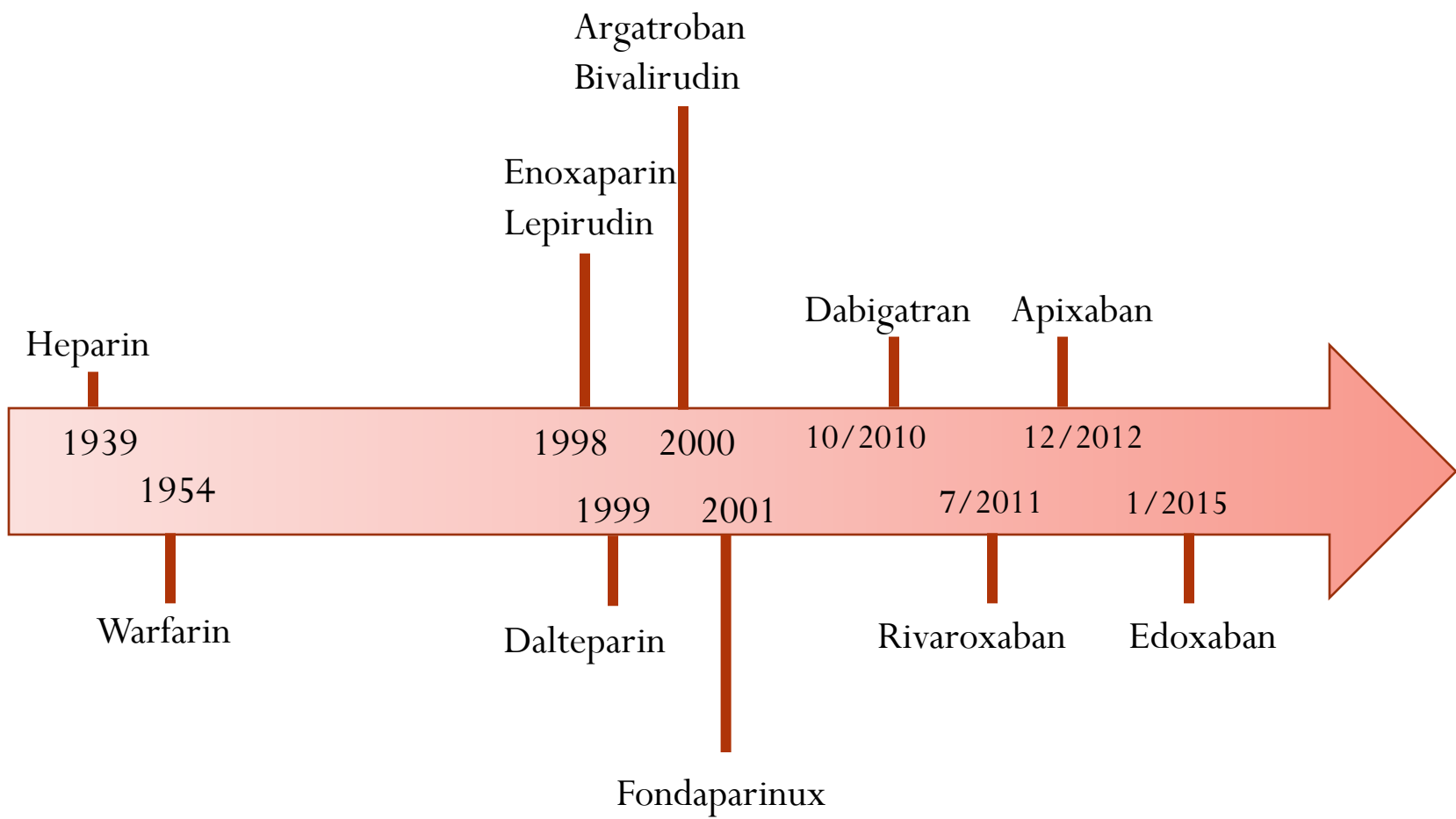


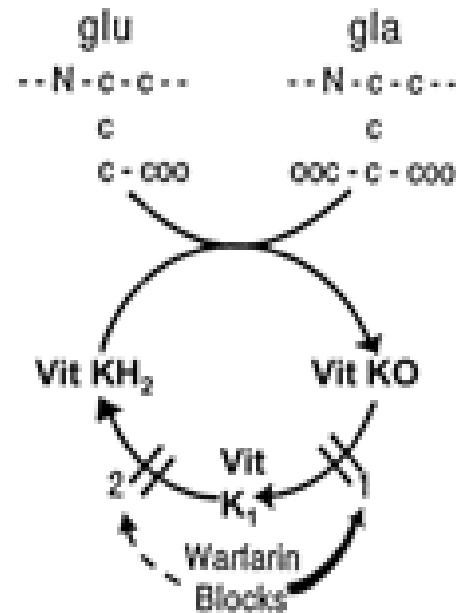
Reversal of Novel Oral Anticoagulants

Angelina The, MD

March 22, 2016

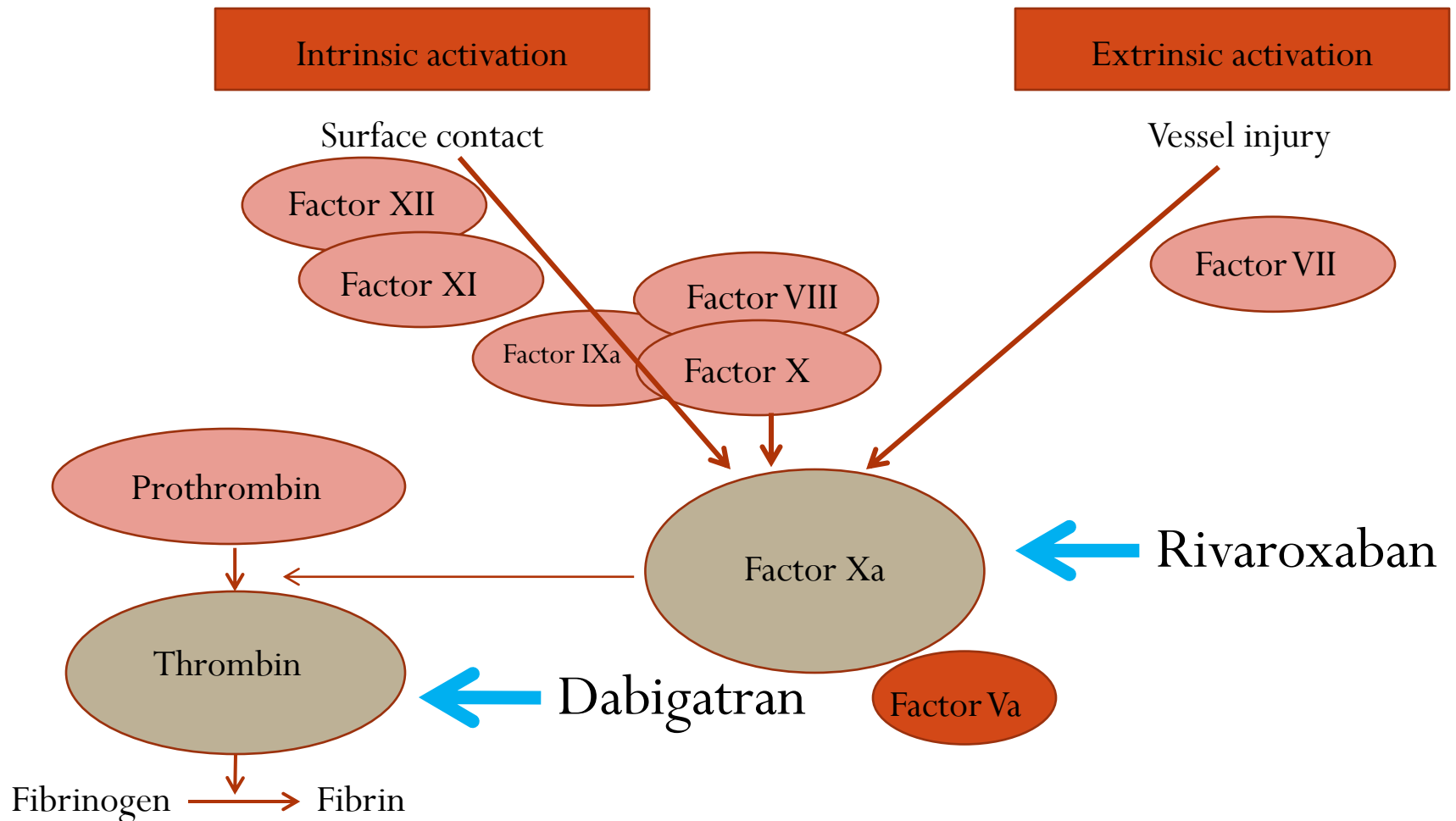


Mechanism of Action - Warfarin



1. **KO - reductase** - warfarin sensitive
2. **K - reductase** - relatively warfarin resistant

Mechanism of Action – Direct thrombin inhibition and factor Xa inhibitors



Advantages of NOACs over VKAs

- Wider therapeutic window
- Quick onset of action
- Shorter $t_{1/2}$ (7-14 hours)
- Bioavailability/fixed dosing
- Noninferior, in some cases superior, to dose-adjusted warfarin for prevention and treatment of thrombosis
- Decreased rate of major bleeding by 28% and the rates of intracranial and fatal hemorrhage by 50%.

- RE-LY Trial †
 - N = 18,113
 - CVA/systemic embolism: 1.69% (w) vs. 1.11% (d 150), $p < 0.001$
 - Major bleeding: 3.36% (w) vs. 3.11% (d 150), $p = 0.31$
 - Hemorrhagic CVA: 0.38% (w) vs. 0.10% (d 150), $p < 0.001$
 - Conclusion: Lower rates of CVA/systemic embolism with dabigatran, but similar rates of hemorrhage.
- ROCKET Trial ‡
 - N = 14,264
 - CVA/systemic embolism: 2.4% (w) vs 2.1% (r), $p < 0.001$ for noninferiority
 - Major and non-major bleeding: 14.9% per year (w) vs 14.5% per year (r), $p = 0.44$
 - ICH: 0.7% (w) vs. 0.5% (r), $p = 0.02$
 - Fatal bleed: 0.5% (w) vs. 0.2% (r), $p = 0.003$
 - Conclusion: Rivaroxaban noninferior to warfarin with respect to CVA/systemic embolism. No difference in bleeding but less intracranial and fatal bleeding in rivaroxaban arm.

†Connolly et al. 2009. NEJM. 361:1139-1151.

‡Patel et al. 2011. NEJM. 365:883-891.

- ARISTOTLE Trial †
 - N= 18,201
 - CVA/systemic embolism: 1.6% per year (w) vs. 1.27% per year (a), p=0.01 for superiority
 - Major bleeding: 3.09% per year (w) vs. 2.13% (a), p<0.001
 - Death: 3.94% (w) vs. 3.52% (a), p = 0.047
 - Hemorrhagic CVA: 0.47% per year (w) vs. 0.24% (a), p<0.001
 - Conclusion: Apixaban was superior to warfarin in preventing CVA/embolism, caused less bleeding, and resulted in lower mortality.

- ENGAGE Afib TIMI Trial‡
 - N=21,105
 - CVA/systemic embolism: 1.5% (w) vs 1.18% (hd-e) vs 1.61% (ld-e), p<0.001 and 0.005 for noninferiority respectively
 - Major bleeding: 3.43% (w) vs. 2.75% (hd-e) vs 1.61% (ld-e), p<0.001 and <0.001 respectively
 - Death: 3.17% (w) vs. 2.74% (hd-e) vs. 2.71% (ld-e), p=0.01 and p=0.008 respectively
 - Conclusion: Both once daily edoxaban doses were noninferior to warfarin with respect to prevention of CVA or systemic embolism and were associated with significantly lower risk of bleeding and death from cardiovascular disease.

†Granger et al. 2011. NEJM. 365: 981-992.

‡Giugliano et al. 2013. NEJM. 369:2093-2104.

- RECOVER Trial†
 - Dabigatran 150 mg bid vs. warfarin titrated to INR 2-3
 - 6 month incidence of recurrent thromboembolism -
 - 2.4% (dabigatran) vs. 2.1% (warfarin)
 - Major bleeding 1.6% (dabigatran) vs. 1.9% (warfarin)
 - Any bleeding 16.1% (dabigatran) vs. 21.9% (warfarin)
 - Conclusion: For the treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has a safety profile that is similar to that of warfarin.

- AMPLIFY Trial‡
 - Apixiban 10 mg bid x 7 days followed by 5 mg bid x 6 months
 - Recurrent symptomatic VTE or death related to VTE –
 - 2.3 % (apixiban) vs. 2.7% (warfarin) - apixaban noninferior (p<0.001)
 - Major bleeding
 - 0.6% (apixiban) vs. 1.8% (warfarin) - apixaban superior (p<0.001)
 - Conclusion: A fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute venous thromboembolism and was associated with significantly less bleeding

- EINSTEIN Trial^
 - Rivaroxaban 15 mg bid x 3 weeks followed by 20 mg daily vs. LMWH/warfarin
 - Recurrent venous thromboembolism
 - 2.1% (rivaroxaban) vs. 3% (warfarin)- rivaroxaban noninferior (p<0.001)
 - Bleeding
 - 1% (rivaroxaban) vs 1.7% (warfarin) – rivaroxaban superior (p = 0.002)
 - Conclusion: The single-drug approach with rivaroxaban resulted in similar efficacy to standard-therapy and was associated with a significantly lower rate of major bleeding

†Schulman et al. 2009. NEJM. 361:2342-2352.

‡Agnelli et al. 2013. NEJM. 369:799-808.

^Bauersachs et al. 2010. NEJM. 363: 2499-2510.

Disadvantages of NOACs...until now

- Lack of an antidote
- Anticoagulation-associated major bleeding events often lead to poor outcomes
 - 10% of patients who are hospitalized with warfarin-related bleeding die within 90
 - Mortality among patients with intracranial hemorrhage can be as high as 50%.

Discontinuation protocol prior to surgery or other invasive procedure

- Dabigatran
 - 1-2 days for CrCl \geq 50
 - 3-5 days for CrCl $<$ 50
- Xarelto
 - At least 2 days
- Apixaban
 - At least 2 days prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding.
 - At least 1 day prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled.
- Edoxaban
 - At least 1 day

Management of anticoagulation-related bleeding

- Discontinuation of anticoagulant
- Hemodynamic resuscitation
- Labs – Coags, CBC, fibrinogen, CMP
- Administration of reversal agent

Antidotes for oral anticoagulants – Pre-2015

- Warfarin
 - FFP, vitamin K, Prothrombin complex concentrates
- Dabigatran
 - Hemodialysis
 - Recombinant Factor VIIa
 - Prothrombin complex concentrates
- Rivaroxaban, Apixaban, Edoxaban
 - Recombinant Factor VIIa
 - Prothrombin complex concentrates

Have you or a loved one been injured while using Pradaxa® ?

You may be entitled to financial compensation!



If you or a loved one has taken **XARELTO®** ?

- Internal Bleeding
- Stroke - Or Death

Call us today!



ING USERS OF AND DABIGATRAN

ptoms

lead to excessive internal bleeding and other complications could cause

SEVERE INJURY OR DEATH

Took Xarelto?



You may be entitled to compensation.



Call 1-800-934-2921 Free Consultation

BrianLoucar.com

1.800.285.4878

1.800.285.HURT

Antidotes for oral anticoagulants – 2015 and onward

- Warfarin
 - FFP, vitamin K
- Dabigatran
 - Idarucizumab (Praxbind)
- Rivaroxaban, Apixaban, Edoxaban
 - Andexanet alfa

Idarucizumab



- Monoclonal antibody fragment
- Binds dabigatran with an affinity that is 350 times as high as that observed with thrombin
- Binds free and thrombin-bound dabigatran and neutralizes its activity

REVERSE-AD Trial

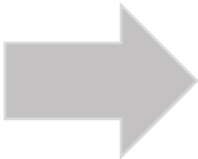
- Prospective cohort study

Group A:

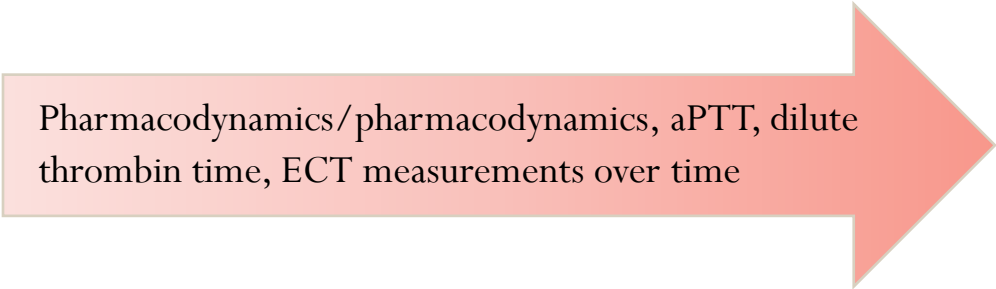
Patients on dabigatran with uncontrollable/life-threatening bleeding

Group B:

Patients on dabigatran requiring surgery or other invasive procedures that could not be delayed for ≥ 8 hrs and for which normal hemostasis was required



Idarucizumab 5 g IV, administered as 50-ml bolus infusions x 2, each containing 2.5 g of idarucizumab, no more than 15 minutes apart



Pharmacodynamics/pharmacodynamics, aPTT, dilute thrombin time, ECT measurements over time

REVERSE-AD Trial

- Primary end point -

Percentage reversal =

(predose test result [secs] – minimum postdose test result [secs])

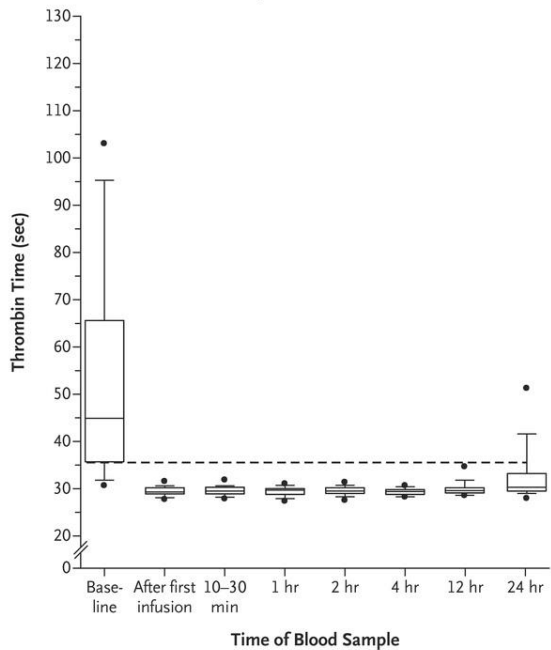
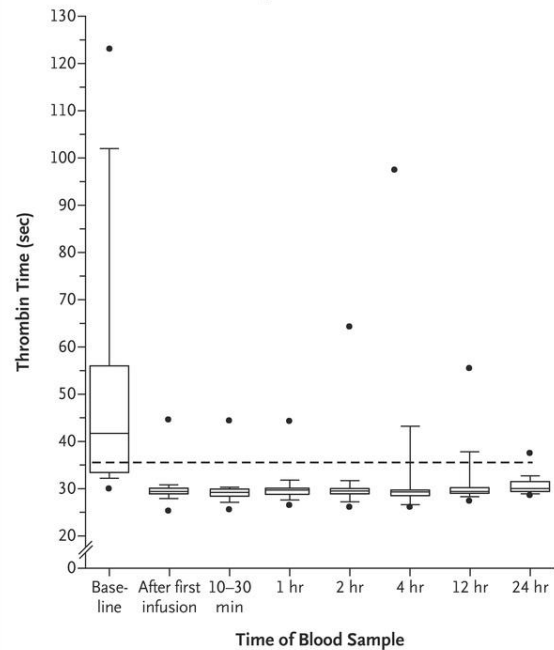
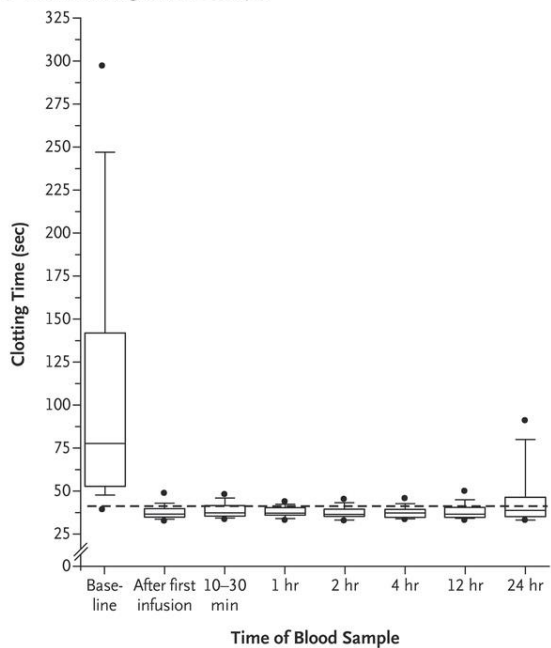
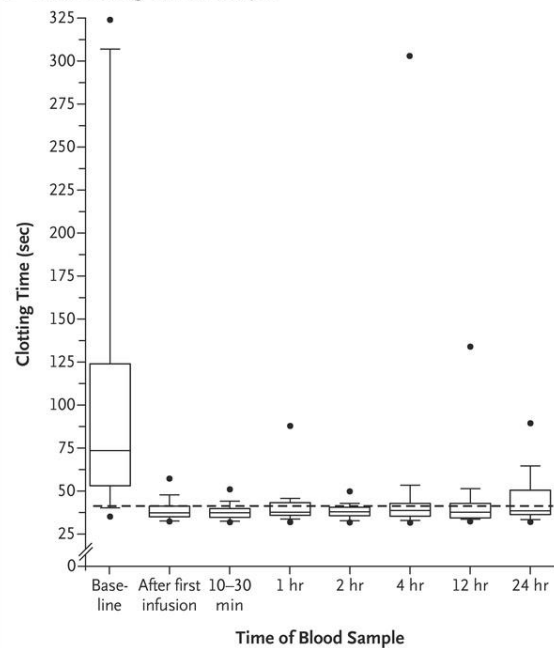
x 100

(predose test result [secs] – ULN range [secs])

- Secondary end point – Clinical outcomes
 - In Group A - Extent of bleeding and hemodynamic stability over time.
 - In Group B - Hemostasis during the intervention was classified by the physician as normal or as mildly, moderately, or severely abnormal.

REVERSE – AD: Results

- Accrued 6/2014 – 2/2015
- N = 90 patients (51 in group A and 39 in group B) were enrolled at 184 sites in 35 countries.
- More than 90% of the patients were receiving dabigatran for stroke prevention in the context of atrial fibrillation.
- Median age = 76.5 years
- Median creatinine clearance was 58 ml per minute

A Dilute Thrombin Time in Group A**B Dilute Thrombin Time in Group B****C Ecarin Clotting Time in Group A****D Ecarin Clotting Time in Group B**

REVERSE-AD Results

- Median maximum percentage reversal in the patients in group A and in those in group B was 100% as assessed by dilute thrombin time and ecarin clotting time
- Clinical outcomes:
 - In Group A (N=51), median investigator-reported time to the cessation of bleeding was 11.4 hours**.
 - In Group B (N=39), normal intraoperative hemostasis was reported in 33 (92%). Mildly or moderately abnormal hemostasis during the procedure was reported in 2 patients and 1 patient, respectively.
- 18 deaths overall, 9 in each study group.
 - 10 deaths were due to vascular causes, including 5 fatal bleeding events. Death within 96 hours after treatment appeared to be related to the index event (2 septic shock, 3 intracranial hemorrhage, and 1 each had multiorgan failure, hemodynamic collapse, respiratory failure, and cardiac arrest), whereas all the later deaths appeared to be associated with coexisting conditions.
- Thrombotic events in 5 patients

Side effects of Idarucizumab

- Headache
- Hypokalemia
- Delirium
- Constipation
- Pyrexia
- Pneumonia

Andexanet alfa

- Recombinant modified human factor Xa decoy protein
- Catalytically inactive but binds factor Xa inhibitors in the active site with high affinity and 1:1 stoichiometric ratio
- Restores activity of endogenous factor Xa

ANNEXA-A and ANNEXA-R Trials

- Phase III, randomized, double-blind, placebo-controlled
- Evaluated the ability of andexanet to reverse anticoagulation with apixaban or rivaroxaban
- Conducted at 2 sites (ANNEXA-A, in Tempe, AZ; ANNEXA-R in Cypress, CA.)
- Enrolled healthy volunteers, 50-75 years of age
 - 3:1 ratio in ANNEXA -A
 - 2:1 ratio in ANNEXA - A

ANNEXA-A



Apixaban 5 mg bid x 3.5 days



Andexanet 400 mg IV bolus
or
Andexanet 400 mg IV bolus
followed by infusion of 4
mg/min for 120 minutes

ANNEXA-R



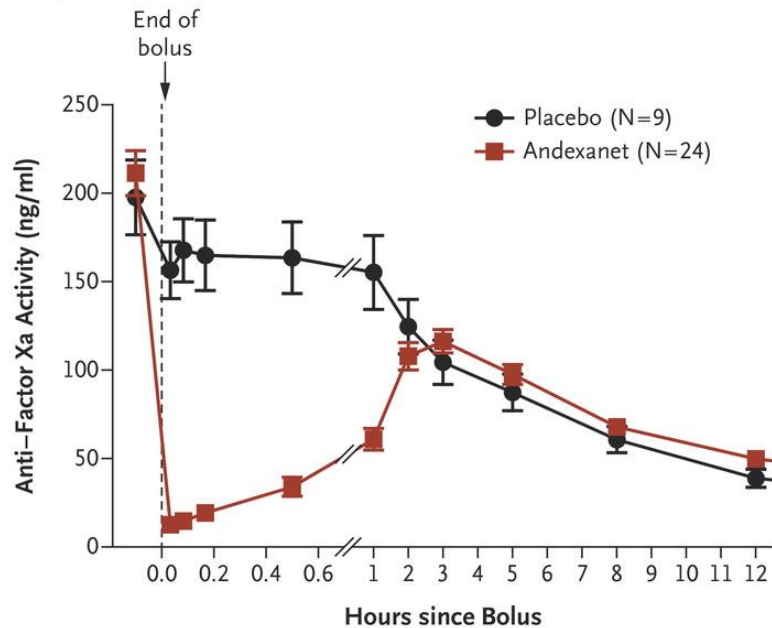
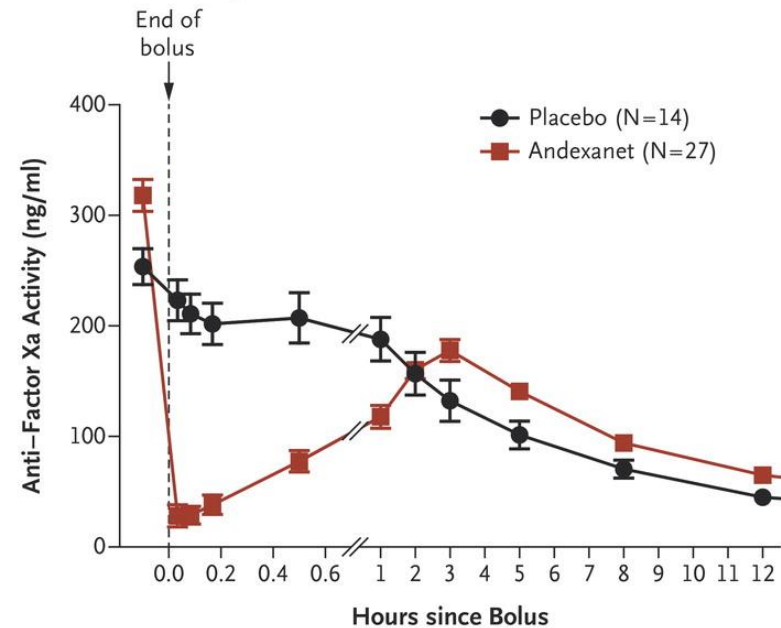
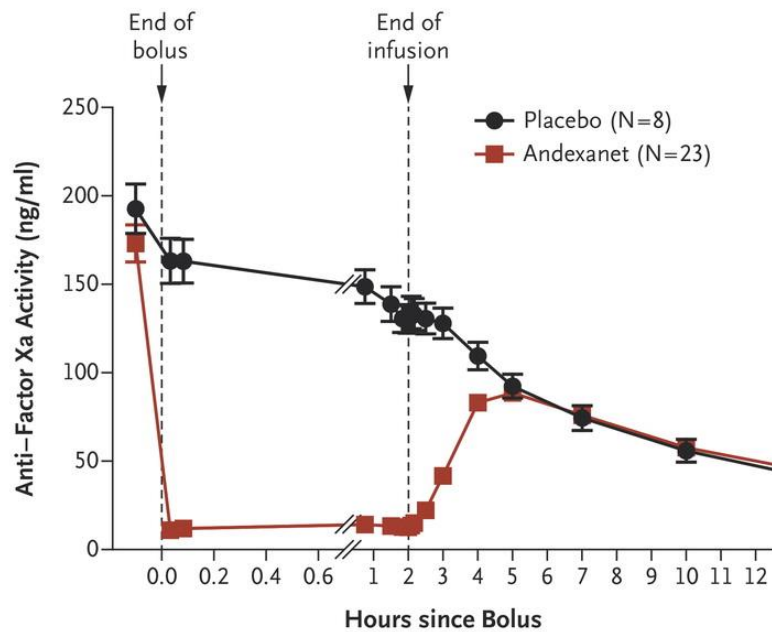
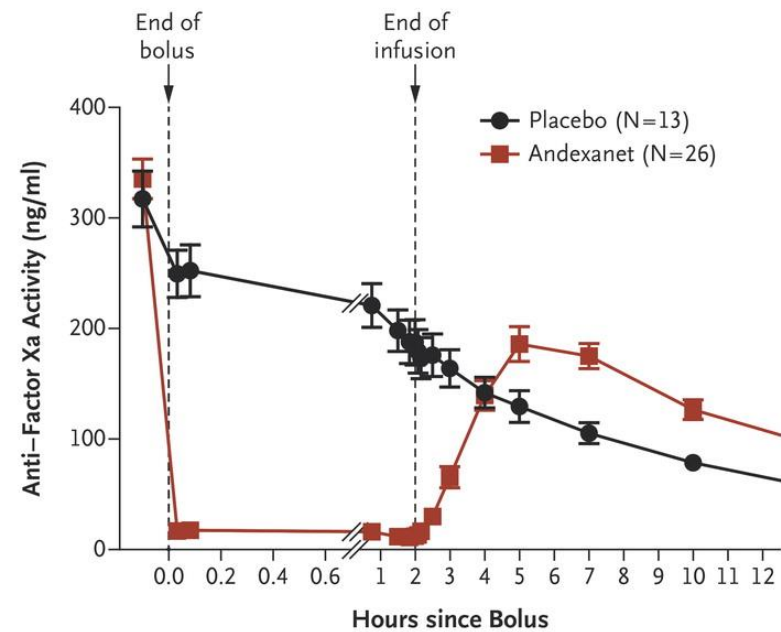
Rivaroxaban 20 mg daily x 4 days



Andexanet 800 mg IV bolus
or
Andexanet 800 mg IV bolus
followed by infusion of 8
mg/min for 120 mg

ANNEXA Trials

- Primary end point
 - % change in anti-factor Xa activity, measured with the use of a validated chromogenic assay of factor Xa enzymatic activity from baseline to nadir.
 - Part 1 – Nadir defined as value of anti-factor Xa activity at 2 or 5 minutes (whichever was smaller) at the end of the bolus
 - Part 2 – Nadir defined as smallest value between 10 min before and 5 min after the end of the continuous infusion.
- Secondary end point
 - Proportion of participants with $\geq 80\%$ reduction in anti-factor Xa activity from baseline to nadir
 - For part 2, % change in anti-factor Xa activity from baseline to post-bolus nadir.

A Apixaban Study, Andexanet Bolus**B Rivaroxaban Study, Andexanet Bolus****C Apixaban Study, Andexanet Bolus plus Infusion****D Rivaroxaban Study, Andexanet Bolus plus Infusion**

ANNEXA Trials - Results

- Andexanet rapidly reversed apixaban-induced and rivaroxaban-induced changes in anti-factor Xa activity and thrombin generation without serious adverse events or clinical thrombosis.
- Reversal of anticoagulant effect was reproducible with a maximal effect within 2-5 minutes after administration and was sustained during the continuous infusion.
- Biomarkers of anticoagulation returned to placebo levels 1-3 hours after cessation of andexanet administration.

Andexanet – Side effects

- Constipation
- Dysgeusia
- Flushing
- Urticaria

Summary

- NOACs offer a viable alternative to warfarin for prevention of stroke among patients with a. fib and for treatment of VTE
- Rising use of NOACs will result in greater prevalence of NOAC associated bleeding. Need for reversal agent.
- Idarucizumab and andexanet quickly reverses anticoagulant effects of dabigatran and factor Xa inhibitors
- Idarucizumab appears to benefit patients actively bleeding and allows effective hemostasis in patients needing emergent surgery or invasive procedures

Reversal Agents: Unresolved Issues

- Lack of control arm in REVERSE-AD trial raises questions whether idarucizumab superior than best clinical care
- REVERSE-AD trial underpowered
- Efficacy and safety of andexanet unknown in patients who require urgent reversal of factor Xa inhibitor because of bleeding or for emergency surgery → ANNEXA-4 Trial
- Optimal duration of administration?
- Cost effectiveness?
- Special considerations in patients with renal or liver dysfunction?

Future

- Aripazine (PER-977, ciraparantag; Perosphere Inc.) is a synthetic small molecule (~ 500 Da) that reverses oral dabigatran, apixaban, rivaroxaban, as well as subcutaneous fondaparinux and LMWH in vivo.
- Anivamersen (RB007; Regado Biosciences Inc.) is an RNA molecule that reverses the anticoagulant effect of the parenteral factor IXa inhibitor pegnivacogin, which is also in development.

The End