Overview of Reversal Agents in Development

Michael B Streiff, MD FACP
Associate Professor of Medicine and Pathology
Medical Director, Johns Hopkins Anticoagulation Service
Chairman, VTE Guideline Committee ,National Comprehensive Cancer Network

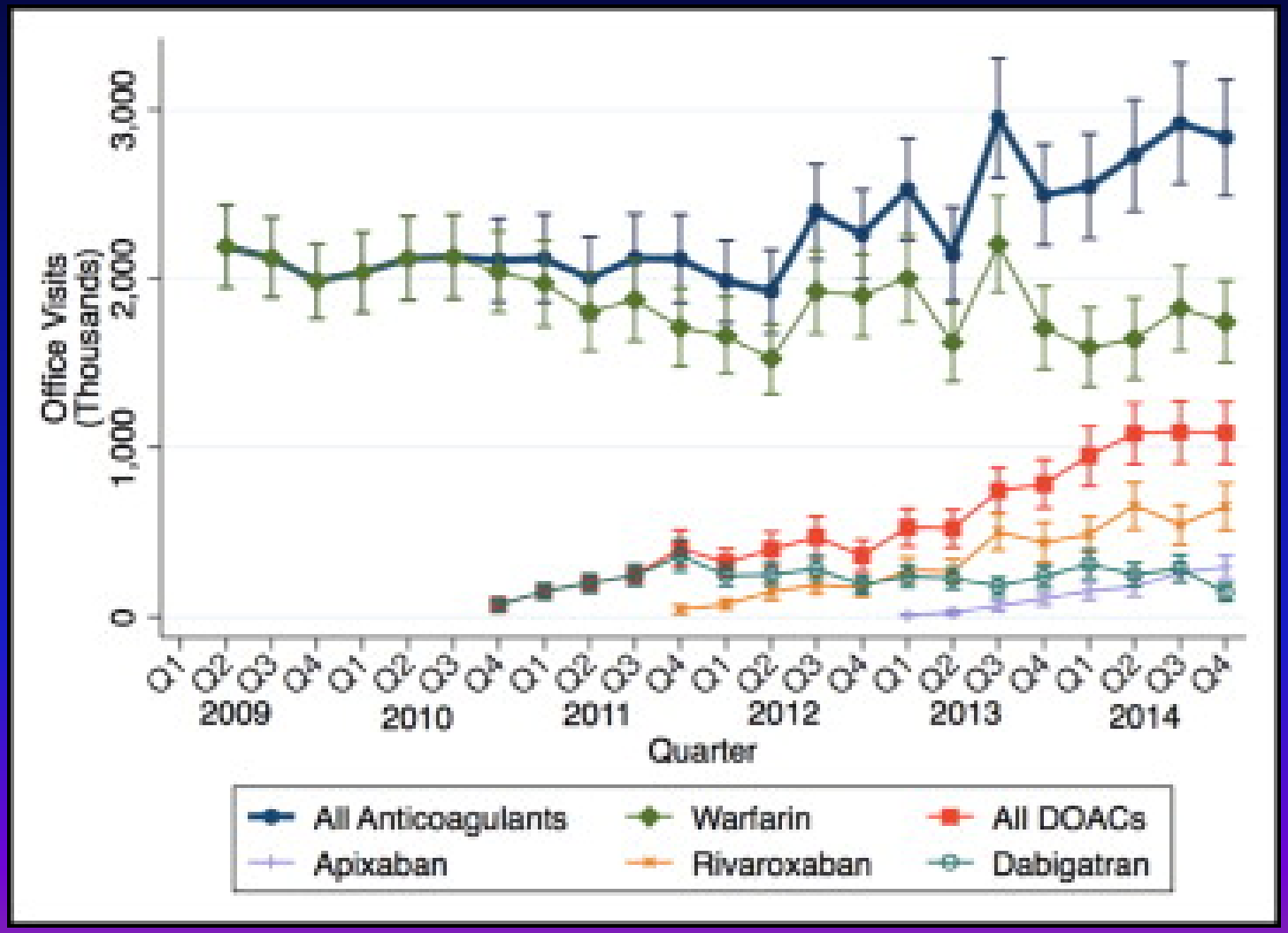
Disclosures- Michael Streiff, MD

- Advisory Board-Clinical Trials
  - Bio2 Medical
  - Janssen HealthCare
- Educational Grants
  - Covidien
- Research support
  - Daiichi-Sankyo
  - Janssen Healthcare
  - PCORI
  - Portola

Objectives

- Overview of the three reversal agents in development
- Review the status of the new agents
  - What is the current status of clinical trials?
  - What published data are available?
  - When is approval anticipated?
- In which scenarios would the agents be indicated, not indicated, discretionary?
- Predictions on the reactions of payers: cost and availability

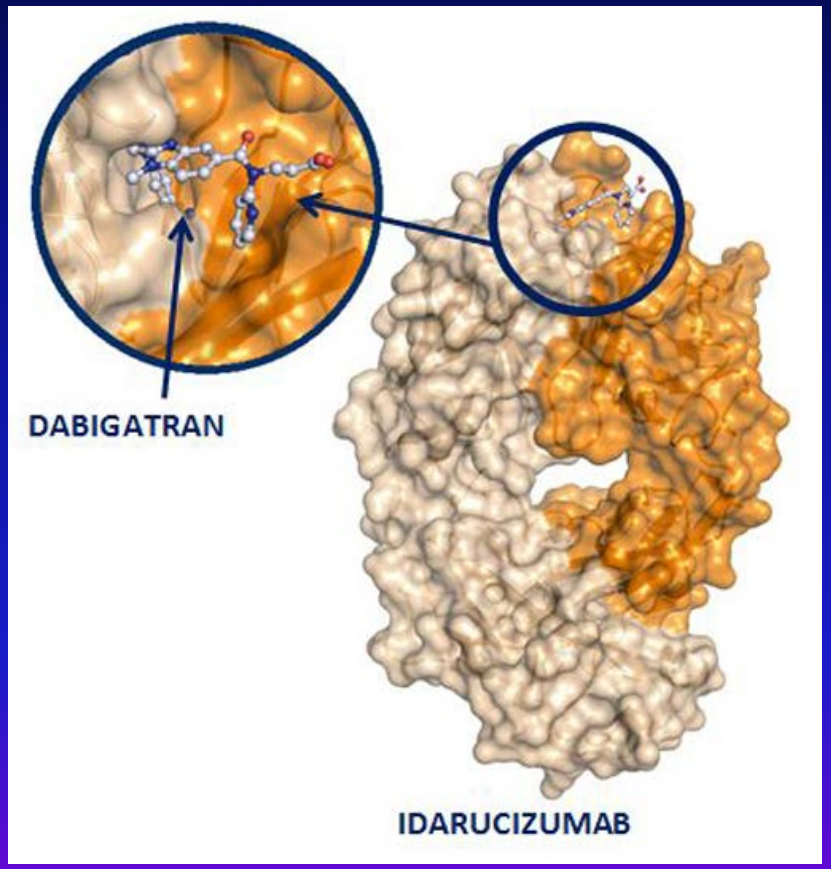
National Trends in Oral Anticoagulant Use



Barnes GD et al. Amer J Med 2015

Idarucizumab

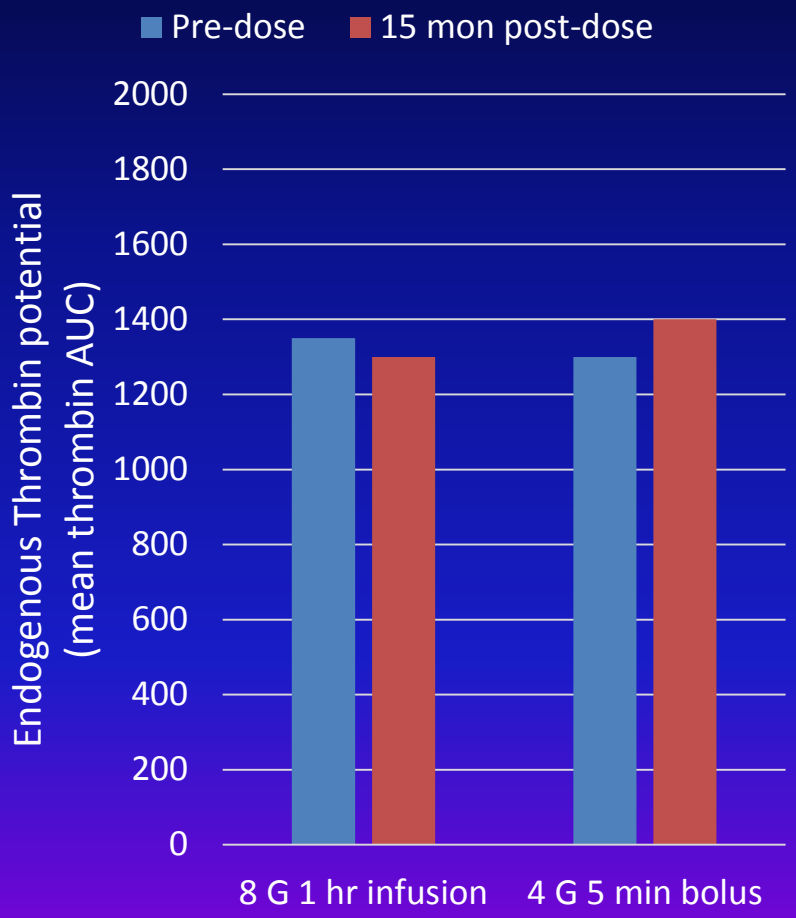
- Humanized mouse monoclonal Fab fragment
- 350-fold higher affinity
  - Binds free and thrombin-bound Dabi
- Dose- 5 g bolus
- Rapid peak (minutes)
- Renal clearance
- Initial Half-life – 45 min



Crowther M and Crowther MA Arterioscler Thromb Vasc Biol 2015; Das A and Liu D. Exp Hematol Oncol 2015

Idarucizumab

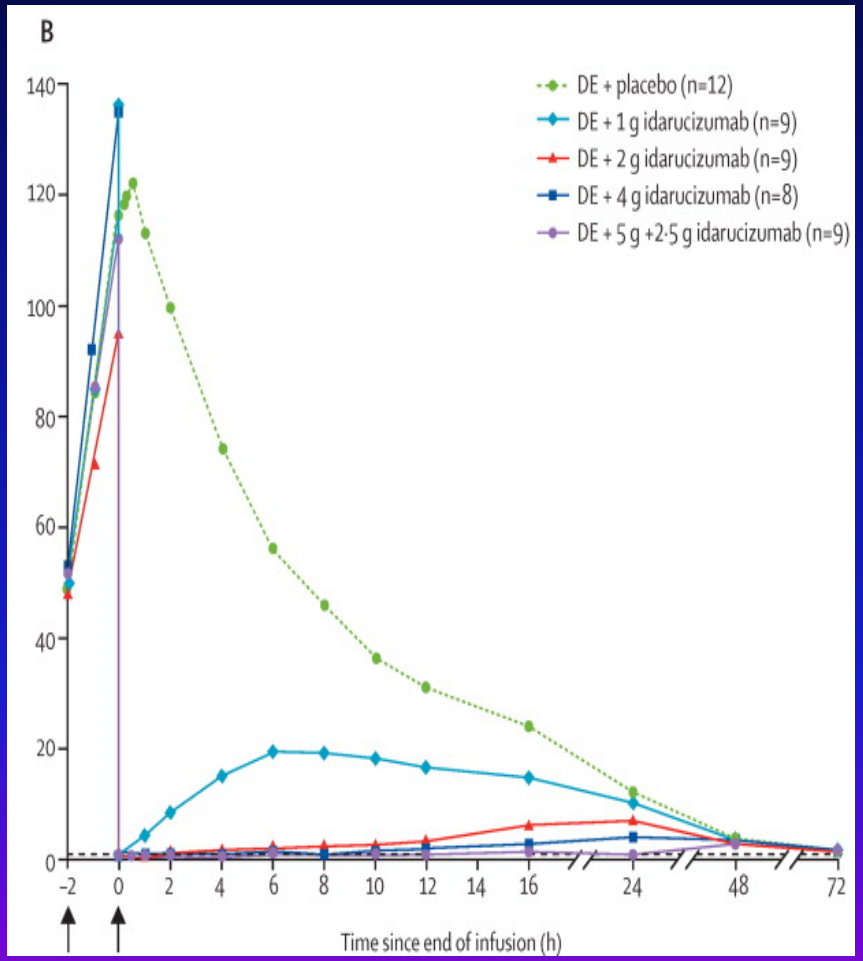
- In 110 normal volunteers no impact of Ida on dTT, ECT, TT, aPTT, ACT or ETP
- AE similar to placebo
- No SAE
- Conclusion- Idarucizumab is safe and well tolerated



Glund S et al. Thromb Haemost 2015

Idarucizumab reduces Dabigatran levels

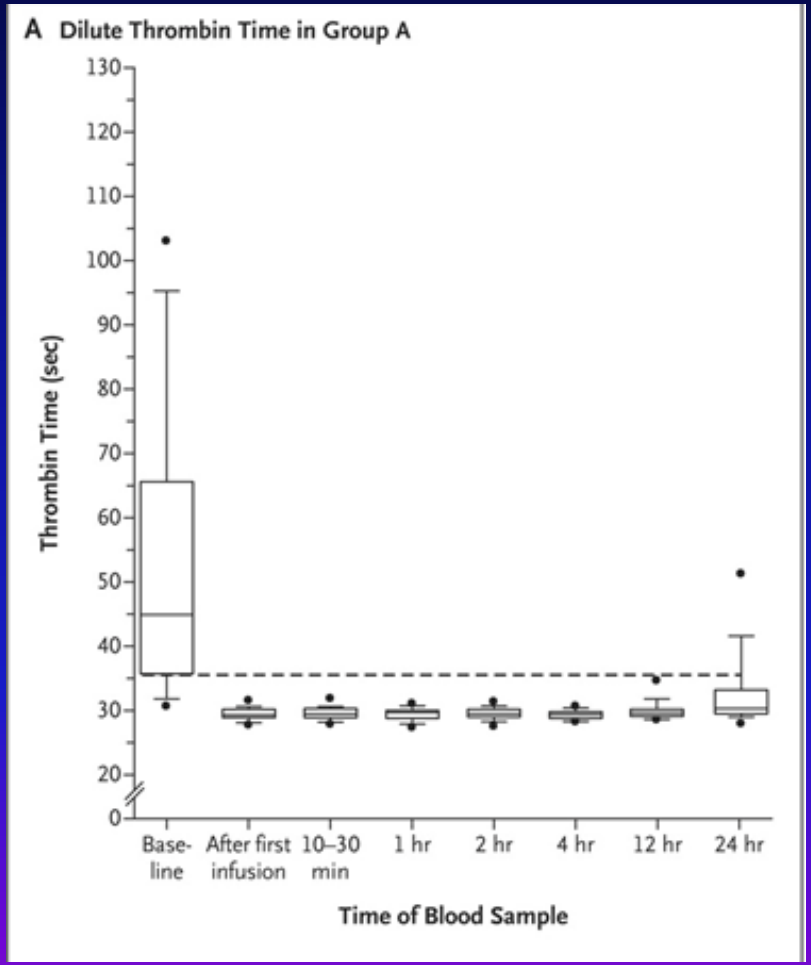
- Phase 1 randomized placebo-controlled double blind trial
- Dabigatran 220 mg BID X 3 days followed by idarucizumab
- Idarucizumab rapidly reduced Dabi levels and anticoagulant activity



Glund S et al. Lancet 2015

Idarucizumab reduces bleeding

- Prospective cohort of 90 Dabi patients with bleeding or in need of surgery
- Ida 2.5 G bolus X 2
- dTT normalized in 98% and 93% of pts.
- Time to cessation of bleeding 11.4 hrs.
- Normal surgical hemostasis in 33/36 (92%)
- Conclusion- Ida reverses Dabi AC effects



Pollock CV et al. NEJM 2015

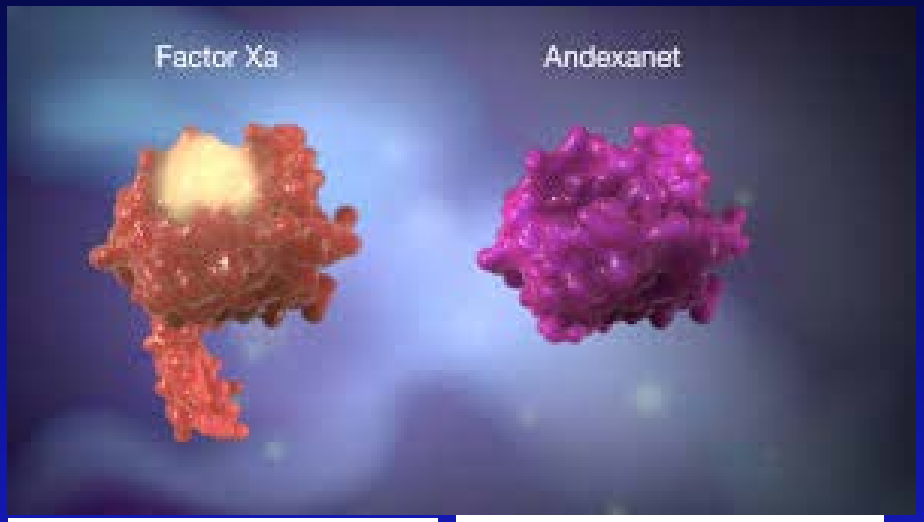
Idarucizumab (Praxbind®)

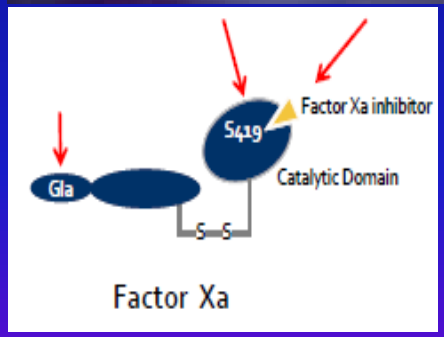
- Approved by the FDA for reversal of Dabigatran October 16, 2015
- REVERSE-AD, a prospective cohort study of idarucizumab is ongoing
  - Projected enrollment 450
  - Projected completion date July 2017

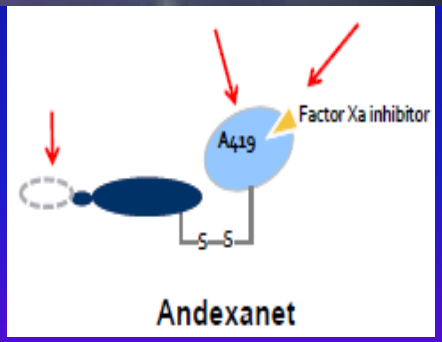
Clinical Trials.gov

Andexanet Alpha

- Andexanet alpha (PRT064445)
- 39 kDa recombinant modified FXa ($Ser^{419} \rightarrow Ala^{419}$) that lacks Gla domain and catalytically inactive
- Binds Direct oral factor inhibitors and AT-bound to fonda, LMWH
- Onset – 2-5 minutes
- Initial half-life- 15 minutes



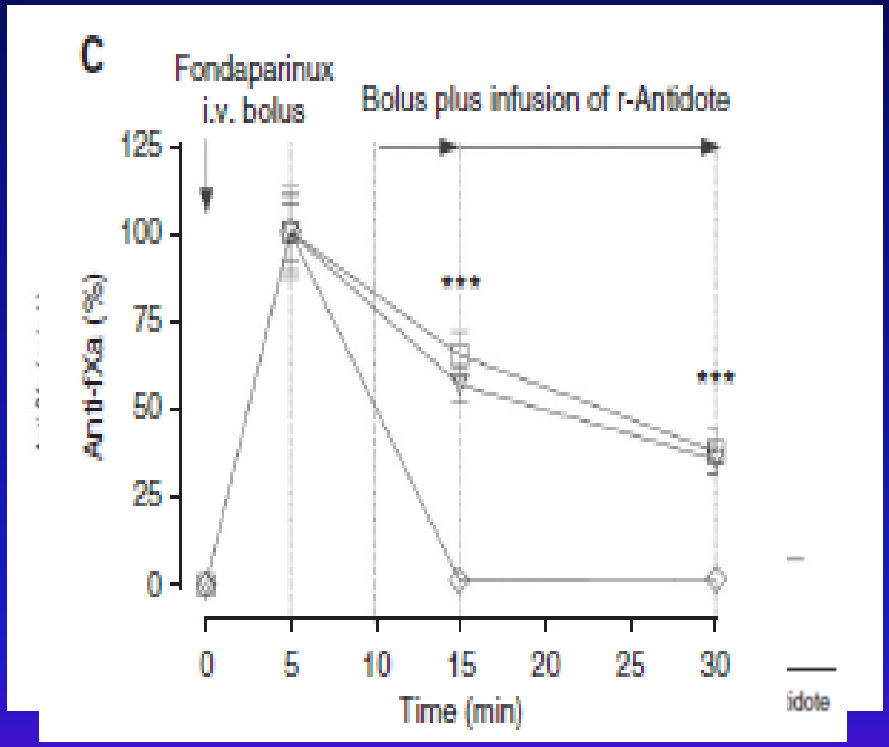




Crowther M Arterioscler Thromb Vasc Biol 2015; Crowther M et al. AHA 2014

Andexanet Alpha

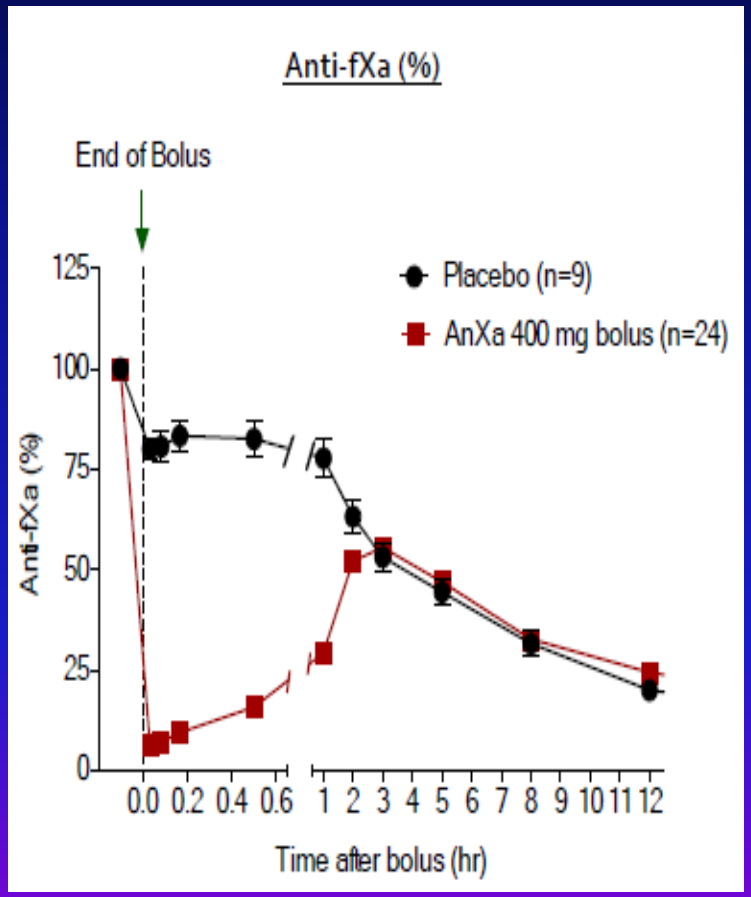
- In animal models , A α corrected coagulation tests and bleeding times with DFXaI, LMWH and Fonda
- In normal volunteers treated with rivaroxaban 20 mg daily, Andexanet reversed anti-Xa activity by 20% and 53% without activation of coagulation



Lu G et al. Nature Med 2013; Crowther M et al, Blood 2013; Crowther M et al. AHA 2014

Andexanet Alpha

- Phase 2 RCT
- Apixaban 5 mg q12h X 6 days
- Andexanet-alpha (N=24) or placebo (N=9)
- Measured anti-Xa, free apixaban and ETP
- Andexanet-alpha reverses apixaban



Crowther M et al. AHA 2014

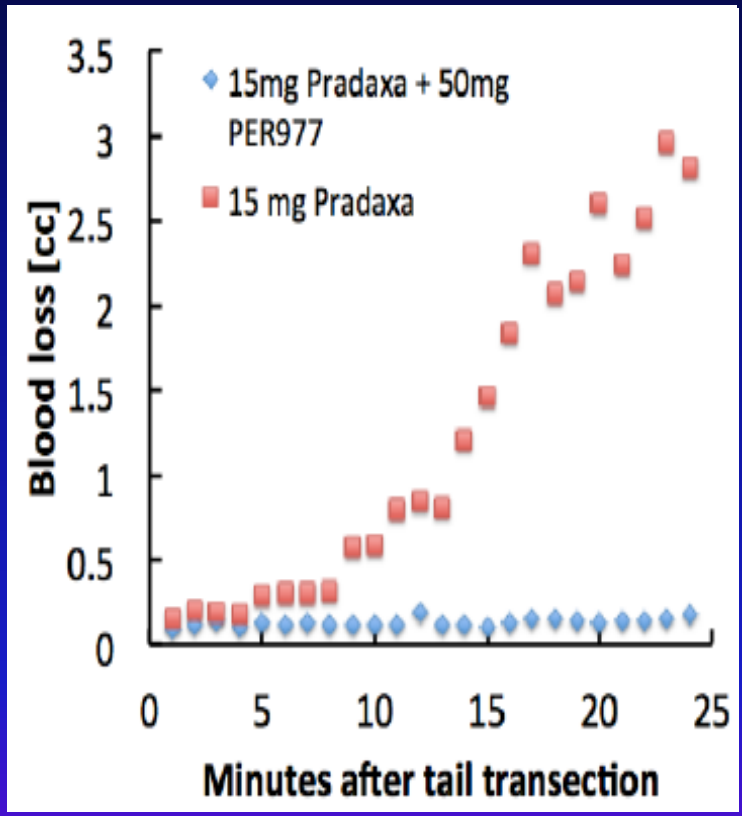
Andexanet Alpha

- Completed Phase 2 proof-of-concept studies for apixaban (5 mg q12h) , rivaroxaban (20 mg q24h), enoxaparin (40 mg q24h).
- Planned Phase 2 studies- Edoxaban (60 mg q24h), Betrixaban (80 mg q24h), Enoxaparin (1 mg/kg q12h)
- Ongoing prospective cohort study in bleeding patients
  - Start Date- January 2015
  - Planned enrollment- 270
  - Estimated completion date- Nov 2022
- Planned submission of FDA biologics license application by Dec 2015

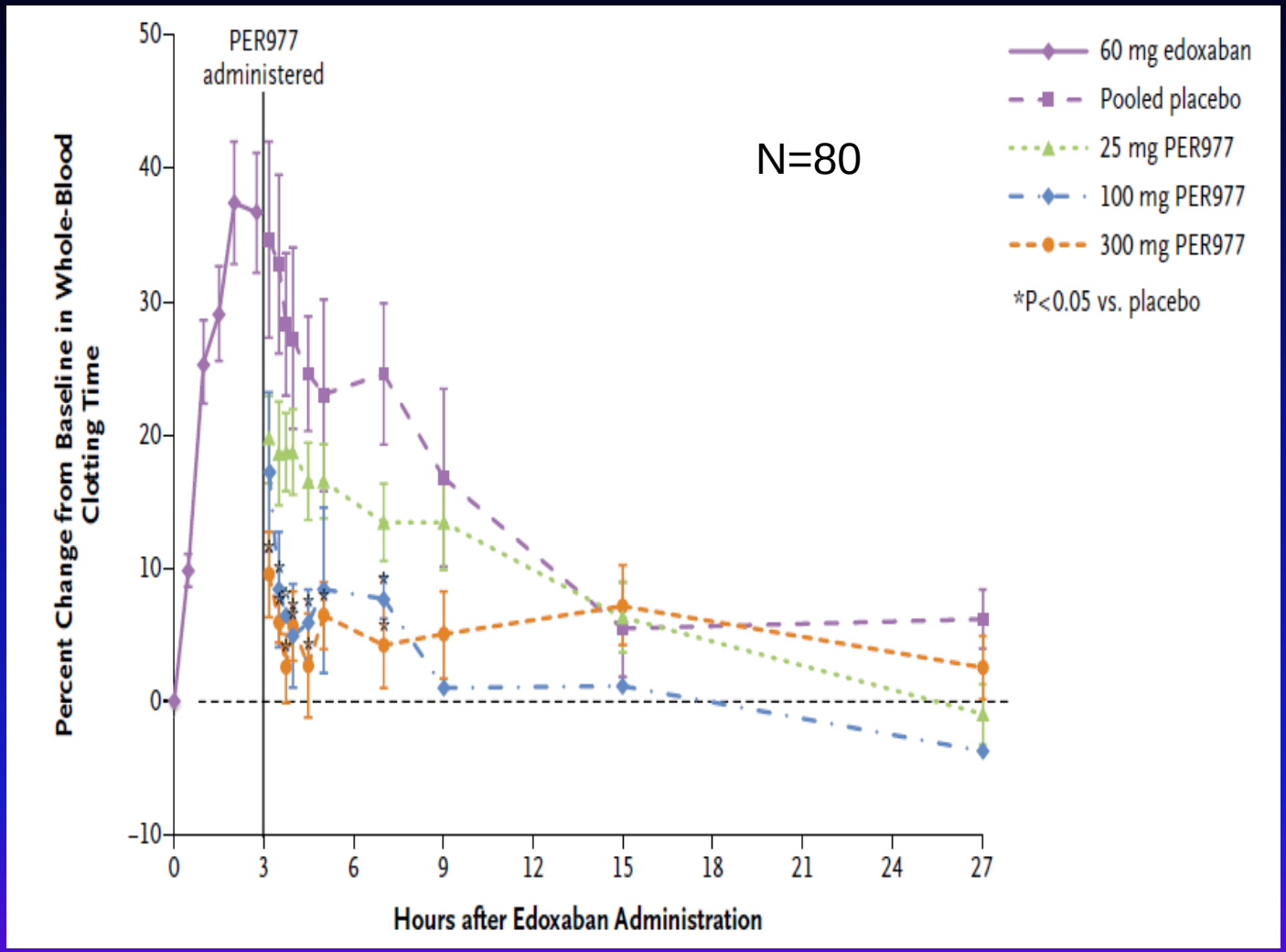
Clinical Trials. Gov accessed 10-16-15; http://investors.portola.com

Aripazine (PER977)

- Aripazine- small (500Da) molecule inhibitor
- Mechanism-noncovalent binding of UFH, LMWH, Fonda, NOACs
- Effective reversal in vivo animal and ex vivo human models
- Rapid onset- within 10 min.
- Duration of effect-24 hours



Costin J et al. Postgraduate Med 2014; Bakhru S et al. THSNA 2012



Double-blind placebo controlled trial of aripazine reversal of edoxaban

Ansell JE et al. NEJM 2014

Aripazine (PER977)

- Phase I/II double blind study of PER977 for reversal of single dose edoxaban in normal volunteers-completed
- Phase I/II study of escalating doses of PER977 for reversal of single 1.5 mg/kg dose of enoxaparin-completed
- Phase I/II study of PER977 reversal of unfractionated heparin-ongoing
  - Start date- June 2014 Target enrollment- 60
  - Estimated completion date- December 2015
- Phase II single blind study of PER977 for reversal of steady-state edoxaban
  - Start date- July 2014 Target enrollment- 69
  - Estimated completion date- July 2015
- FDA granted PER977 fast track designation April 2, 2015

Clinical Trials. Gov accessed 10-16-15; www.businesswire.com accessed 10-16-15

Is Aripazine (PER977) prothrombotic?

- In a rabbit liver laceration model PER977 reduced bleeding in non-anticoagulated animal
- PER977 did not reduce PT, aPTT, anti-Xa or rivaroxaban levels in an animal model or in human plasma
- PER977 potentiated factor X activation by factor IXa and platelet activation by ADP

Hollenbach S et al. Circulation 130(Suppl 2) A14657; Lu G et al. Circulation 130(Suppl 2)A18218

NOACs and major bleeding

- Intracranial hemorrhage
  - NOAC (297/57850 [0.51%]) versus VKA (485/44757 [1.08%]) (RR 0.43; 95% CI 0.37-0.50)
  - Dabigatran- RE-LY (0.31%.yr) and RECOVER (0.1%/yr), Real World AF (0.6%)
  - Rivaroxaban- ROCKET (0.5%/yr) and EINSTEIN (0.1%/yr)
  - Apixaban- AVEROES/ARISTOTLE (0.4% and 0.33%/yr) and AMPLIFY (0.1%/yr)
  - Edoxaban- ENGAGE-AF (0.39% and 0.26%/yr) and HOKUSAI (0.1%/yr)

Chai-Adisaksopha C et al. Blood 2014; Connolly S et al. NEJM 2009; Alonso A et al. Stroke 2014
Hart et al Stroke 2012; Patel M et al. NEJM 2011; Connolly S et al. NEJM 2011; Giugliano RP et al. NEJM 2013

NOACs and major bleeding

- Major Gastrointestinal Bleeding
  - NOACs 1123/53753 (2.09%) vs. VKA 690/40650 (1.7%)
    - Dabigatran- RE-LY (1.5%/yr) and Real World (2.29%/yr)
    - Rivaroxaban- ROCKET (3.2%/yr) and Real World (2.84%/yr)
    - Apixaban- ARISTOTLE (0.76%/yr)
    - Edoxaban- ENGAGE AF (1.51%/yr) and (0.82%/yr)

Abraham NS et al. BMJ 2015; Connolly S et al. NEJM 2011; Giugliano RP et al. NEJM 2013

Indications for Reversal Agents

- Estimated AF prevalence in US 5 million in 2010, 12 million in 2030
- VTE Incidence 900,000 annually
- Market share- Warfarin 57%/NOACs 43%
  - Rivaroxaban 800,000 (48%), Apixaban 500,000 (34%), Dabigatran 300,000 (18%)
- Intracranial hemorrhage (reversal indicated)
  - Dabigatran 0.31%/yr = 900 per year
  - Rivaroxaban (0.5%/yr) + Apixaban (0.4% /yr) = 4000/yr + 2000/yr = 6000/yr

Collili S et al. Am J Cardiol 2013: CDC 2014; Naderi S et al Am J Med 2013; Barnes GD et al. Am J Med 2015; Connolly S et al. MEJM 2009; Patel M et al. NEJM 2011; Connolly S et al. NEJM 2011

Indications for Reversal Agents

- Major GI Hemorrhage-1-3%/year (Reversal discretionary)
  - 20%-30% require ICU care (Sengupta N et al Amer J Gastro 2015; Witt D et al. Arch Intern Med 2012)
  - Dabigatran 0.4% /yr = 1200/yr
  - Apixaban (0.2%) + Rivaroxaban (0.8%) = 1000/yr + 6400/yr= 7400/yr
- Emergency surgery (Reversal indicated)
  - Total US patients on AC for thromboembolism = 5-6 million
    - 1.6 million patient visits on NOACs
  - Annual acute care surgery rate 1290 per 100,000 (Gale SC et al. J Trauma 2014)

Connolly S et al. MEJM 2009; Patel M et al. NEJM 2011; Connolly S et al. NEJM 2011

Predictions of reactions by payers

- Cost
  - Idarucizumab- cost per dose? $5-10,000?
  - Andexanet alfa- cost per dose- unknown?
  - PER977- cost per dose- unknown?
- Availability- broad- most major medical center emergency departments

Questions ?