients **do not have enough** of Factors II, VII, IX, and X. We just need to give them back.
- Intravenous vitamin K lets them make their own!
- It has some effect as early as 4-6 hours, but full effect can take 24 hours.
- Until then, we need to deliver the 4 clotting factors!



FFP (Plasma)

- Donated blood is split into:
 - ▶ PRBCS (packed red blood cells)
 - ▶ Platelets
 - ▶ Plasma
 - ▶ Plasma is then “Fresh Frozen”
 - ▶ It contains ALL the coagulation factors!!!
 - ▶ (Including the 4 that are missing in warfarin patients)
 - ▶ Costs \$200-\$400 for 4 units



PCC (Prothrombin Complex Concentrate)

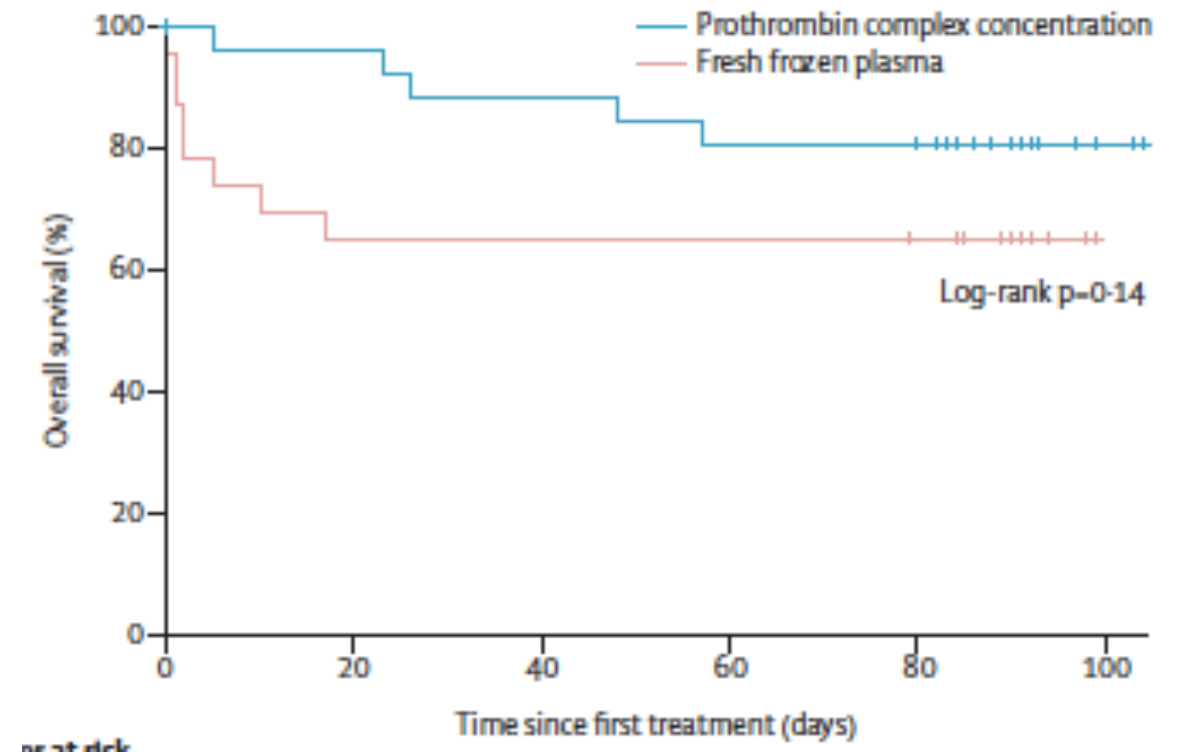
- The major one available in the US is “Kcentra”
- A concentrate of the 4 coagulation factors (Factor II, VII, IX, X, plus protein C, S, and some heparin)
- No type/screening necessary
- Infuse in <20 minutes
- *RAPID INR correction*
- Can cost \$2000-\$5000



500 unit range for use with 20 mL vial
of Sterile Water for Injection, USP

PCC vs. FFP for ICH

- There have been a few randomized trials of PCC.
- In the INCH trial, 54 patients with warfarin-ICH were randomized to PCC vs. FFP.
- PCC showed faster INR reversal, less ICH expansion, and a nonsignificant trend towards lower mortality.



Steiner T. et al, Lancet Neurology April 2016

PCC Dosing

- Standard dosing is based on weight and INR

Pre-treatment INR	2–< 4	4–6	> 6
Dose* of Kcentra (units† of Factor IX) / kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

- However, many hospitals use an initial fixed dose (1000-1500 units)
 - ▶ Easy to calculate, more rapid delivery, often lower cost, and is effective for many patients.

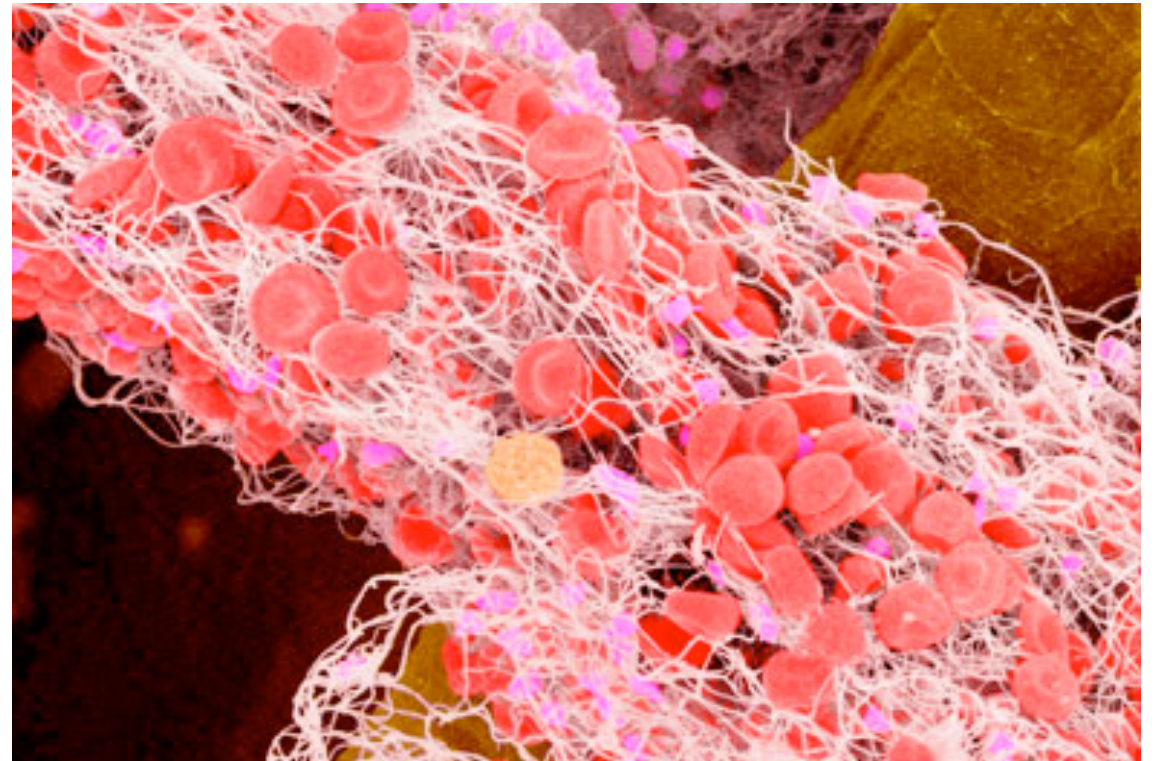
Warfarin reversal

- For ICH with elevated INR (over 2.0):
- Treat with IV Vitamin K and PCC if available.
- If PCC is not available:
 - ▶ IV vitamin K and FFP.

Question

Direct Oral Anticoagulants

- Factor IIa Inhibitor: Dabigatran
- Factor Xa Inhibitors: Rivaroxaban, Apixaban, Edoxaban
- How to reverse these?



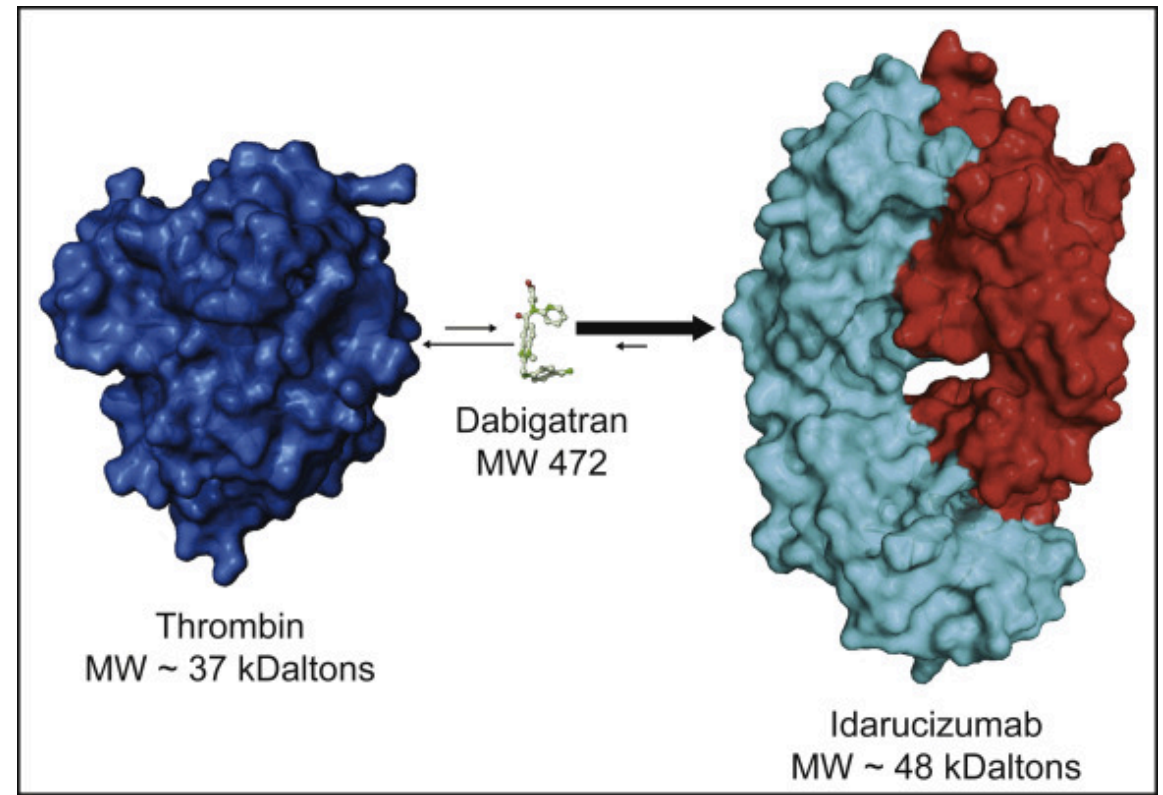
Time can be a reversal agent!

- Half life in healthy subjects:
 - ▶ Rivaroxaban: 5-9 hours
 - ▶ Dabigatran: 7-9 hours
 - ▶ Apixaban: 12 hours
 - ▶ Edoxaban: 10-14 hours
 - ▶ **Warfarin: 40 hours**

- *N.B. These times are longer with older age, renal insufficiency*

Dabigatran (Pradaxa) reversal

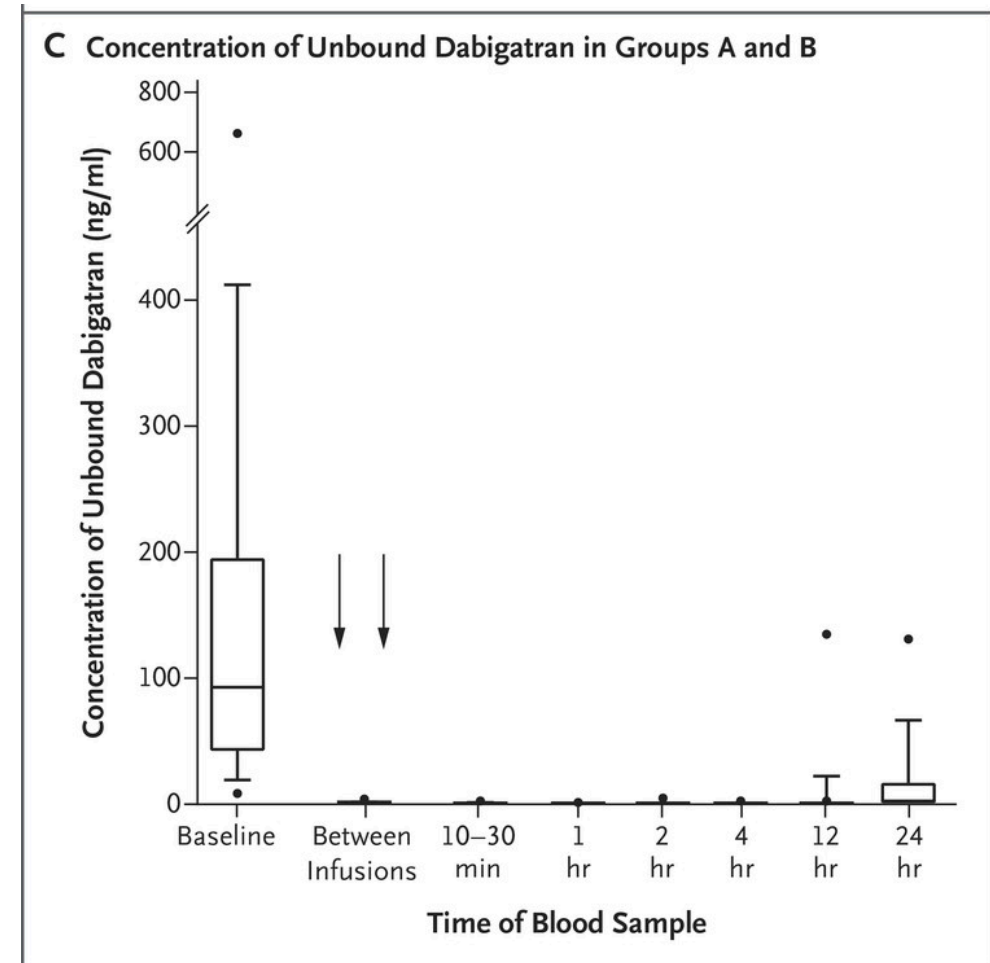
- Idarucizumab (Praxbind)
 - ▶ Monoclonal antibody – binds dabigatran
 - ▶ 2 IV boluses, given 15 minutes apart
- Some use PCC for this purpose
 - ▶ PCC contains Factor II
 - ▶ Goal is to give “extra” Factor II



Dabigatran reversal

- Single arm trial (no comparison arm)
- Reversal is rapid, and lasts at least 24 hours.
- Cost: Approx. \$3500

- 90-day mortality: 19%
- 90-day thrombo-embolism: 6.8%



Dabigatran reversal

- Time as a reversal agent
 - ▶ Can the patient wait?
- Idarucizumab is a specific reversal agent
- PCC is often used off label as a nonspecific reversal agent
 - ▶ (no clinical trials of this)

Question

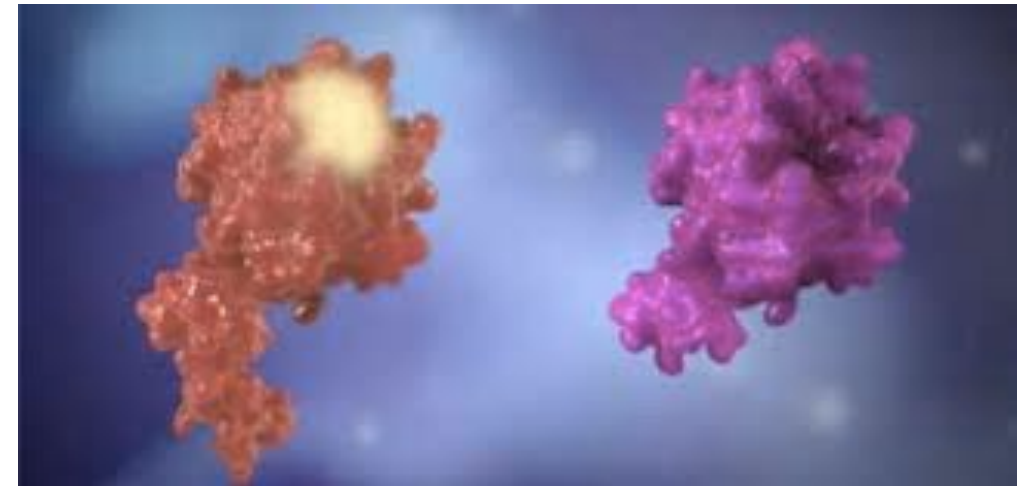
Factor Xa inhibitor reversal

- How to check if the patient is “anticoagulated?”
 - ▶ Laboratory test: Anti-Xa level (not widely available quickly)
 - ▶ PT/PTT can be false negative up to 44% of the time

Rivaroxaban/Apixaban reversal

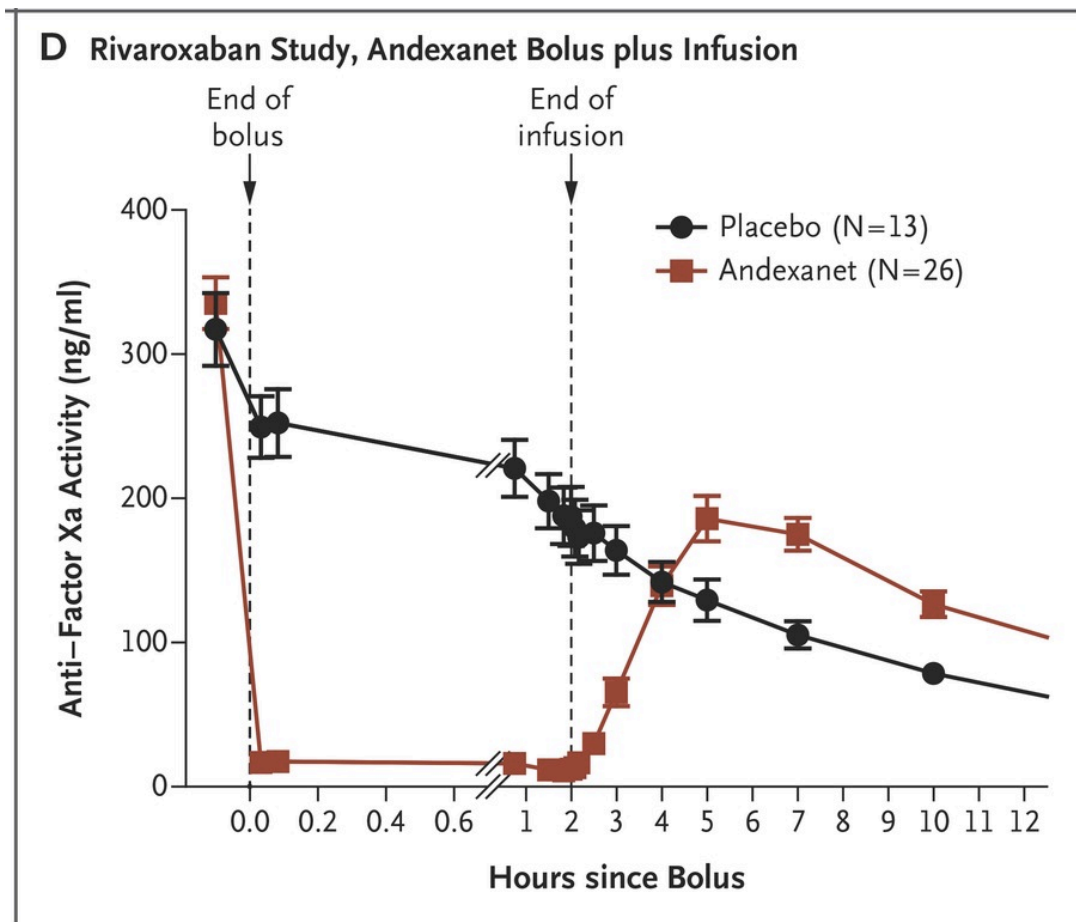
- Andexanet (Annexa)
 - ▶ Monoclonal antibody – binds Factor Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban). It binds low molecular weight heparins (enoxaparin) as well.
 - ▶ IV bolus then 2 hour infusion
- Some use PCC for this purpose
 - ▶ PCC contains Factor X
 - ▶ Goal is to give “extra” Factor X

Factor Xa



Andexanet

Andexanet – Rivaroxaban/apixaban reversal

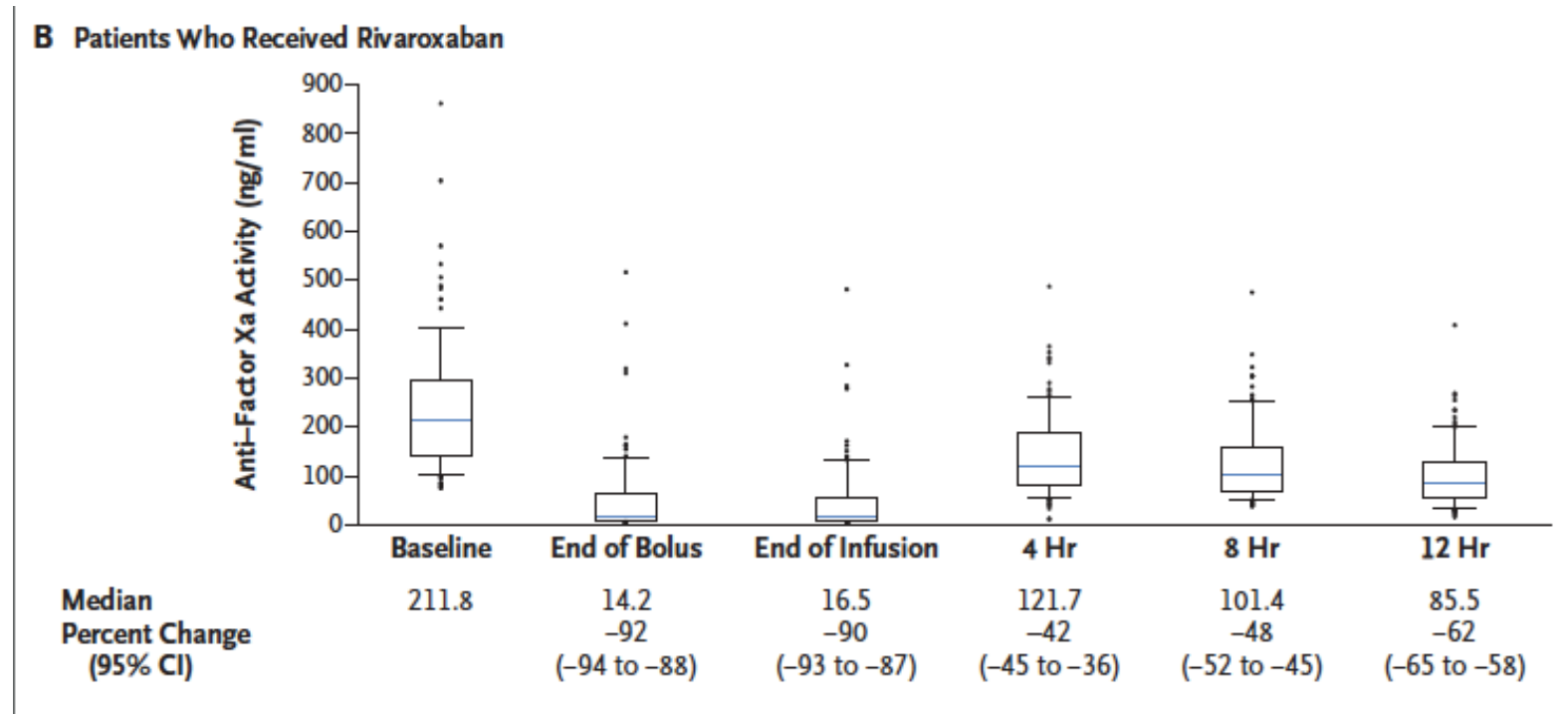


Randomized trial in healthy volunteers

Siegel DM et al, NEJM 2015

Andexanet

- Single arm trial (no comparison arm)
- Reversal is rapid:
 - ▶ Complete during 2 hour infusion
 - ▶ Then, between 4-5 hours, anti-Fxa activity rises (still below baseline).
 - ▶ Cost: Between \$26,000-\$58,000
- 90-day mortality: 14%
- 90-day thrombo-embolism: 10%



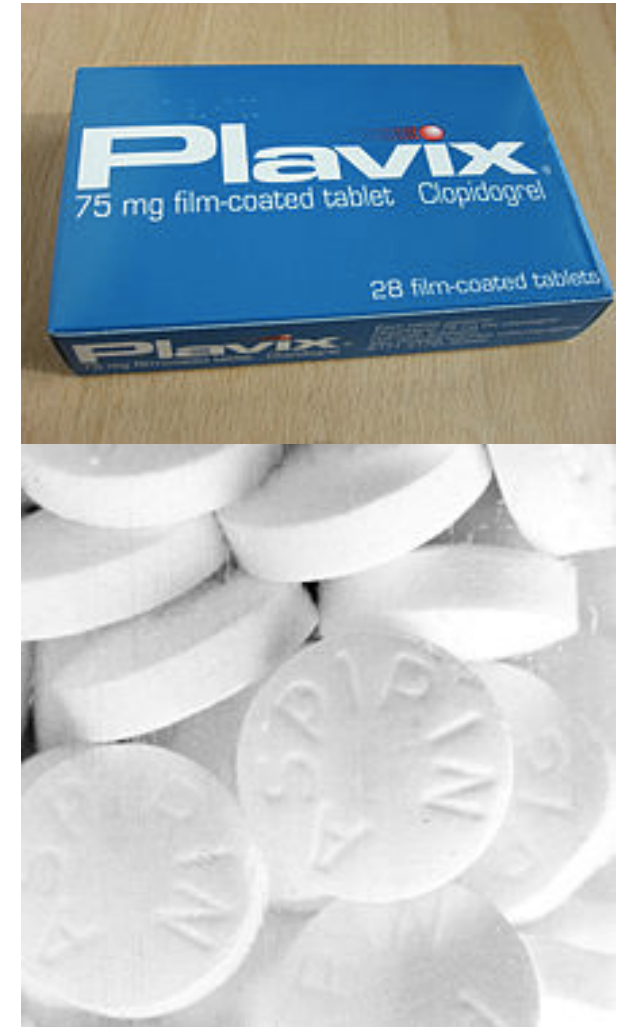
Question

Guidelines:

- Neurocritical Care Society (NCS):
 - ▶ Give 4F-PCC (50U/kg) or FEIBA if ICH occurred within 3-5 half lives of drug
- ENLS (Emergency Neurologic Life Support, from NCS)
 - ▶ Andexanet as first line agent, PCC as second line
- American Heart Association:
 - ▶ FEIBA, other PCCs, or rFVIIa might be considered
- American College of Chest Physicians:
 - ▶ Use specific reversal agents where available, rather than nonspecific agents.

Antiplatelet agents

- Most common agents in the US are aspirin and clopidogrel (Plavix).
- These are platelet inhibitors. They circulate and **BLOCK** platelet activity
 - ▶ Patients still have plenty of platelets in their bodies!
- Can platelet transfusion help?
 - ▶ Goal: Give extra platelets, hopefully override these drugs.
 - ▶ Does this work? Or are we just giving extra platelets to be blocked?



Antiplatelet agents

- PATCH trial: Randomized 190 ICH patients to platelet transfusion or not.
- Platelet transfusion led to significantly WORSE outcome!

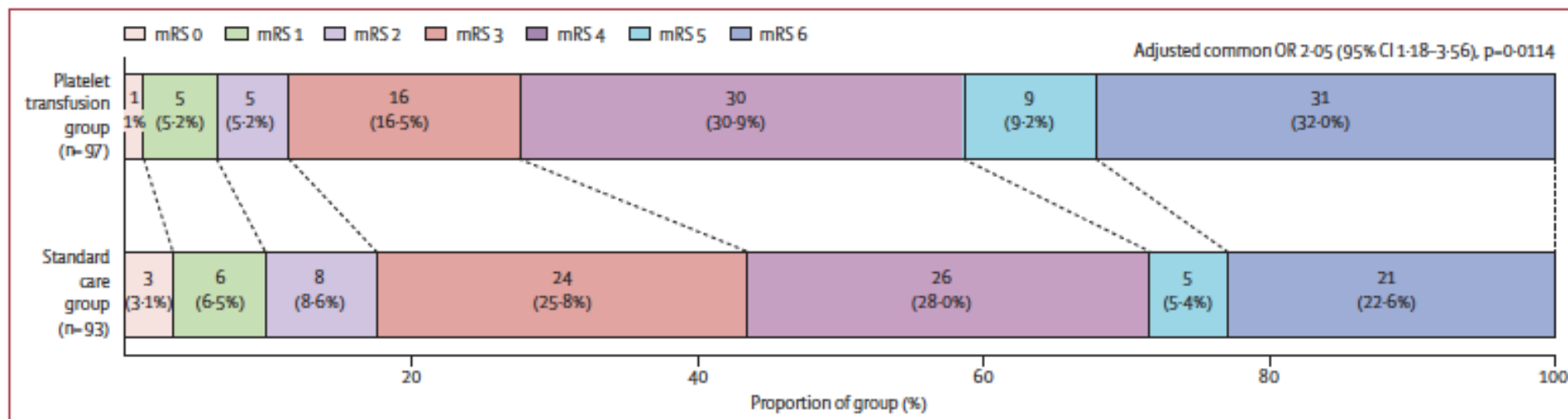


Figure 2: Distribution of mRS score at 3 months
mRS=modified Rankin Scale. OR=odds ratio.

Conclusion: Do not transfuse platelets

Is there anything to reverse in antiplatelet-ICH?

- It may be that there is no currently effective way to “reverse” antiplatelets.
- Some authors check platelet activity – this is not easy to do at many hospitals.
 - ▶ Consider platelet activation assays or TEG to guide therapy if available.
- Observational study:
 - ▶ GWTG analysis of 82,000 ICH patients, examining whether antiplatelet use was associated with outcome
 - ▶ Those on single antiplatelet - no difference in outcome compared to those on no antiplatelet.
 - ▶ Those on dual antiplatelet regimens, however, had worse outcomes.
 - ▶ **Conclusion: Perhaps only those on dual antiplatelet regimens “need” reversal.**

Conclusions

- Warfarin reversal
 - ▶ IV vitamin K plus PCC
- Dabigatran reversal
 - ▶ Idarucizumab – specific agent
 - ▶ PCC – nonspecific agent
- Factor Xa inhibitor reversal
 - ▶ Andexanet – specific agent
 - ▶ PCC – nonspecific agent
- Antiplatelet reversal
 - ▶ No current clear “reversal” agent

Question

Thank You