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Reversal of anticoagulation

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Laurence Torsher. 11-й Британо-Український Симпозіум. Київ, 2019





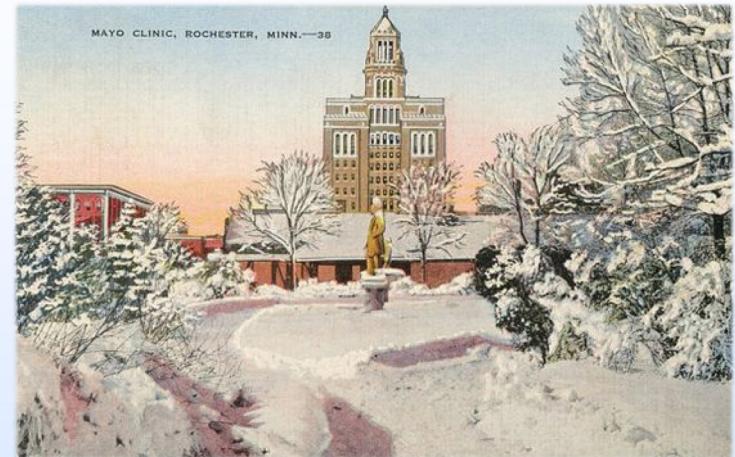
Disclosure Summary

- I have no financial connections to disclose





Mayo Clinic Rochester



Downtown Campus



Saint Marys Campus





A case

- 72 year old man has fallen and has symptomatic epidural hematoma
- Neurosurgery feel they need to drain epidural
- P_{Hx}:
 - Chronic atrial fibrillation
 - Anticoagulated for stroke prophylaxis
 - Stable coronary artery disease
 - Hypertension
 - Transient ischemic attack (TIA) 5 years ago





Neurosurgeon says...

- I am concerned the bleed is expanding. We need to go immediately.
- What to do about his anticoagulation?





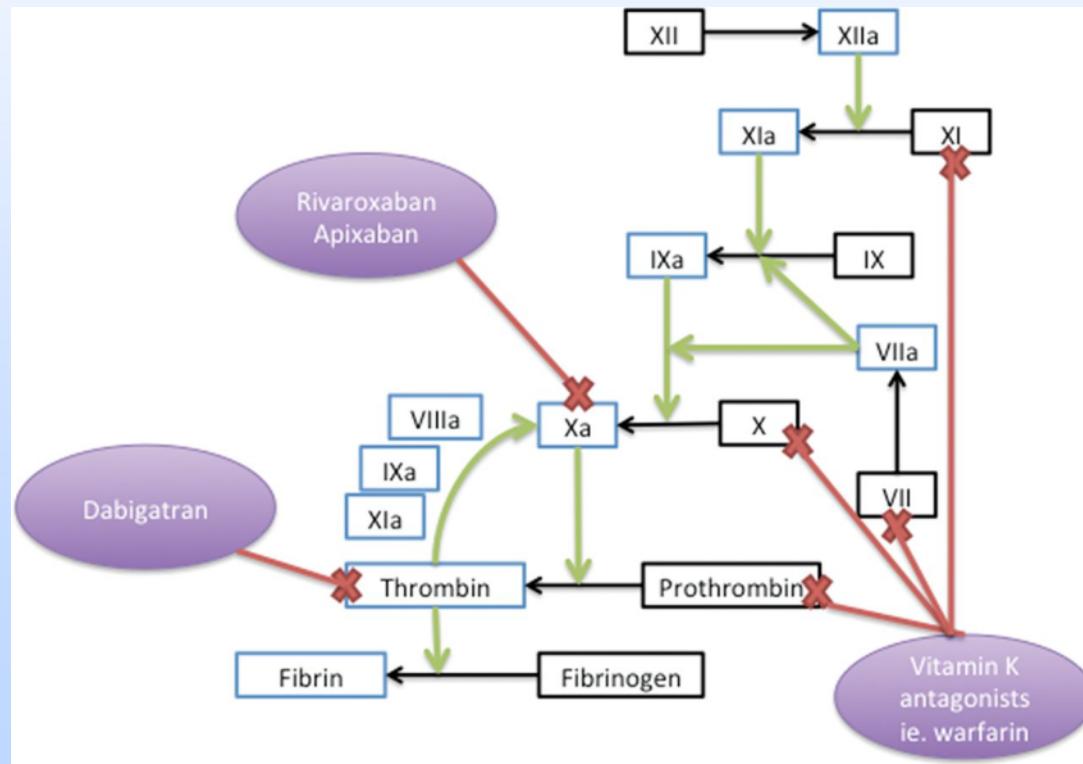
Anticoagulation

- Options
 - Warfarin (Coumadin)
 - Dabigatran (Pradaxa)
 - Apixaban (Eliquis)
 - Rivaroxaban (Xarelto)
 - Other Factor Xa inhibitors



Warfarin

- Vitamin K antagonist
 - Block Vitamin K dependent clotting factors



Postgrad Med J 2014;



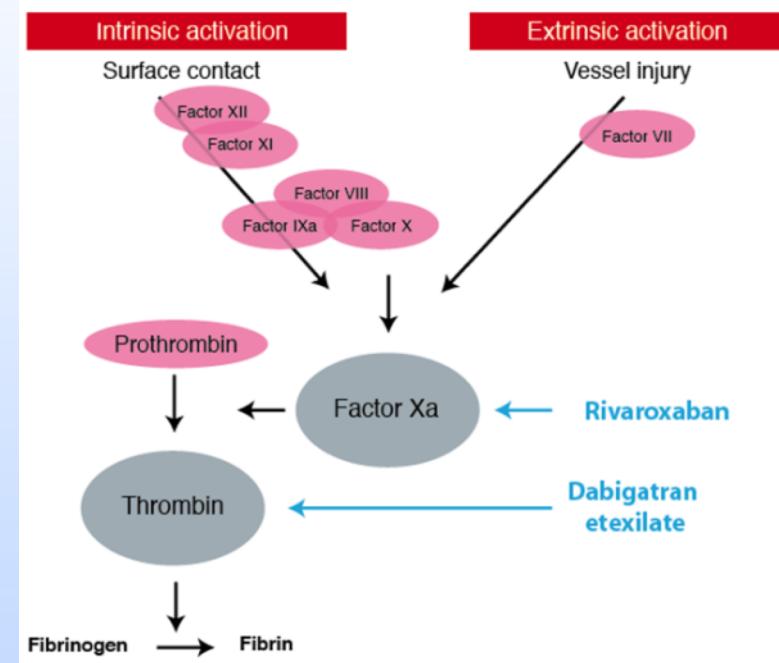
Warfarin

- How do I reverse it?
 1. Stop warfarin – 3-5 days recovery
 2. Vitamin K (p.o. or i.v.) – 24-48 hours
 - Slow but cheap and no blood product exposure
 3. Fresh frozen plasma (FFP) & vitamin K
 - Rapid and time proven
 - May not be as effective or predictable as we thought
 4. Prothrombin complex concentrates (PCC)
 - 3 component may require supplementation
 - 4 component has all vitamin K dependent factors
 - Fast
 - More efficacious than FFP
 - No blood products and minimal volume
 - ?cost?



Dabigatran (Pradaxa)

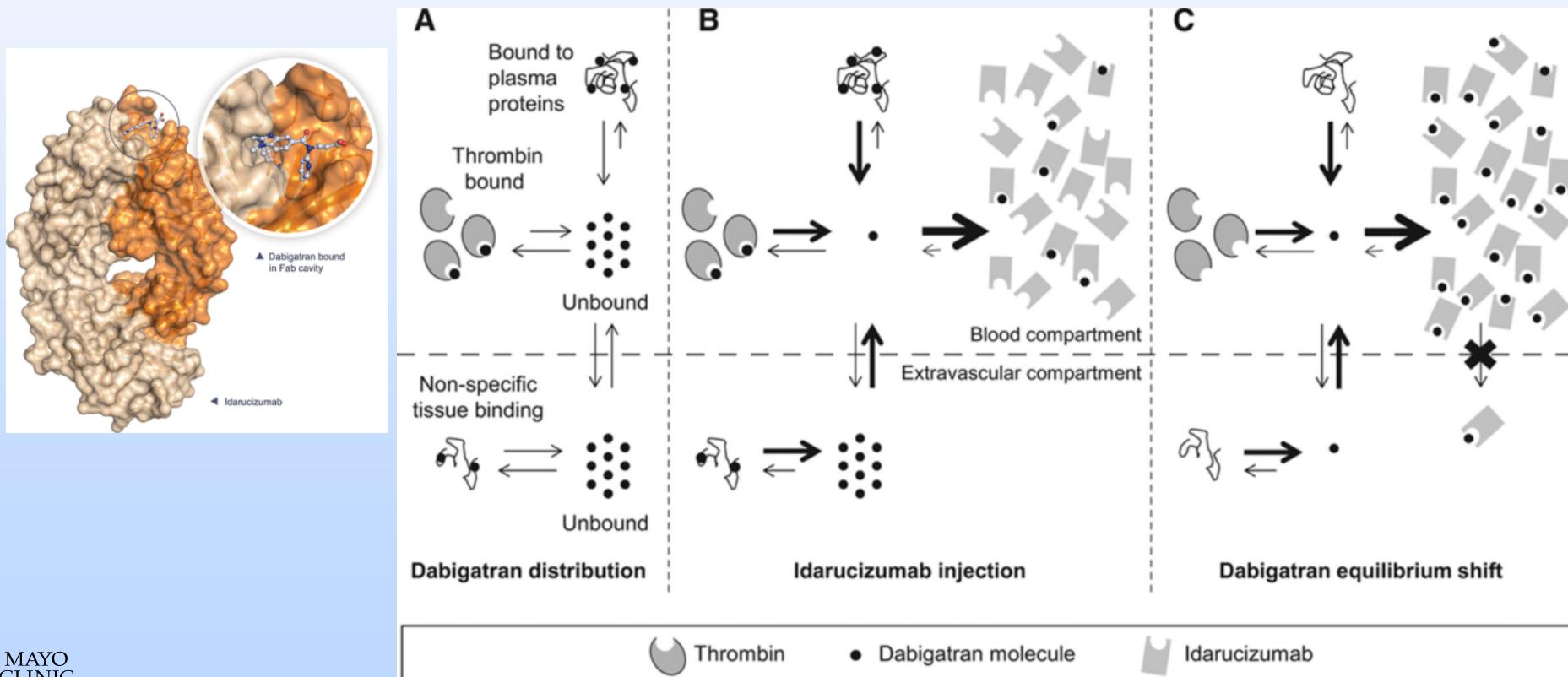
- Oral direct thrombin inhibitor
- As safe as warfarin but more convenient and predictable dosing and no need for INR assessments
- No easy assay for degree of anticoagulation
 - INR, PTT are not helpful.
 - Thrombin time and TEG/ROTEM may be helpful
- Until recently reverse by holding for ~3 days or dialysis





Idarucizumab (Praxbind)

- Dabigatran reversal
- Monoclonal antibody to dabigatran





Idarucizumab (Praxbind) - 2

- 503 patients taking dabigatran who were either bleeding or emergently needed an invasive procedure
- 5 g IV idarucizumab
- laboratory and clinical assays

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal —
Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D.,

NEJM 2017;377: 431-41



Idarucizumab (Praxbind) - 3

- reversed dabigatran effects by laboratory assay (TT, ecarin clotting time, [unbound dabigatran])
- clinically
 - Cessation of spontaneous bleeding
 - Normal hemostasis during procedure in 93%
 - No serious adverse effects
- Reversal was rapid (<1hr)
 - Independent of age, sex, renal function or dabigatran concentration at initiation of therapy
- Effect persisted out to 24 hours in most patients
- Thrombotic events in 24 of 503 patients within 30 days



I don't have idarucizumab?!?

- PCC may be as effective
 - At least in an animal model

CRITICAL CARE MEDICINE

Reversing Dabigatran Anticoagulation with Prothrombin Complex Concentrate versus Idarucizumab as Part of Multimodal Hemostatic Intervention in an Animal Model of Polytrauma

Markus Honickel, M.D., Till Braunschweig, M.D., Rolf Rossaint, M.D., Christian Stoppe, M.D., Hugo ten Cate, M.D., Ph.D., Oliver Grottke, M.D., Ph.D.

ABSTRACT

Background: Although idarucizumab is the preferred treatment for urgent dabigatran reversal, it is not always available. Prothrombin complex concentrate (PCC) may be an alternative and, with bleeding in trauma, additional hemostatic therapy may be required. The authors investigated multimodal treatment in a preclinical polytrauma model.

Methods: Dabigatran etexilate (30 mg/kg twice daily) was given orally to 45 male pigs for 3 days. On day 4, animals received a dabigatran infusion before blunt liver injury and bilateral femur fractures. After injury, animals were randomized 1:1:1:1 to receive placebo (control), tranexamic acid (TXA; 20 mg/kg) plus human fibrinogen concentrate (FCH; 80 mg/kg) (TXA-FCH group), PCC (25 U/kg or 50 U/kg) plus TXA plus FCH (PCC25 and PCC50 groups), or 60 mg/kg idarucizumab (IDA) plus TXA plus FCH (IDA group). Animals were monitored for 240 min after trauma, or until death.

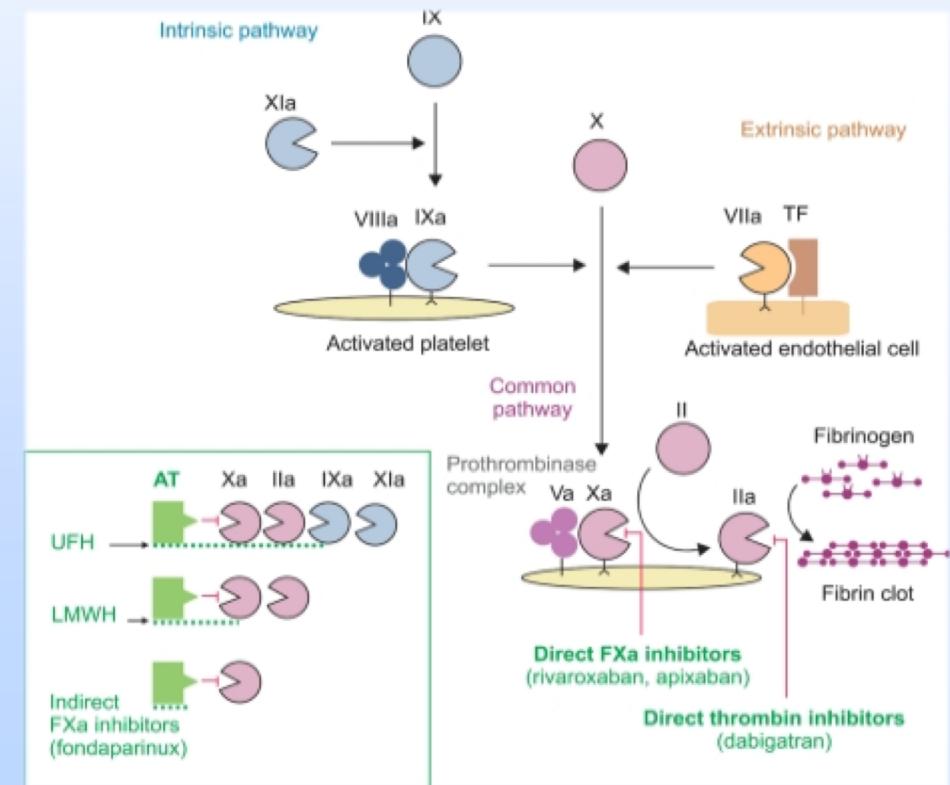
Results: The degree of injury was similar in all animals before intervention. Control and TXA-FCH animals had the highest total postinjury blood loss ($3,652 \pm 601$ and $3,497 \pm 418$ ml) and 100% mortality (mean survival time 96 and 109 min). Blood loss was significantly lower in the PCC50 ($1,367 \pm 273$ ml) and IDA (986 ± 144 ml) groups, with 100% survival. Thrombin-antithrombin levels and thrombin generation were significantly elevated in the PCC50 group.

Conclusions: Idarucizumab may be considered the optimal treatment for emergency reversal of dabigatran anticoagulation. However, this study suggests that PCC may be similarly effective as idarucizumab and could therefore be valuable when idarucizumab is unavailable. (*ANESTHESIOLOGY* 2017; 127:852-61)



Rivaroxaban (Xarelto) or Apixaban (Eliquis)

- Direct factor Xa inhibitor blocking enzymatic function of Xa that would normally convert prothrombin (II) to thrombin(IIa)
- Easier dosing
- INRs not needed





Xa inhibitor reversal in emergency

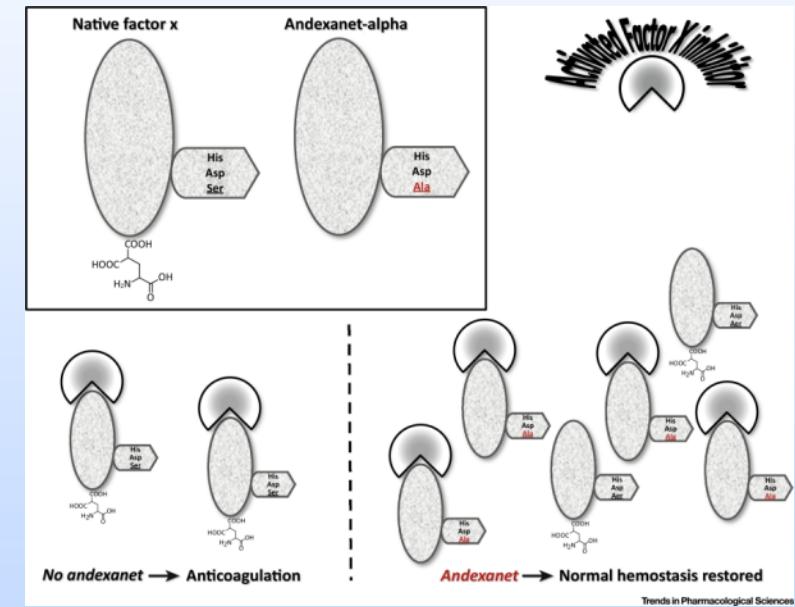
- Hold medication
 - 2-3 days depending on drug and renal function
 - Monitor effect by anti-Xa level
- PCC (4 factor) may help
- On the horizon....





Adexanet alfa

- Modified recombinant Xa **without** procoagulant activity
- Binds Xa inhibitors acting as a “decoy protein”
- Works for any Xa mediated drug
 - Rivaroxaban
 - Apixaban
 - Edoxaban
 - Betrixaban
 - LMWH
 - fondaparinux





Does it really work?

- 67 patients with major bleeding who had received either apixaban or rivaroxaban within 18 hours
- All received andexanet bolus followed by 2 hour infusion
- They had lab evaluation as well as clinical evaluation of the effect of the drug as well as 30 day follow-up

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

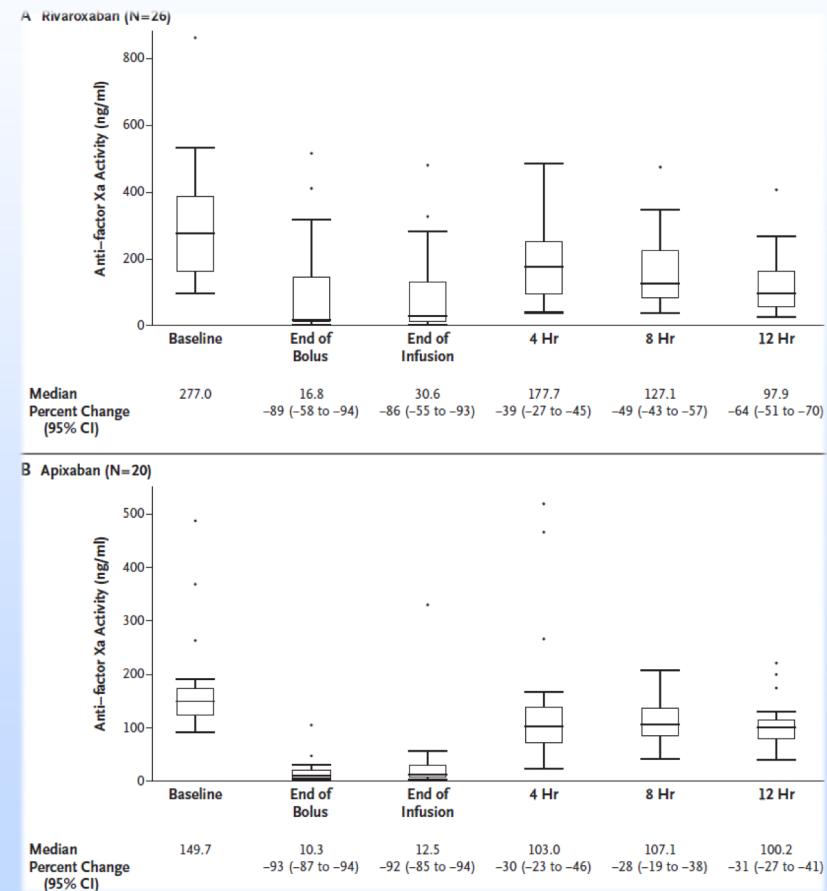
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D.,



Andexanet Alfa study

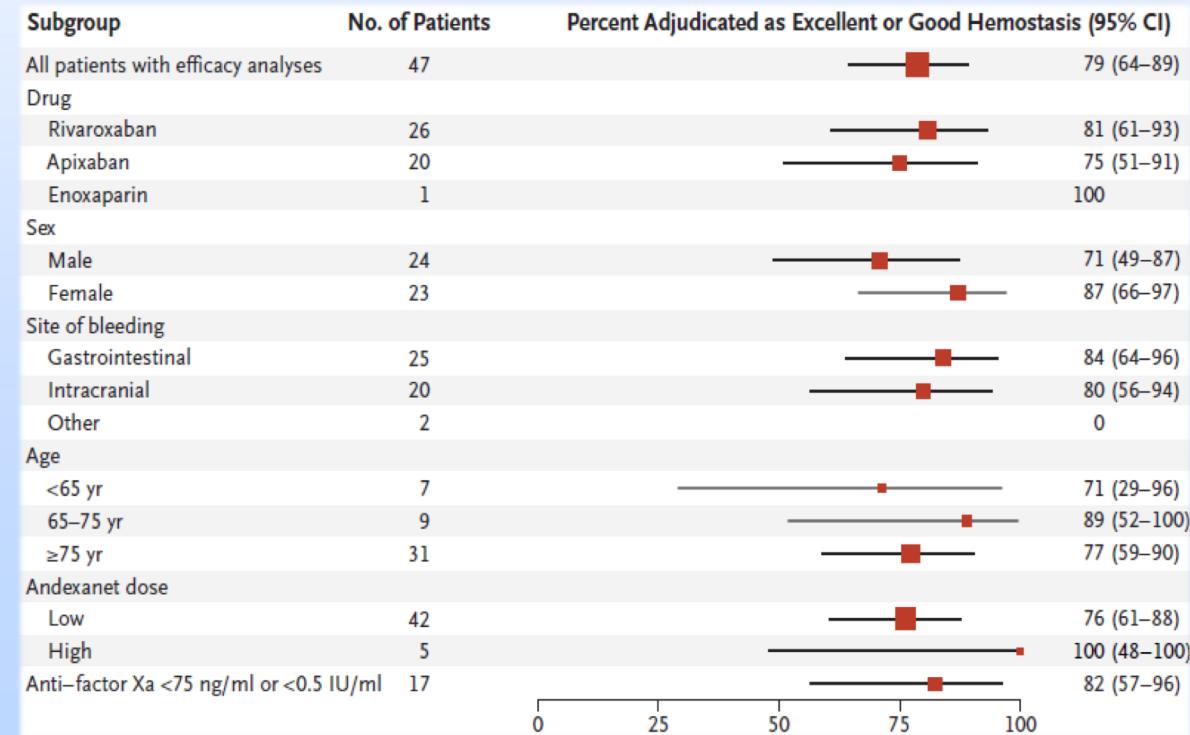
- They found:
 - after bolus 89% decrease in anti-Xa activity (rivaroxaban) and 93% decrease (apixaban)
 - Levels remained low during infusion
 - 4 hours after the anti-Xa activity was recovering in both groups





Adexanet Alfa study

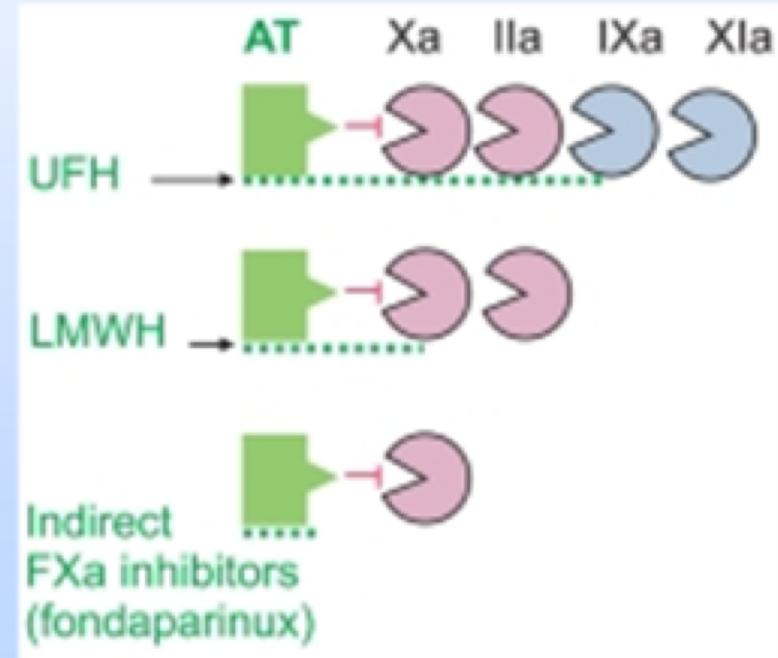
- Clinically at 12 hours they found hemostasis in 79%
- No early thrombotic events
- No reactions
- No control
- Shorter duration
- Studies ongoing





Heparin

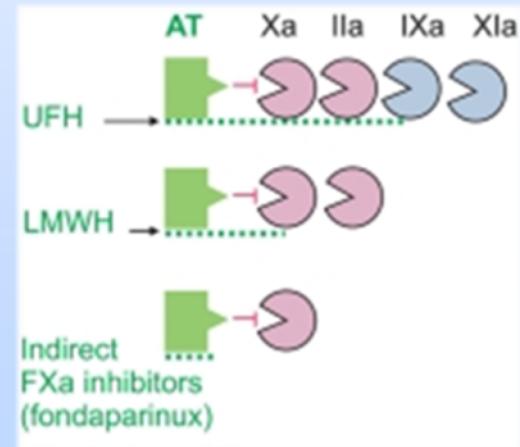
- Time
- Protamine





Low molecular weight heparin (LMWH)

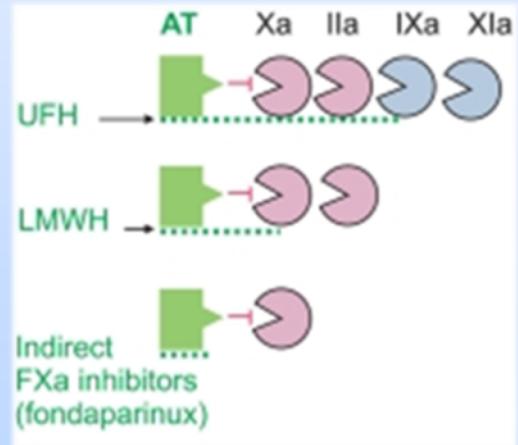
- Time
- Maybe protamine (partial reversal)
- Adexanet alfa ?





Fondaparinux

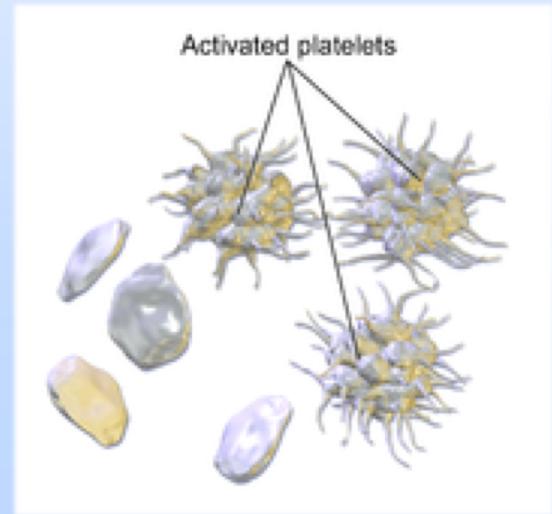
- Time
- Adexanet alfa





Suppose he has a coronary stent...

- Many are on platelet inhibitors
 - ASA, dipyridamole
 - Clopidogrel, prasugrel
 - All “poison” the platelet
 - Time for new platelet production
 - Platelet transfusion





Summary - 1

- Anticoagulation in the community is common
- For elective procedures delay case for spontaneous recovery is cheapest and safest
- Warfarin
 - Time, Vitamin K, FFP, PCC
- Dabigatran
 - Time, dialysis, idarucizumab
- Xa inhibitors
 - Time, PCC, ?adexanet alfa



Summary - 2

- Heparin
 - Time, protamine
- LMWH
 - Time, protamine (partial), ?adexanet alfa
- Platelet Poisons
 - Time, platelet transfusions





THANK YOU!

Peace and Blessings for 2019

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https://youtu.be/R-5PQkJM_8g

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