ANTIDOTES POUR ANTICOAGULANT ORAL DIRECT :

ACTUALITÉS ET PRATIQUES

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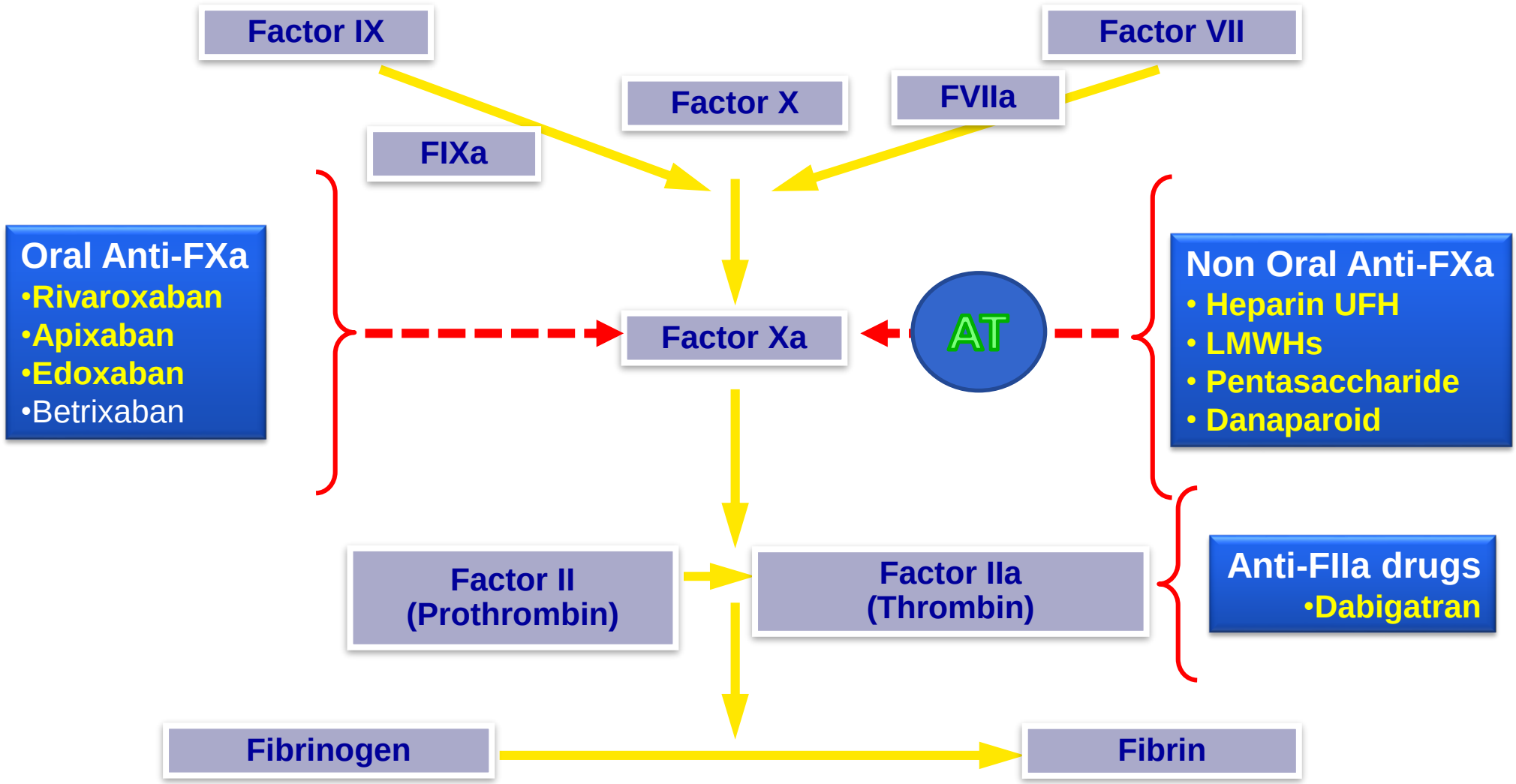
LIENS D’INTÉRÊT PROFESSIONNEL
PR I ELALAMY

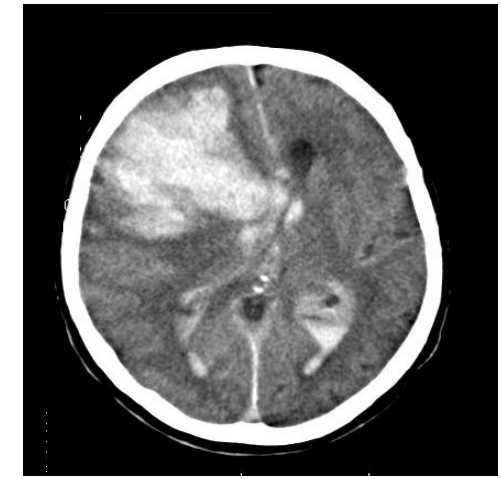
- Daiichi-Sankyo, Boehringer-Ingelheim, Bayer, Sanofi-Aventis, BMS, Pfizer, Astra-Zeneca, Eli-Lilly

ANTICOAGULANT TARGET SITES



QUESTIONS PRATIQUES CHEZ LES PATIENTS AODS : COMPLICATIONS HÉMORRAGIQUES

- Interrompre
- Mesures de Base :
  - Hémostase locale.
  - Remplissage (éviter colloides, si possible)
  - Traitement de Support
  - produits (CG, FFP, si nécessaire)
  - Agents anti-fibrinolytiques (Tranexamic acid) (Surtout muqueux hyper-fibrinolytique)
  - Maintien d'une diurèse



- PCC 25-50 IU/kg

  - **Bases : mêmes mesures que pour les hémorragies sous AVK menaçant le pronostic vital (excepté administration de Vit.K-)**

Bauersachs RM, et al Im Namen der Rivaroxaban Konsensus Gruppe. Perioperatives Management der Antikoagulation mit Rivaroxaban. Klinikarzt 2012;41:i

Qu’est-ce qui caractérise un véritable antidote?

A true antidote

- is efficacious
- provides immediate, complete, and sustained reversal

A specific antidote

- acts only against the target drug
- provides benefits in terms of safety
- no other interactions
- no prothrombotic effects

Qu'est-ce qui caractérise un véritable antidote?

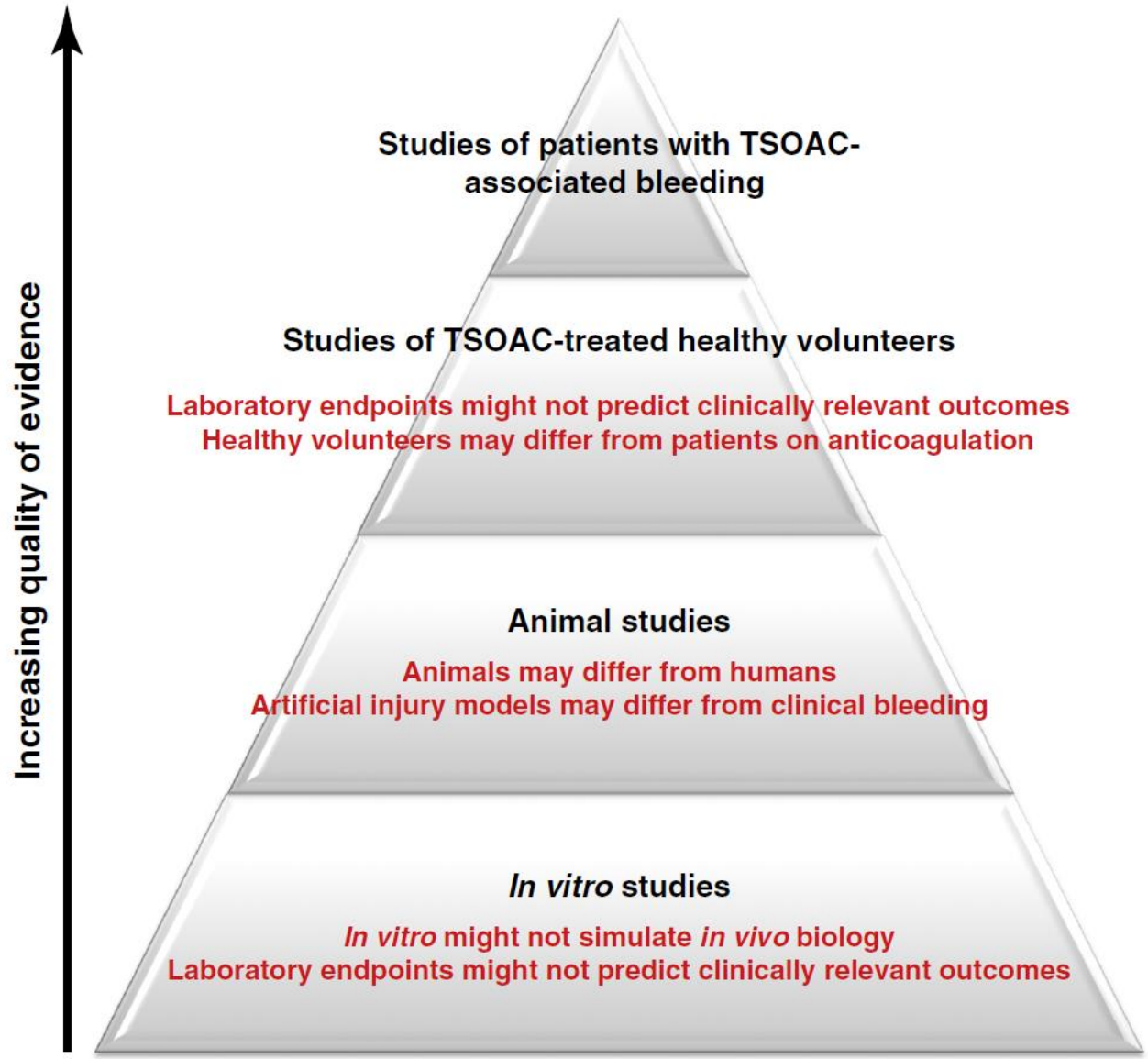
	Target	Mechanism of action	Investigation status
Idarucizumab Praxbind®	Dabigatran	Humanized Fab: specifically binds dabigatran (binding affinity ~350× higher than binding of dabigatran to thrombin)	Bleeding patients and surgical patients[2]
Andexanet alfa (PRT064445)	FXa inhibitors	Recombinant human FXa variant: competitive affinity for direct FXa inhibitors	Healthy volunteers[3–5]
Aripazine (PER977) Ciraparantag	Universal	Synthetic small molecule: charge–charge interactions (heparin); hydrogen bonds (NOACs)[6]	Phase I[7]

Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

Fab, fully humanized antibody fragment; FXa, Factor Xa

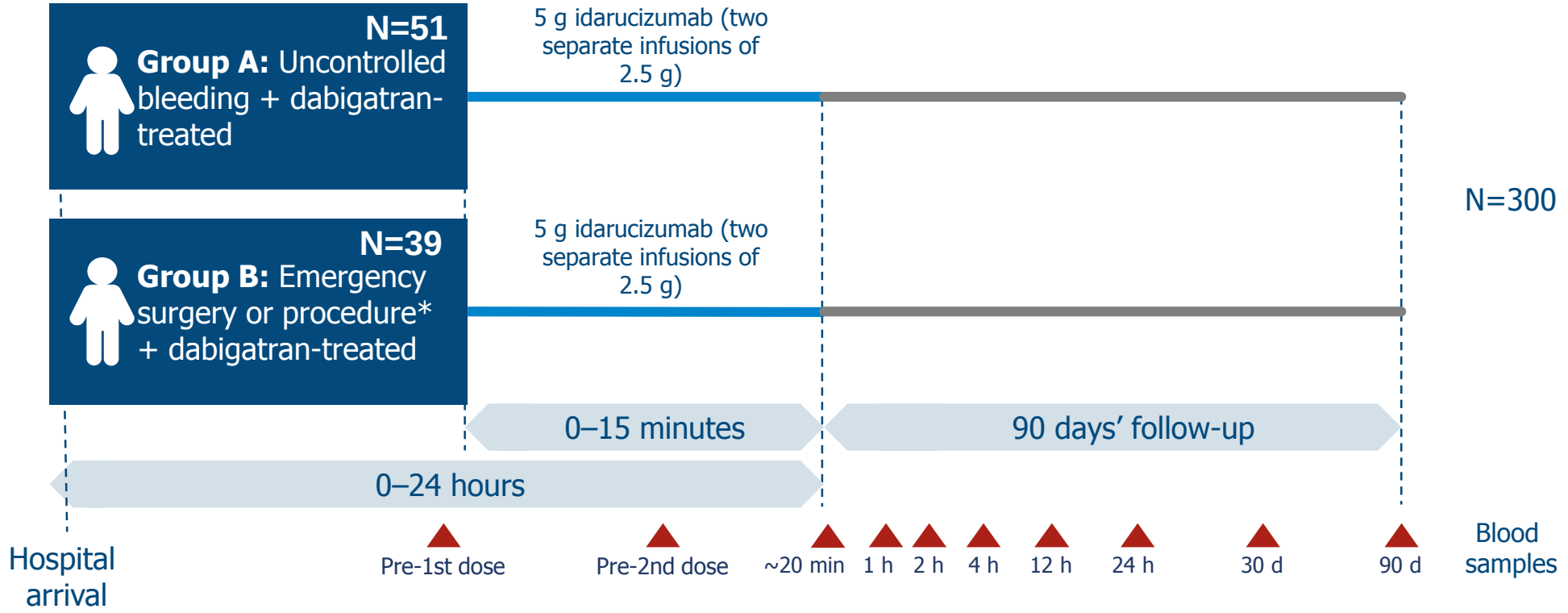
1. Adapted from Lauw M et al. Can J Cardiol 2014;30:381–4; 2. Clinicaltrials.gov: NCT02104947;
3. Clinicaltrials.gov: NCT02220725; 4. Clinicaltrials.gov: NCT02207725; 5. Bakhru S et al. AHA 2013; abstr 11395;
6. Crowther et al. S100ab - Session CS.03 - Management of Cardiovascular Disease. AHA 2014, Chicago, USA;
7. http://www.perosphere.com/content/news/httpwww.perosphere.comcontentnewsreleases042513.htm accessed September 2014

STRATÉGIE DE DÉVELOPPEMENT DES ANTIDOTES



Siegal et Cuker Drug Discov Today 2014

RE-VERSE AD™ is a multicentre, open-label, single-arm Phase III trial



Primary endpoint

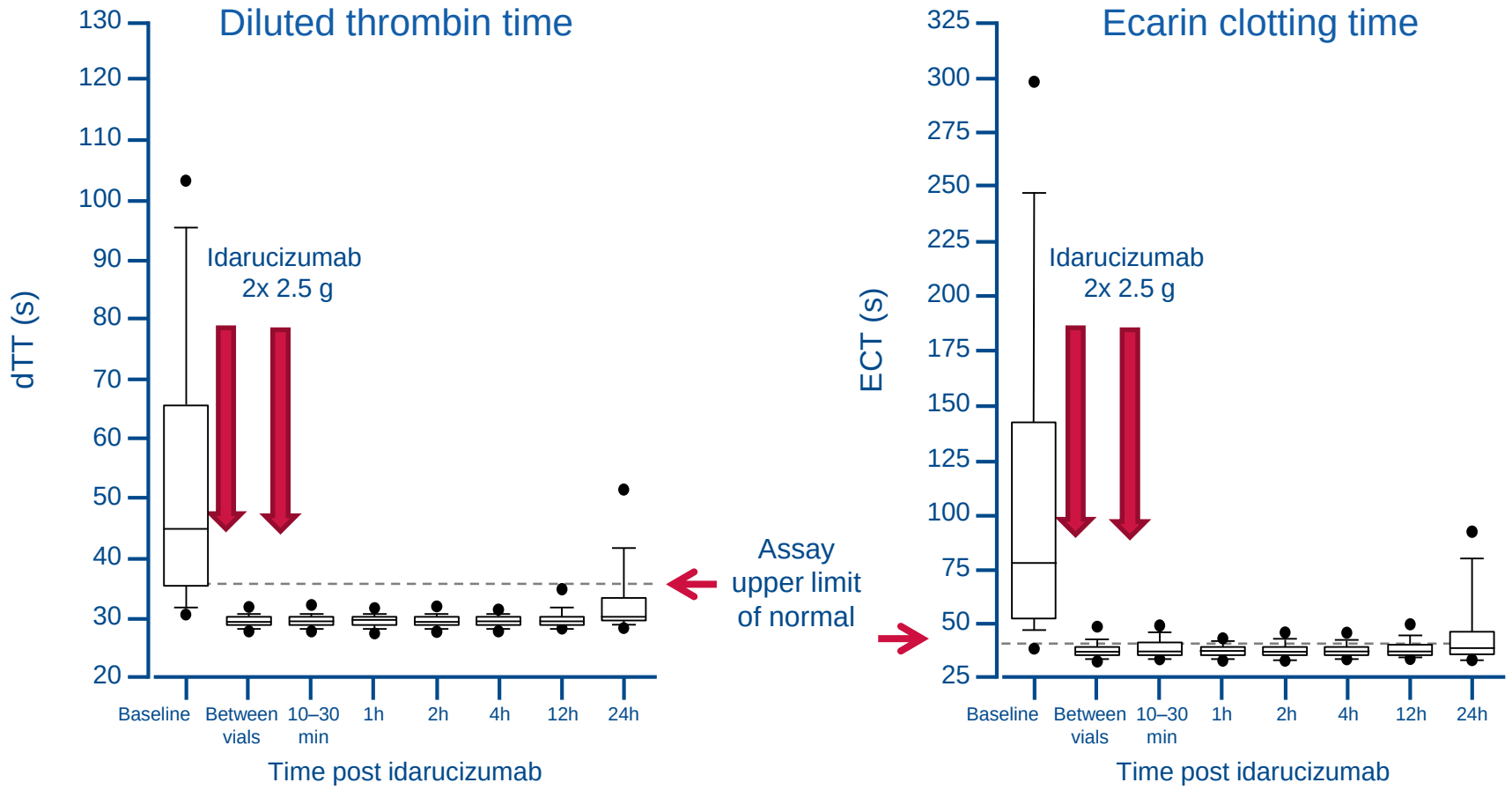
Reversal of dabigatran activity

Multiple safety endpoints

Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

*Other than bleeding; Pollack et al. Thromb Haemost 2015

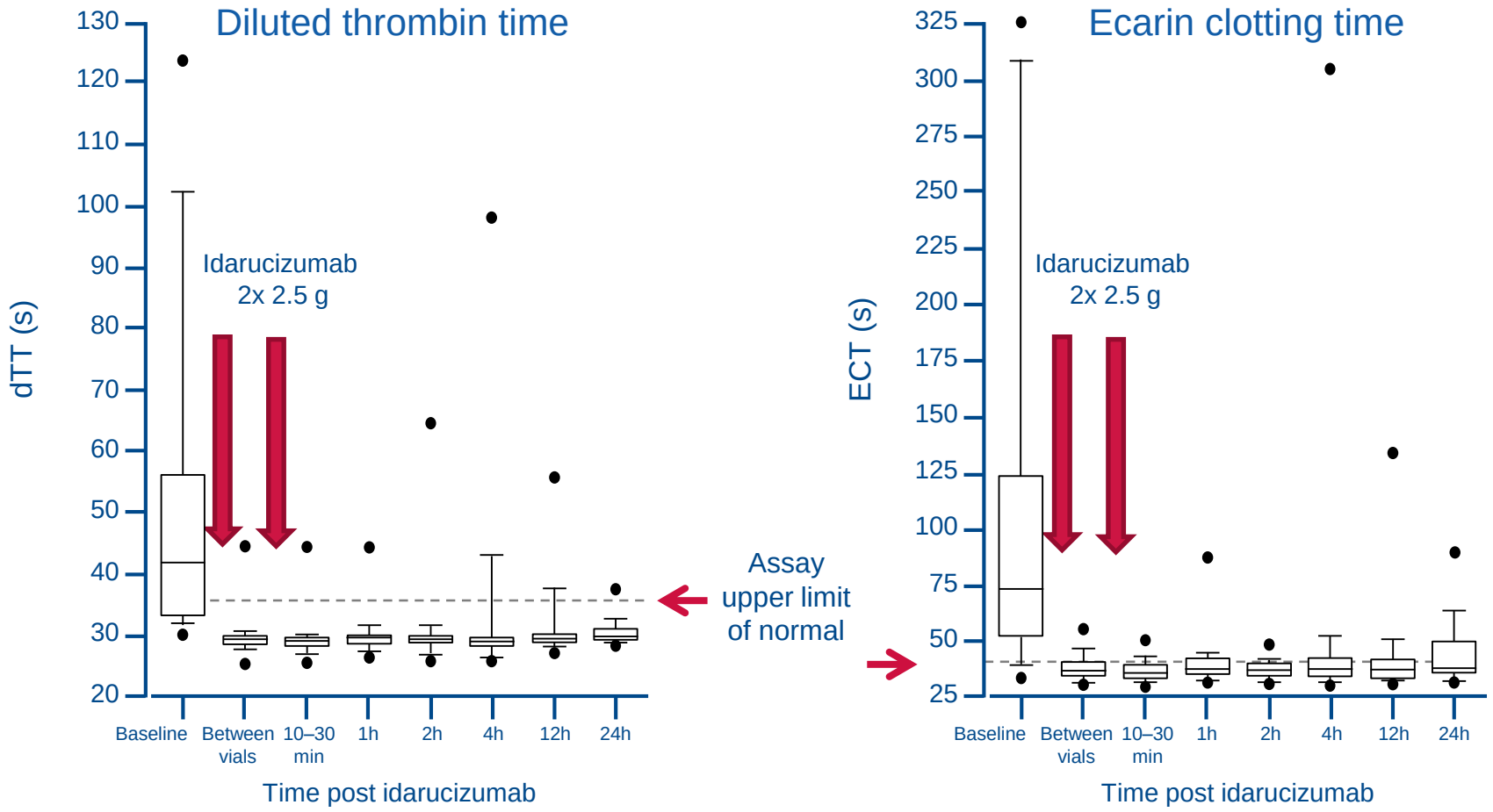
RESULTS: Primary endpoint in Group A: dTT and ECT
Reversal of dabigatran-anticoagulation with idarucizumab



Pollack et al. NEJM 2015

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

RESULTS: Primary endpoint in Group B: dTT and ECT
Reversal of dabigatran-anticoagulation with idarucizumab



Pollack et al. NEJM 2015

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

RE-VERSE AD™: thrombotic events

- Thrombotic events reported in only five patients over a period of 90 days of follow up
  - 1 early event (DVT + PE) 2 days after idarucizumab administration
  - None of these 5 patients were receiving any antithrombotic therapy when the events occurred

25 sept 2015
CHMP of EMA issued a positive opinion recommending EUROPEAN APPROVAL of Idarucizumab
If final EU approval adopted => grant marketing authorization in EU by the end of November 2015…

These events reflect the underlying thromboembolic potential of these patients when not on anticoagulation therapy

Pollack et al. NEJM 2015

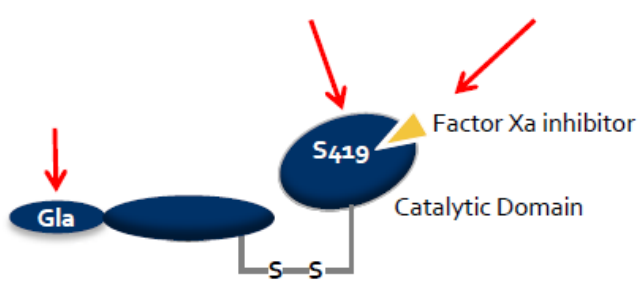
RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

Andexanet: Designed to Reverse Activity of Factor Xa Inhibitors

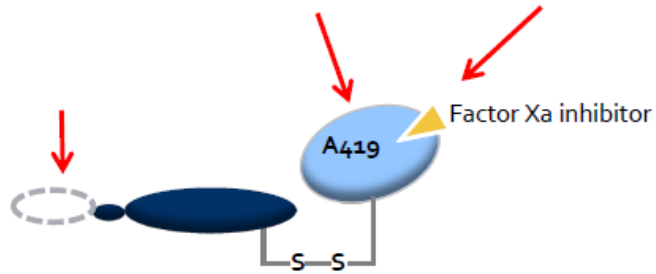
Nature Medicine (2013),19(4): 446-51

Recombinant engineered version of human factor Xa produced in CHO cells

- Acts as a fXa decoy and retains high affinity for all direct fXa inhibitors
- Change of Serine to Alanine to eliminate catalytic activity and prevent prothrombin cleavage
- GLA domain removed to prevent anticoagulant effect

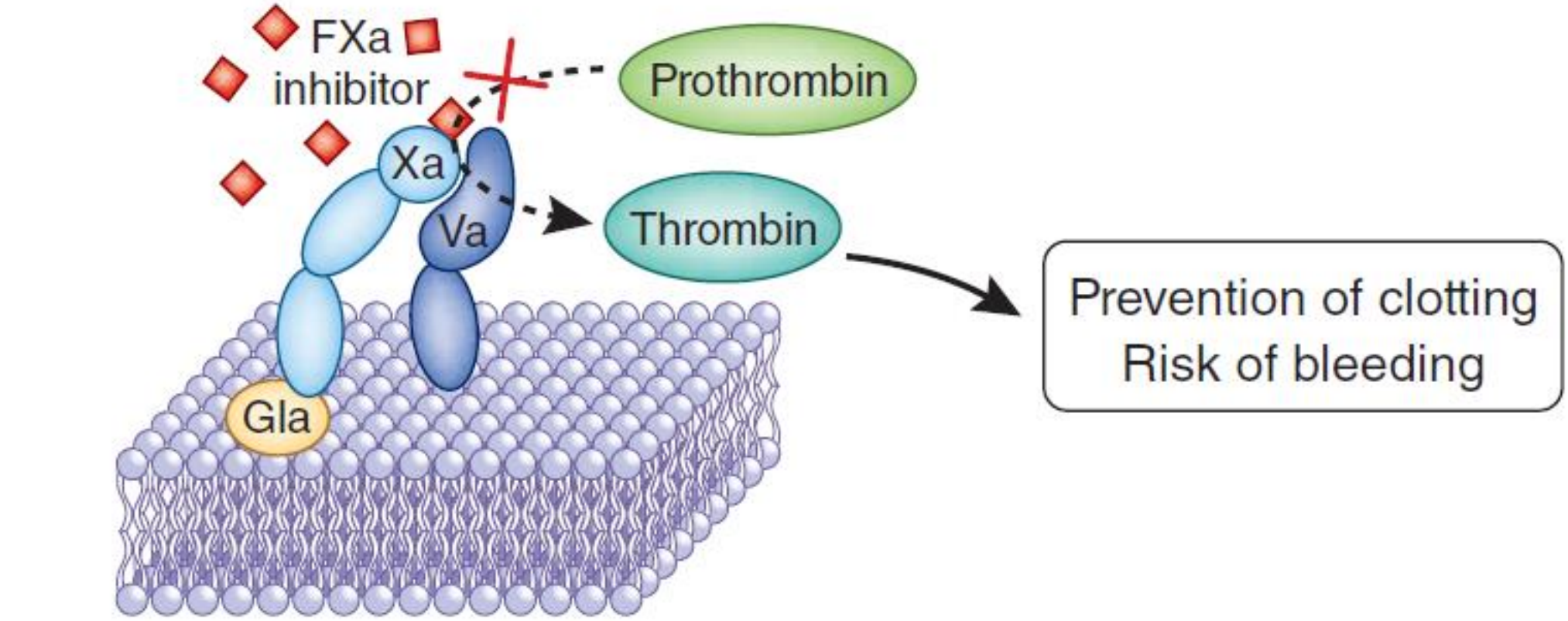


Factor Xa



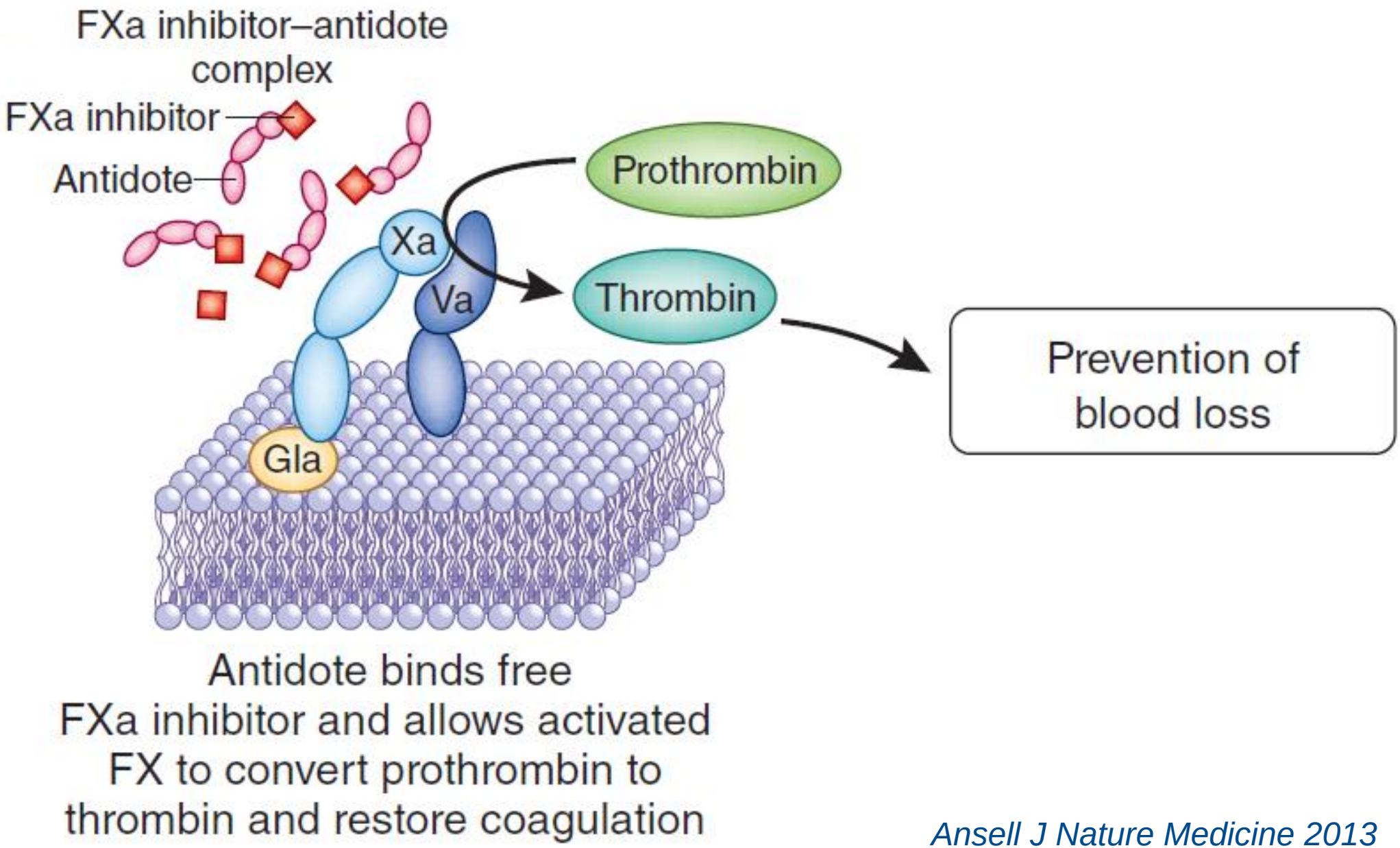
Andexanet Alfa

- No known interaction with other coagulation factors except Tissue Factor Pathway Inhibitor (TFPI)
- Retains high affinity for Antithrombin III-inhibitor complex and can reverse ATIII-dependent anticoagulant effects of enoxaparin and fondaparinux in vitro and in vivo



FXa inhibitor binds activated FX and prevents thrombin generation

Ansell J Nature Medicine 2013



Ansell J Nature Medicine 2013

ANDEXANET ALPHA FOR THE REVERSAL OF FACTOR XA INHIBITOR ACTIVITY

ANDEXANET ALFA A NOVEL ANTIDOTE TO THE ANTICOAGULANT EFFECTS OF FXA INHIBITORS

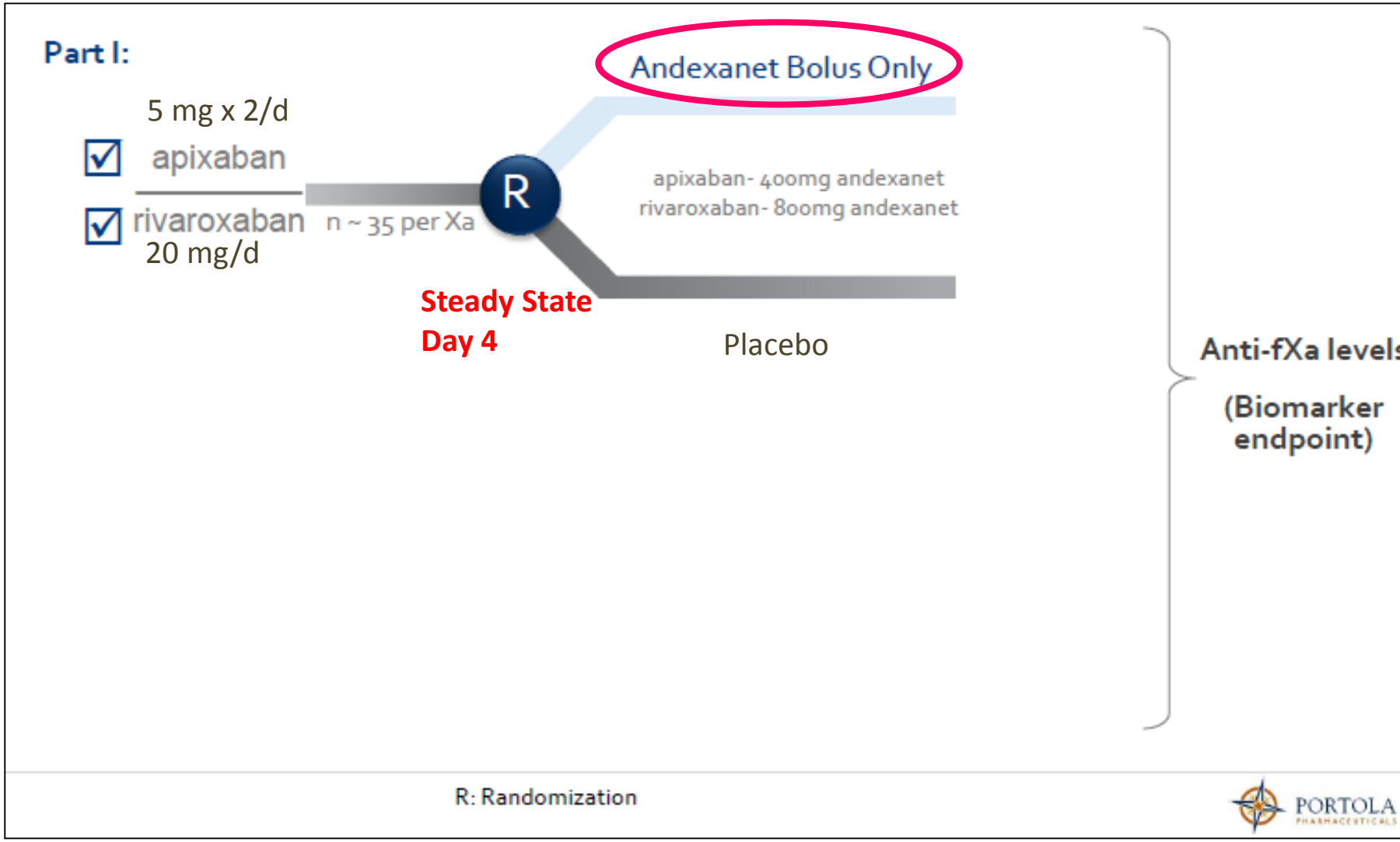
ANNEXA-A : Apixaban

ANNEXA-R : Rivaroxaban

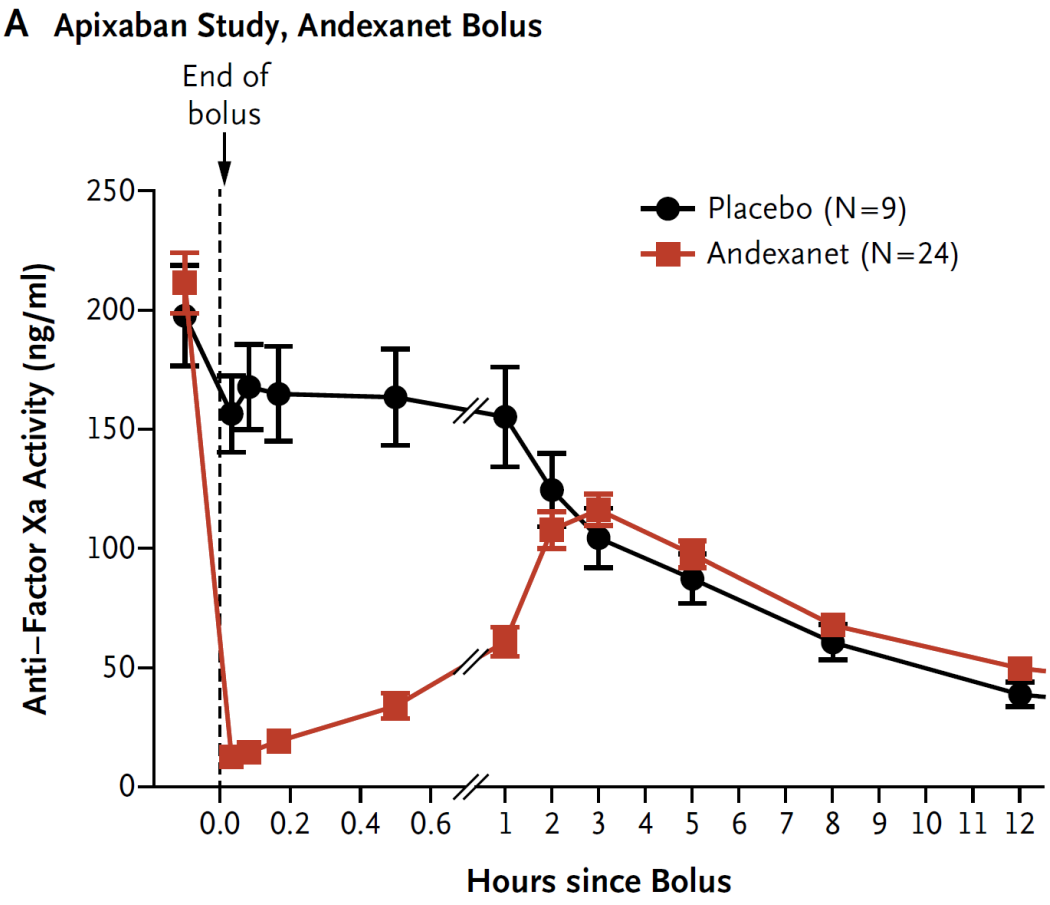
Siegal et al N Engl J Med 2015;373: 2413-2424

*On July 7, 2014, Portola announced that it has entered into another clinical collaboration agreement with Daiichi Sankyo, to study andexanet alfa with edoxaban in a Phase III program called **ANNEXA-E***

ANNEXA studies - Design



RESULTS: PRIMARY END-POINTS

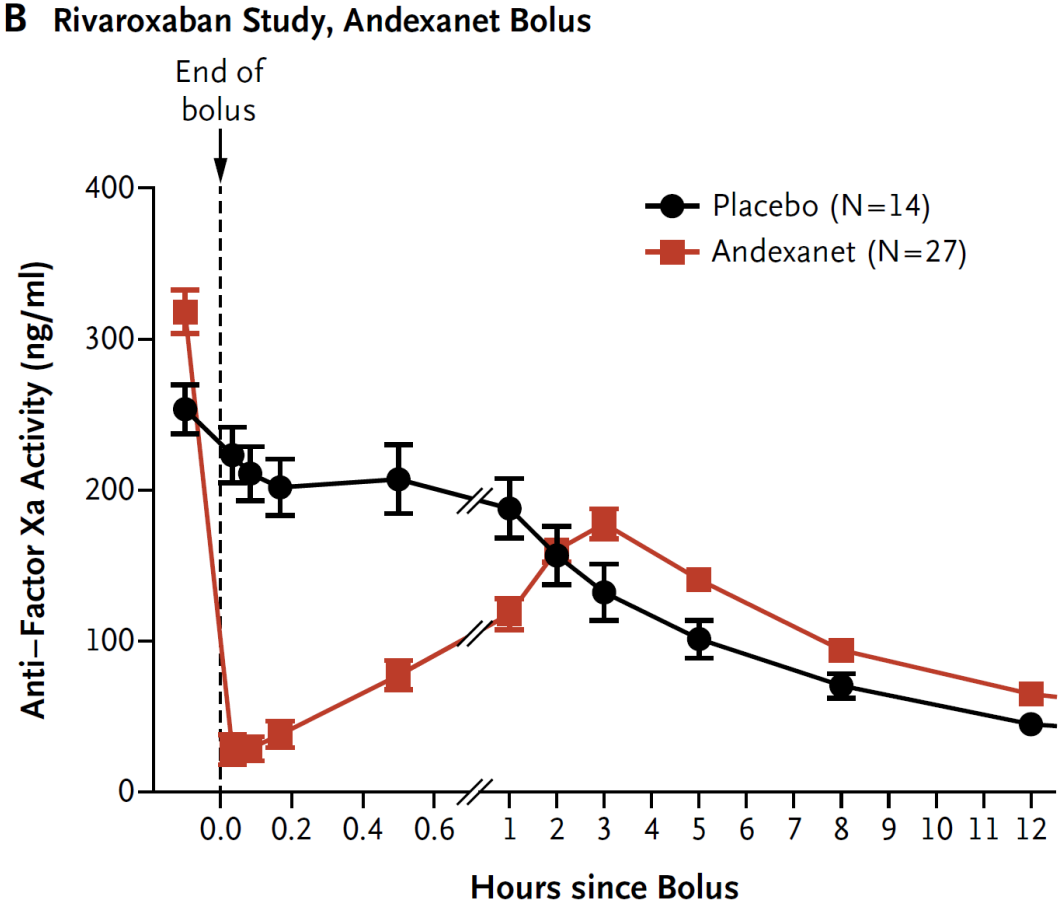


Anti-Xa activity Reduction

94 ± 2% Andexanet

21 ± 9% placebo

p<0.001



Anti-Xa activity Reduction

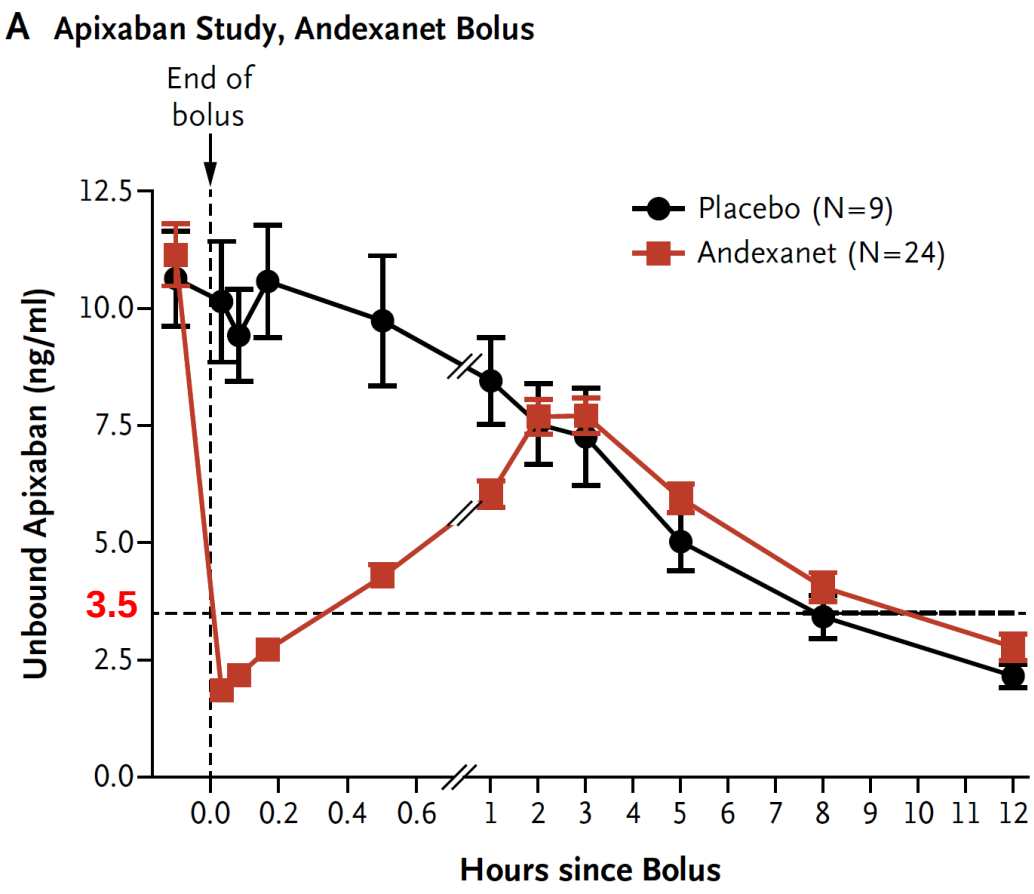
92 ± 11% Andexanet

18±15% placebo

p<0.001

Siegal et al N Engl J Med 2015;373: 2413-2424

RESULTS: SECONDARY END-POINTS

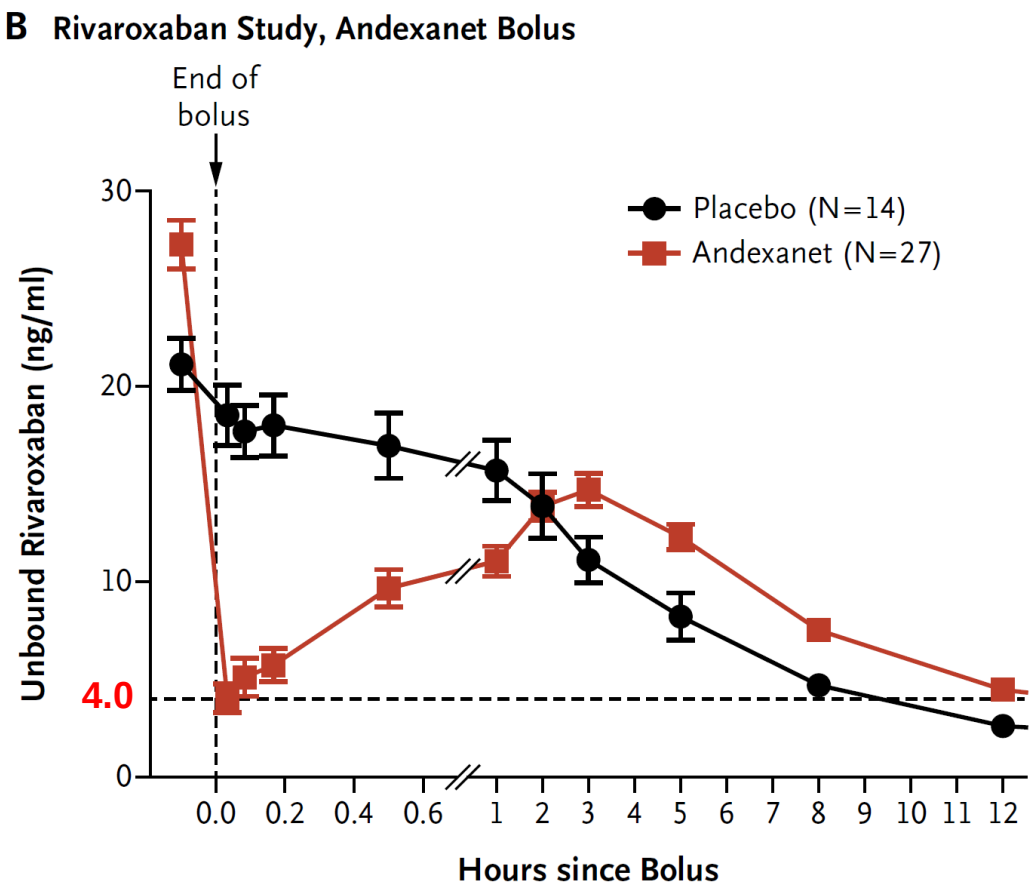


Unbound Xa Inbibitor Reduction

83% Andexanet

13% placebo

p<0.001



Unbound Xa Inbibitor Reduction

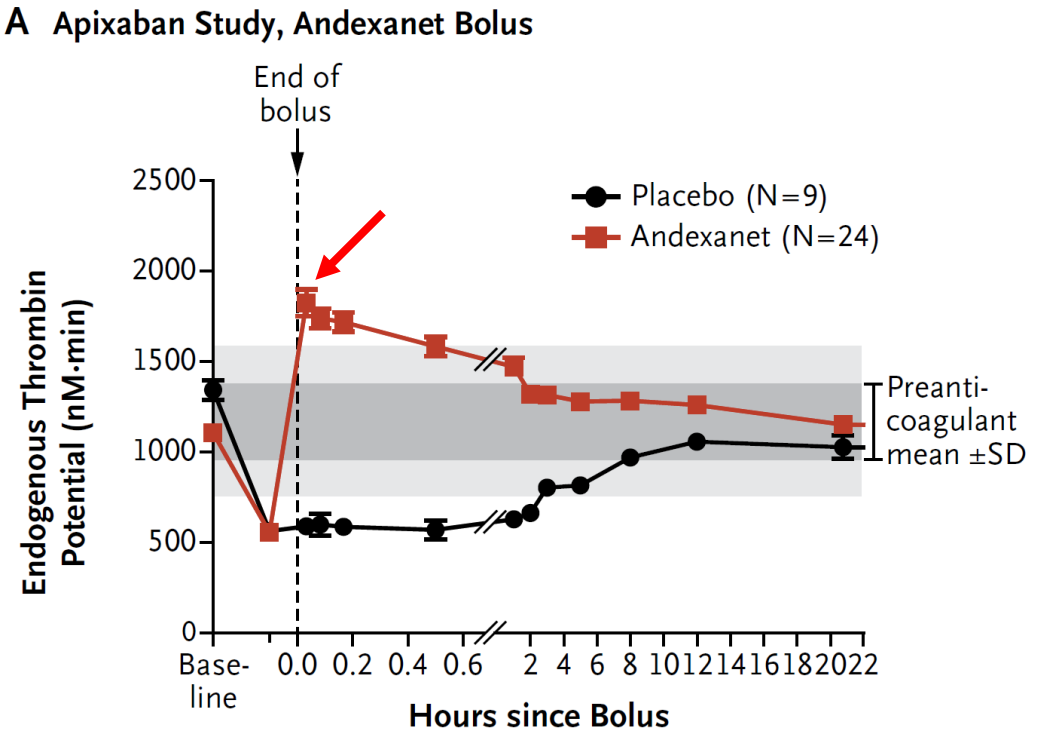
86% Andexanet

19% placebo

p<0.001

Siegal et al N Engl J Med 2015;373: 2413-2424

RESULTS: SECONDARY END-POINTS

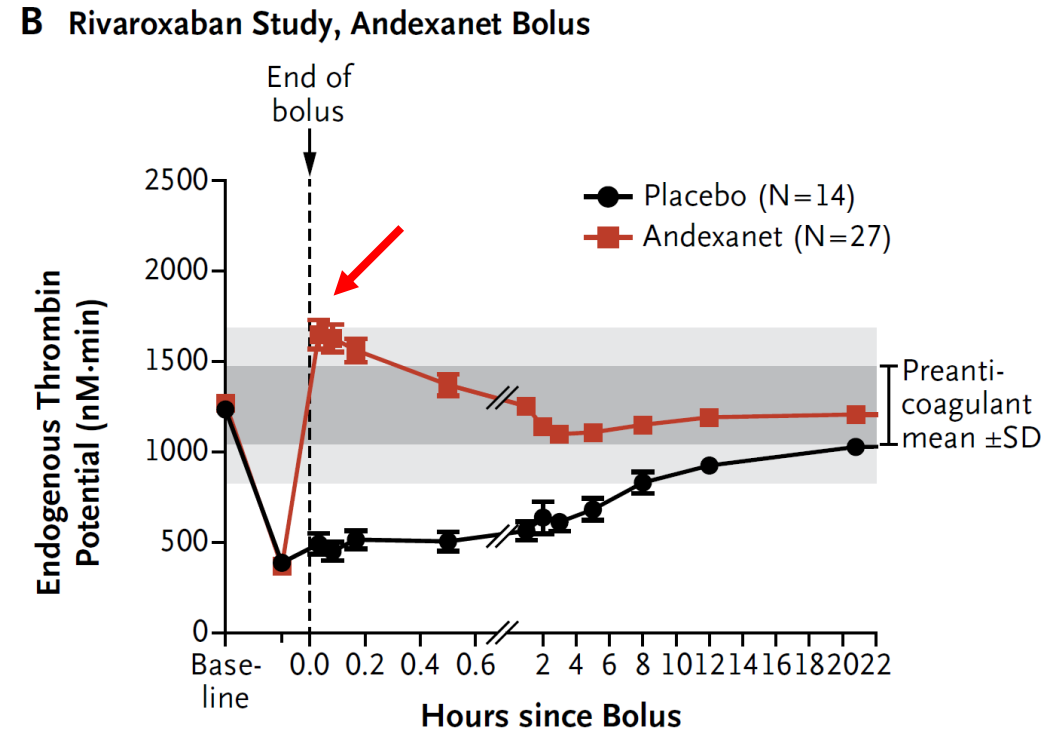


Restored Thrombin Generation

1323 ± 335 nM.min Andexanet

88 ± 125 nM.min placebo

p<0.001



Restored Thrombin Generation

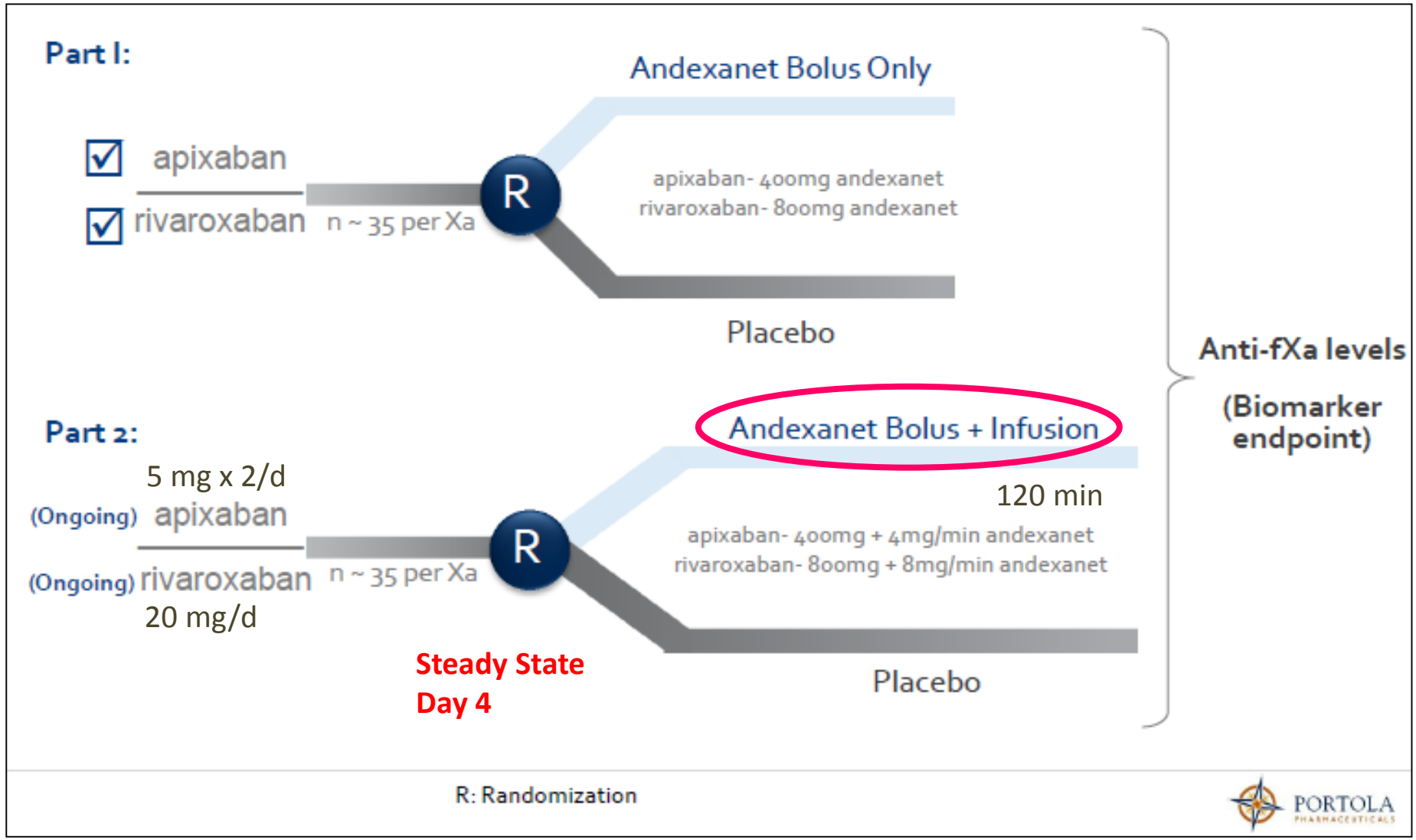
1314 ± 331 nM.min Andexanet

174 ± 104 nM.min placebo

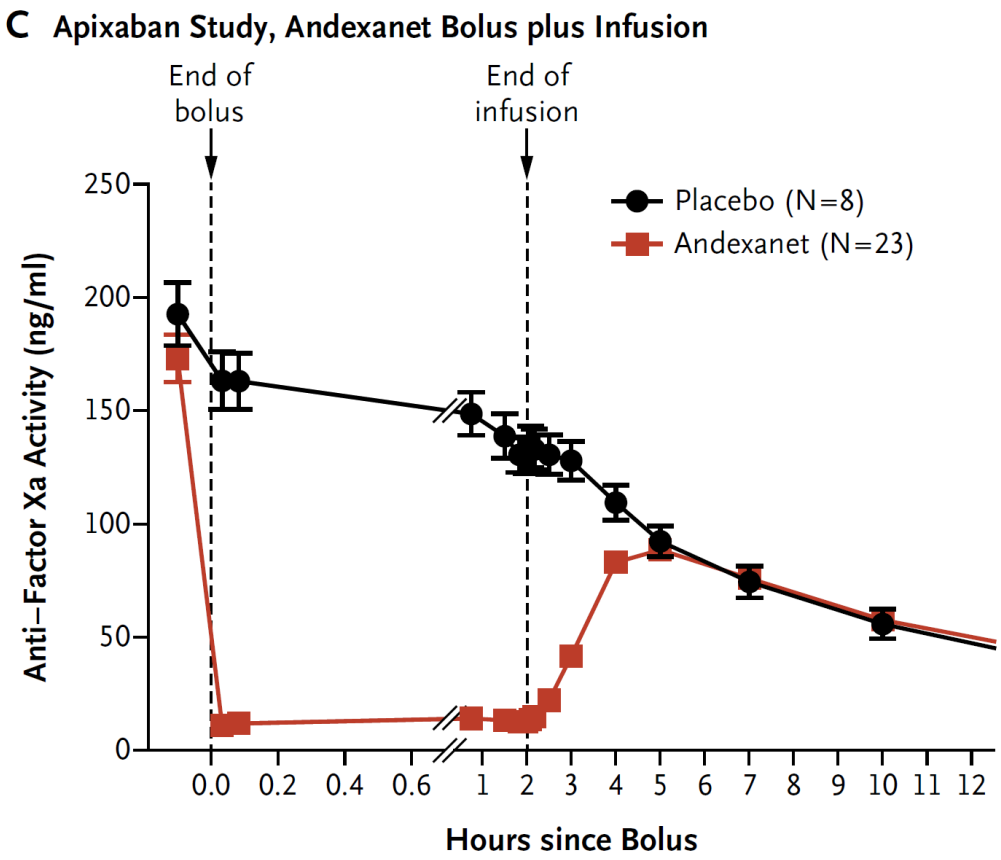
p<0.001

Siegal et al N Engl J Med 2015;373: 2413-2424

ANNEXA studies - Design



RESULTS: PRIMARY END-POINT

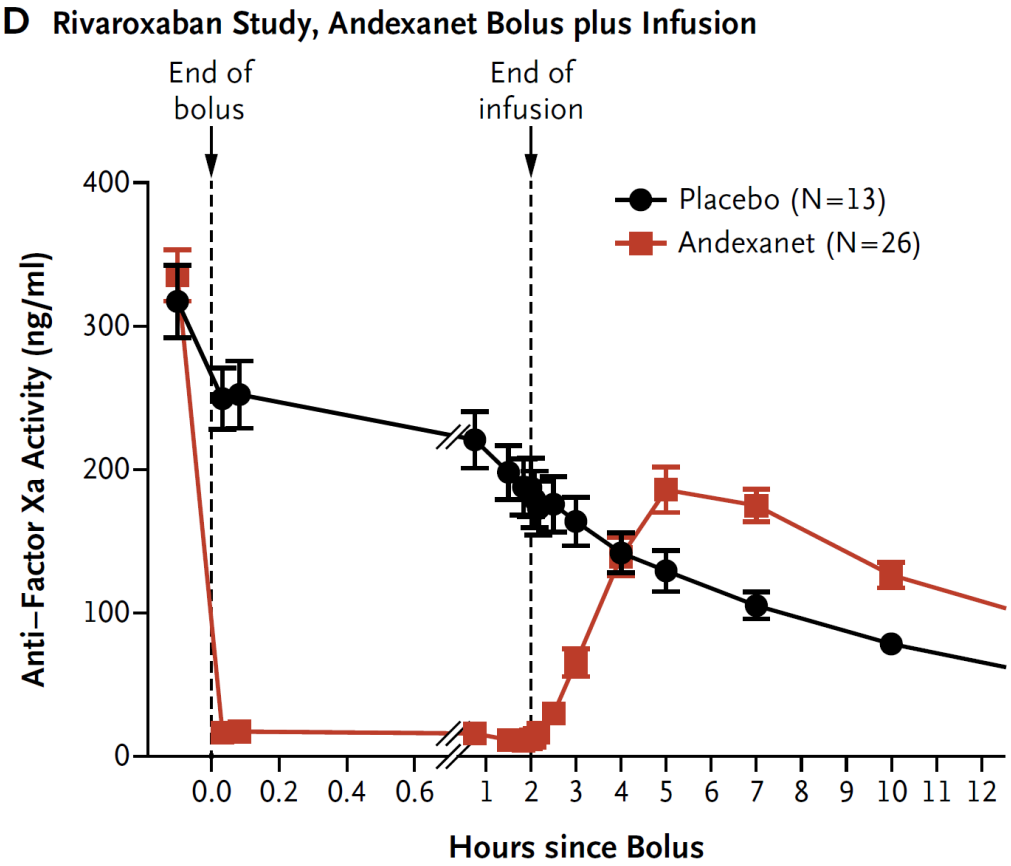


Anti-Xa activity Reduction

92 ± 3% Andexanet

33 ± 6% placebo

p<0.001



Anti-Xa activity Reduction

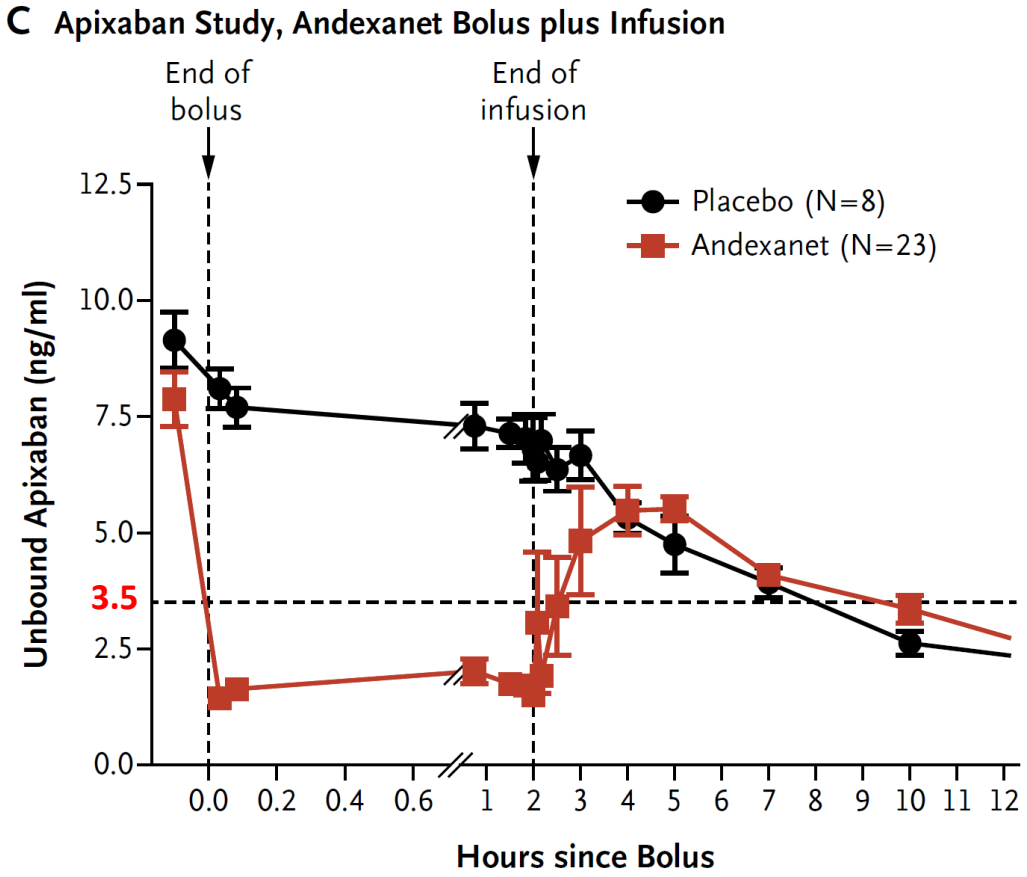
97 ± 2% Andexanet

45±12% placebo

p<0.001

Siegal et al N Engl J Med 2015;373: 2413-2424

RESULTS: SECONDARY END-POINT

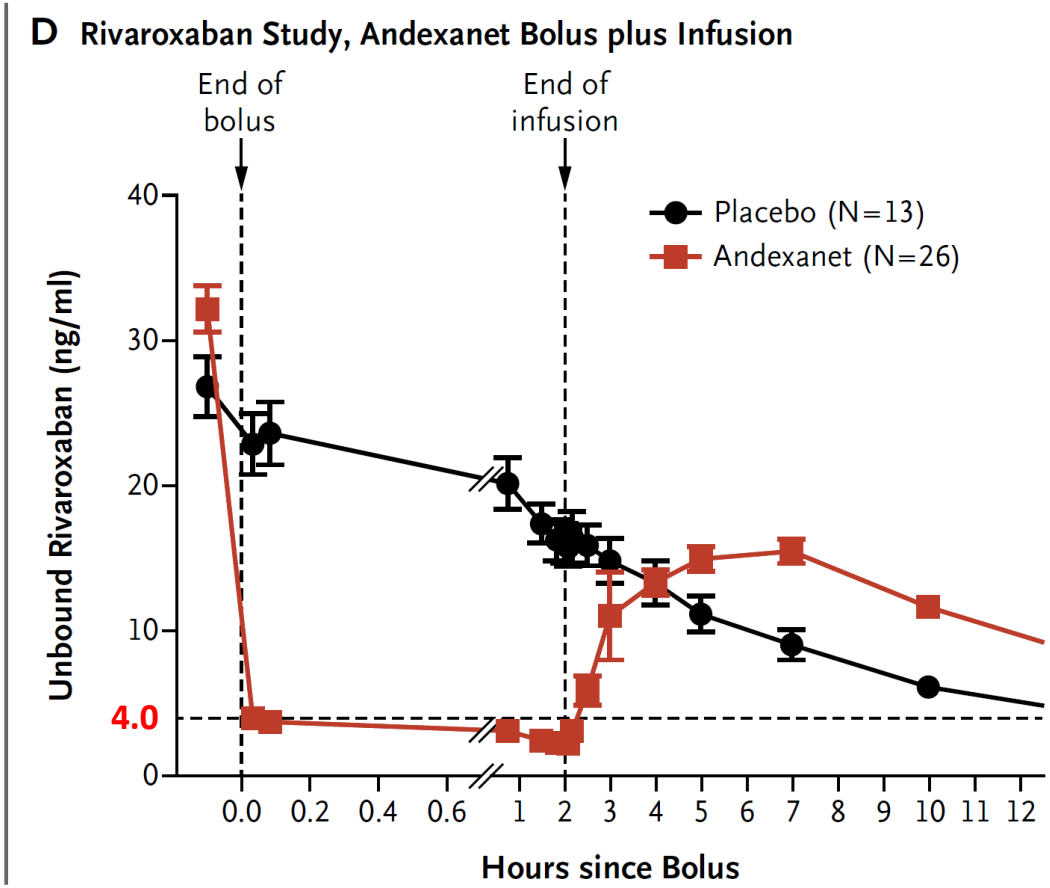


Unbound Xa Inbibitor Reduction

82% Andexanet

16% placebo

p<0.001



Unbound Xa Inbibitor Reduction

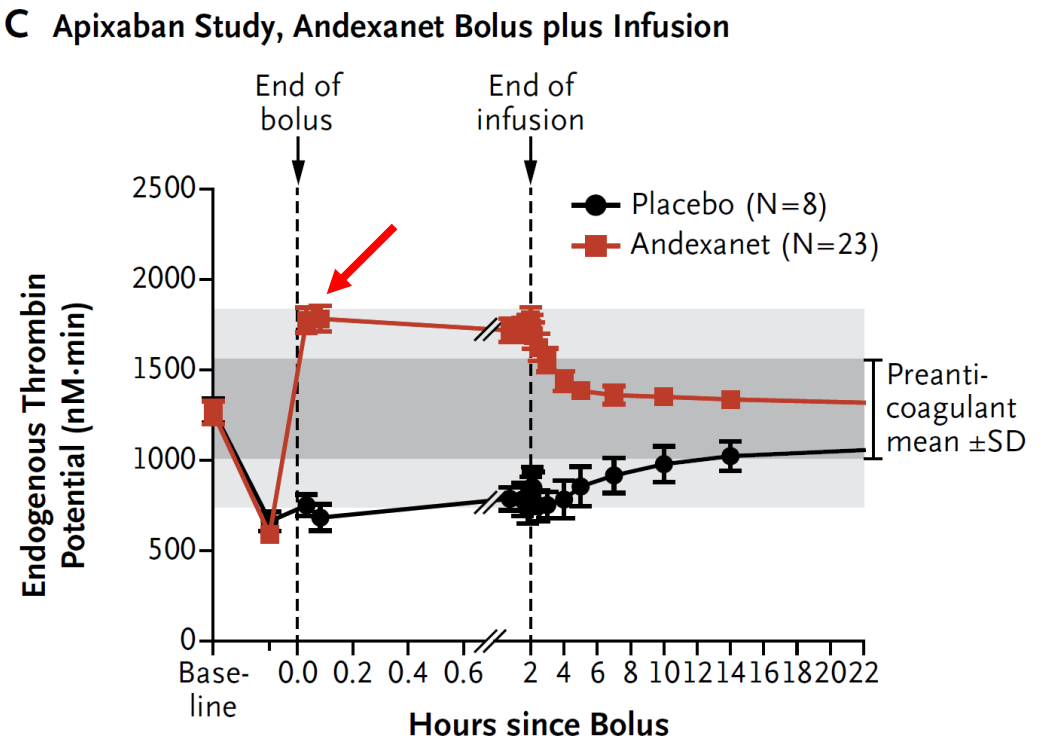
90% Andexanet

19% placebo

p<0.001

Siegal et al N Engl J Med 2015;373: 2413-2424

RESULTS: SECONDARY END-POINT

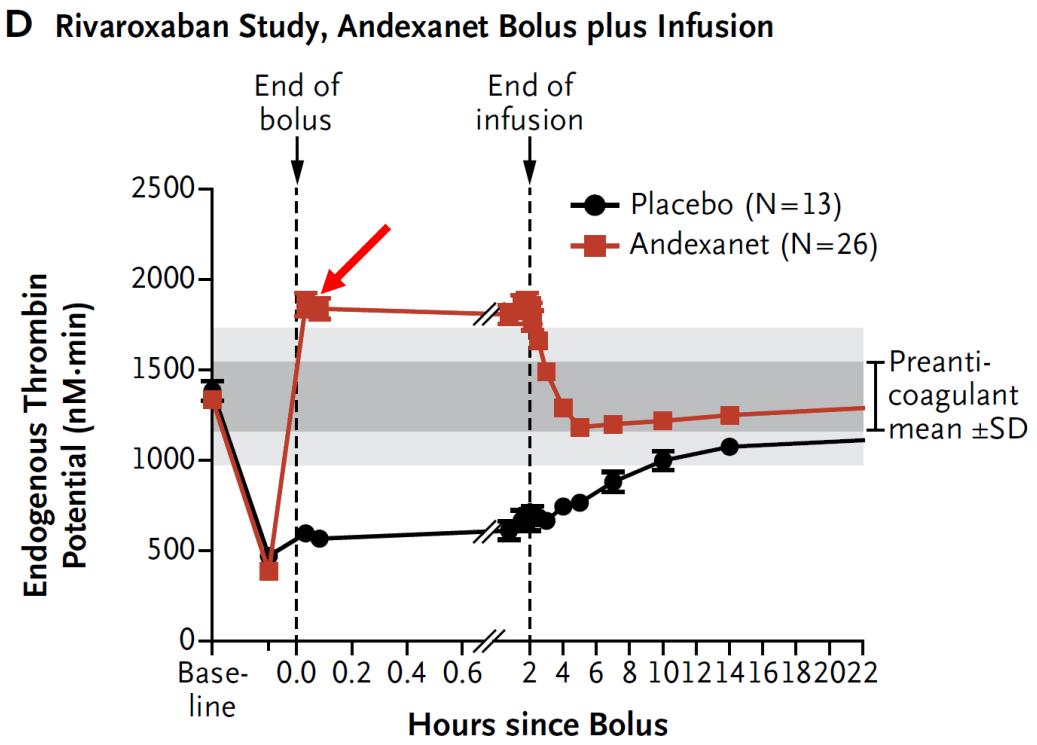


Restored Thrombin Generation

1193 ± 263 nM.min Andexanet

189 ± 185 nM.min placebo

p<0.001



Restored Thrombin Generation

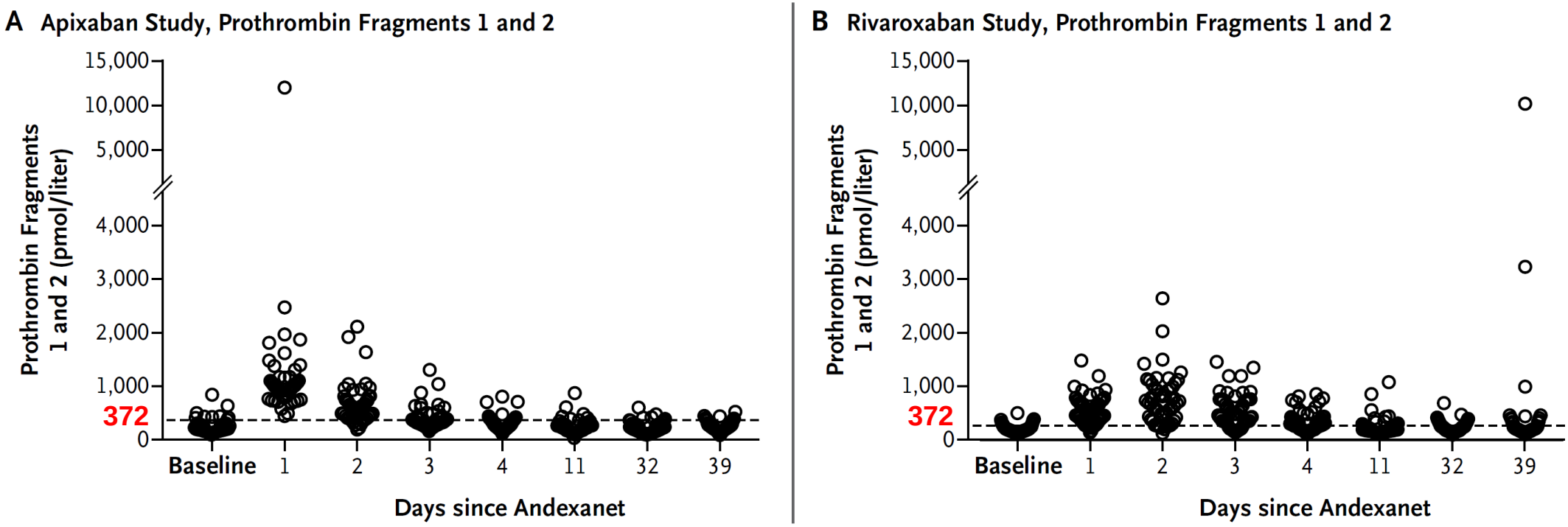
1510± 345 nM.min Andexanet

264 ± 141 nM.min placebo

p<0.001

Siegal et al N Engl J Med 2015;373: 2413-2424

RESULTS: SAFETY OUTCOMES

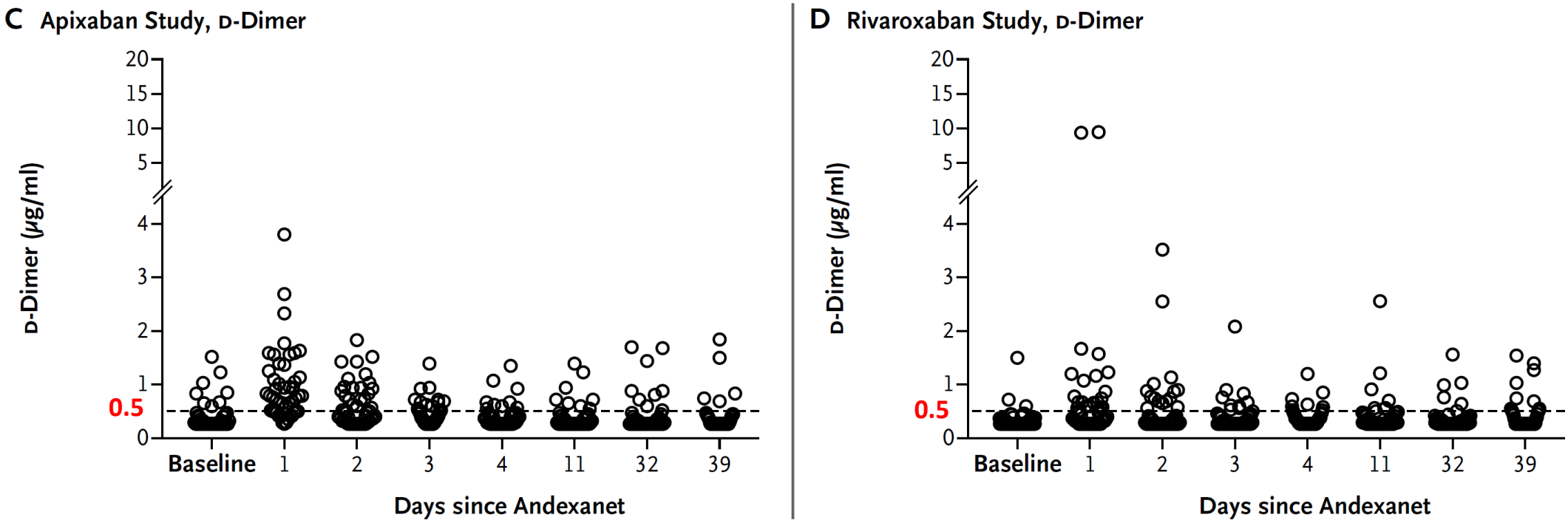


Transient elevations and return to normal range in 24 to 72 hours
No clinical thrombotic event
No correlation with increased thrombin generation

(All Part1 and Part2 Andexanet patients)

Siegal et al N Engl J Med 2015;373: 2413-2424

RESULTS: SAFETY OUTCOMES

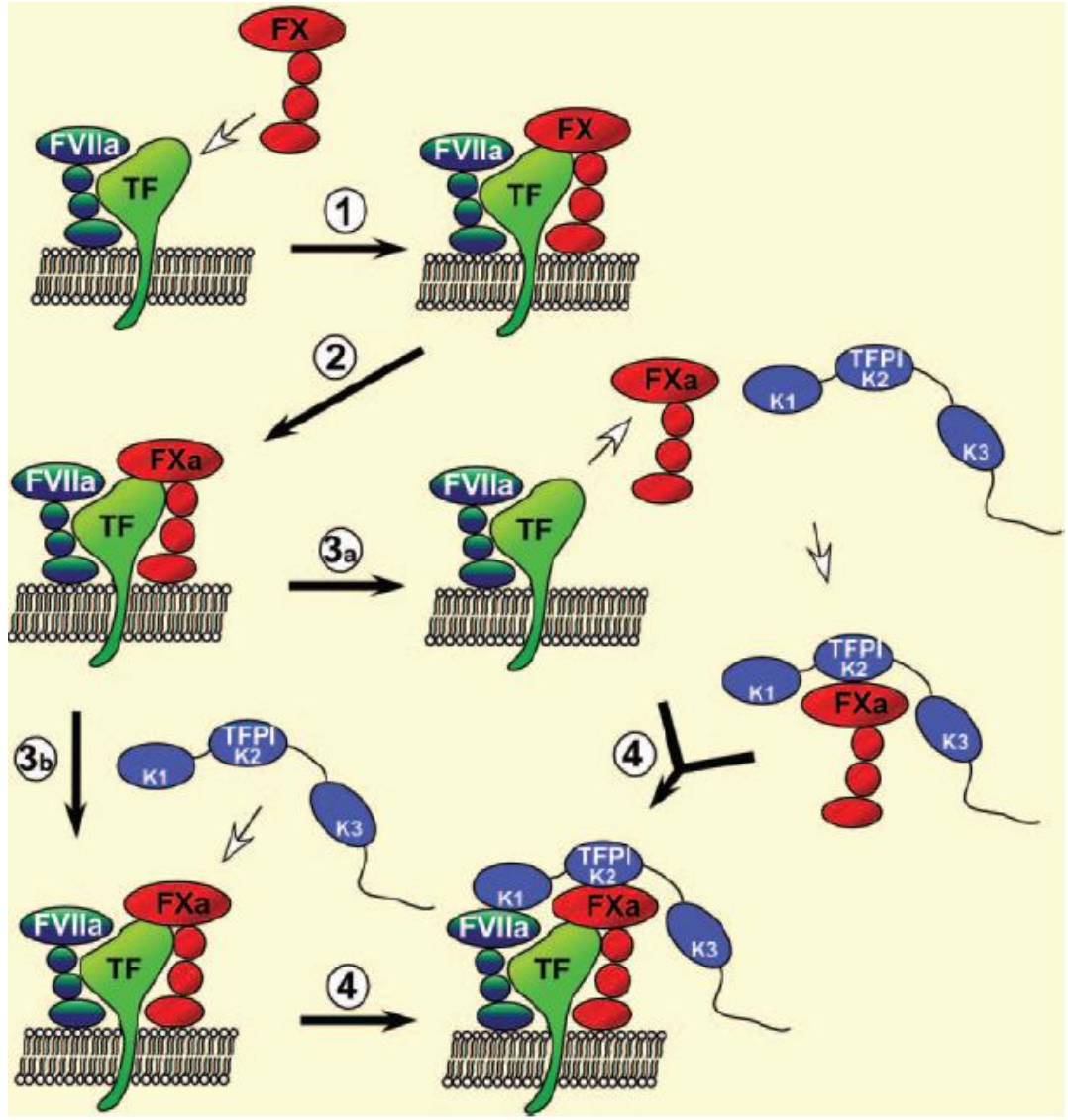


Transient elevations and return to normal range in 24 to 72 hours
No clinical thrombotic event
No correlation with increased thrombin generation

(All Part1 and Part2 Andexanet patients)

Siegal et al N Engl J Med 2015;373: 2413-2424

INHIBITION OF TF-DEPENDENT COAGULATION BY TFPI



Crawley M et al Arterioscl Thromb Vasc Biol 2008; 28:233-242

ANNEXA 4 *(to be conducted)*
Phase IV in bleeding patients

ANNEXA™-4 on Apixaban, Rivaroxaban and Enoxaparin

- **An open-label, multinational study in patients receiving fXa inhibitors presenting with acute major bleeding**
  - Two Primary Endpoints
    - First primary: Percent change from baseline in anti-fXa activity
    - Second primary: Occurrence of patients achieving "effective hemostasis" as adjudicated by an Independent Endpoint Adjudication Committee
- **Study is ongoing; to be conducted at over 50 sites in North America and Europe**
- **Plan to add edoxaban to study by mid-2015**

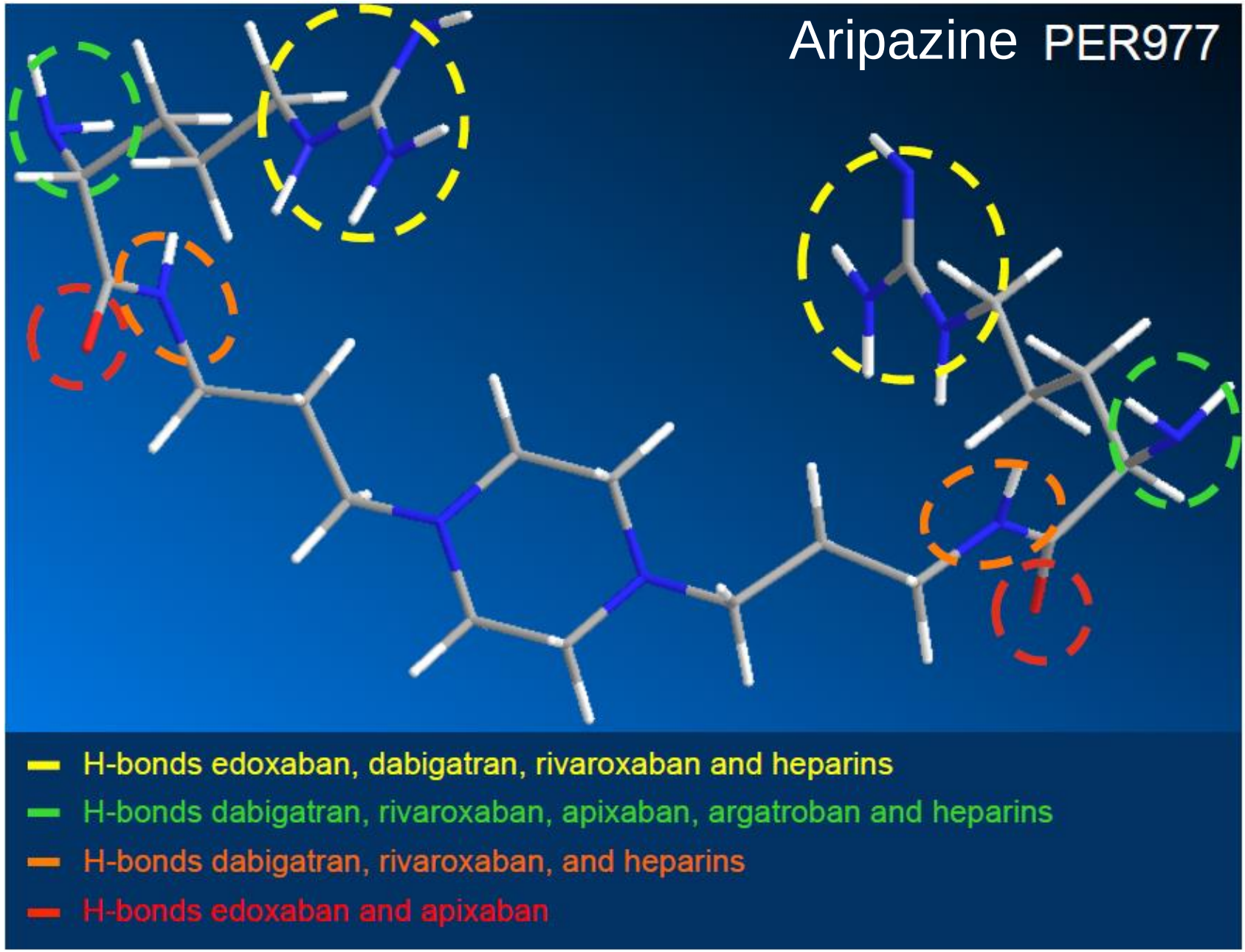
phase 3b–4 study "Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding"
(ClinicalTrials.gov number, NCT02329327)

Perosphere Inc.

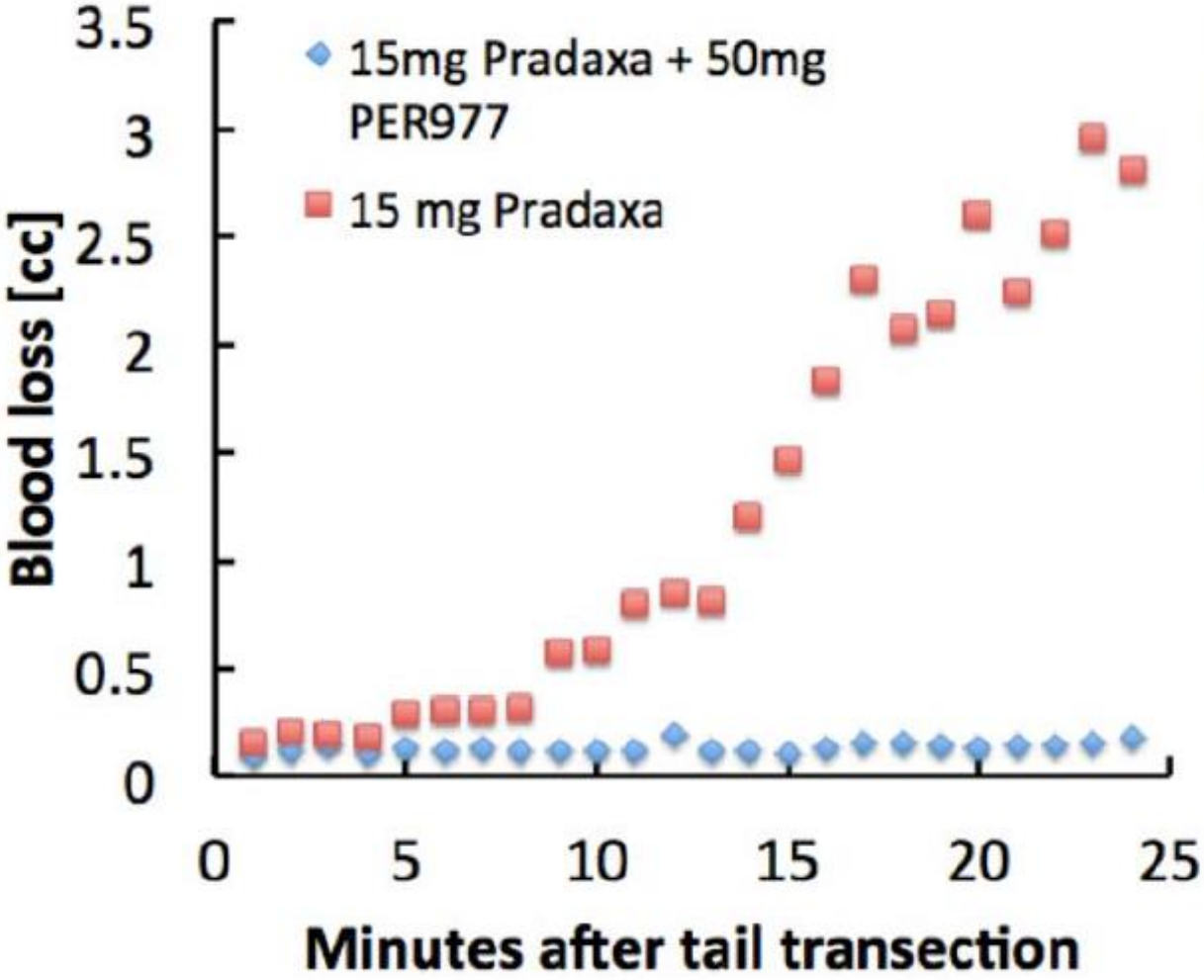
Ciraparantag

500 Da
Synthetic
Water soluble
Cationic
Stable >1y RT

Laulicht et al AHA 2012
Shah et al AMSRJ 2014

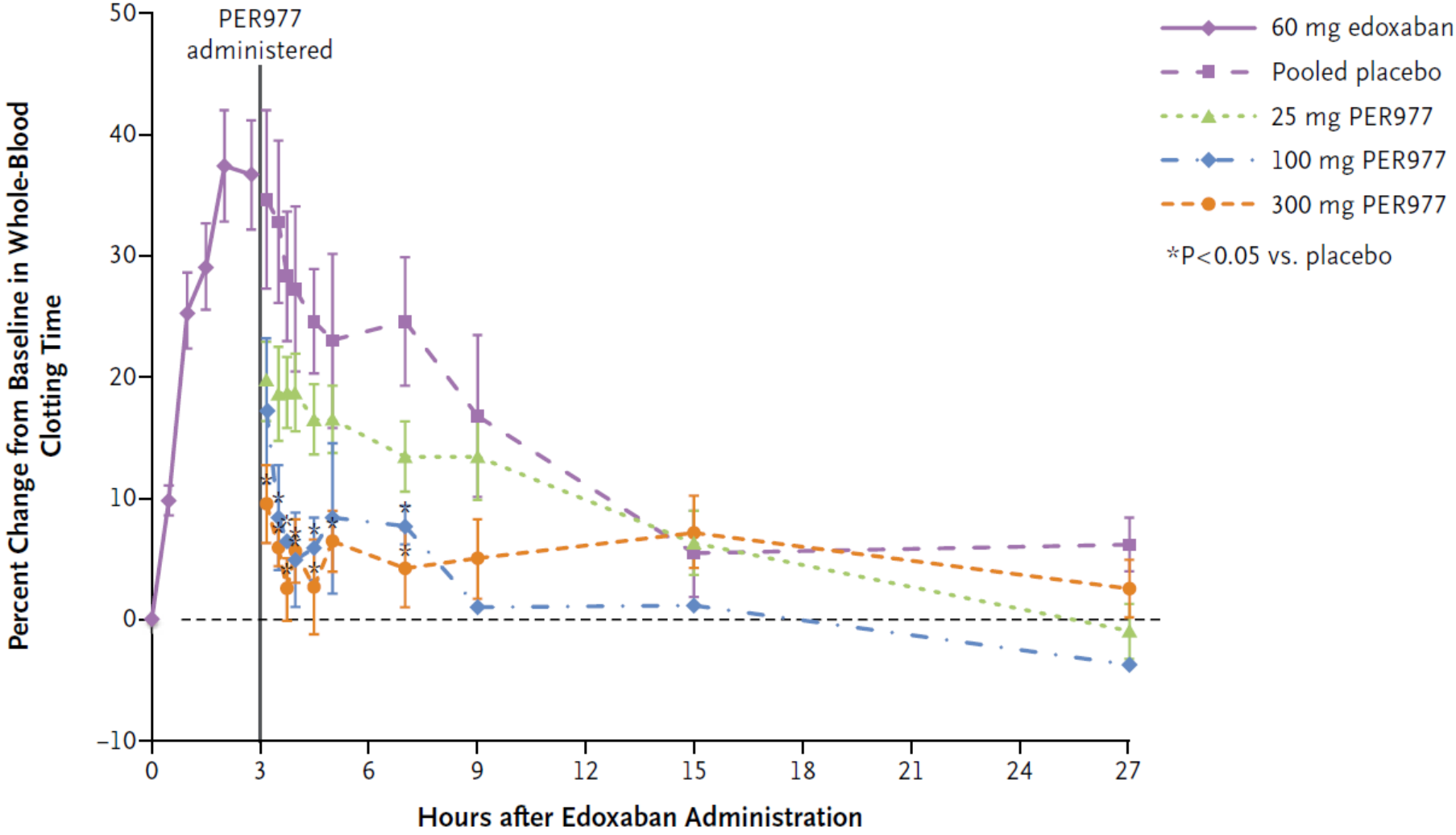


PER977 reverses ~100x overdose of dabigatran etexilate (15mg p.o.) in a rat tail transection model



No PER977 50mg PER977

80 healthy volunteers
60 mg Edoxaban po and bolus IV PER977 at peak



Ansell et al New Engl J Med 2014

AOD ET ANTIDOTES … ANTIDOUTES?

Co-morbiditités +++
Confirmation en pratique?
Co-administration et Coût…

RESPECT BONNES PRATIQUES

STOP SAIGNEMENT?

Modèles Animaux
Hétérogéneité+++

NEUTRALISATION CIBLÉE

REVERSION

Ex-vivo Testing
Modèles Animaux
Volontaires Sains

CAPACITE HEMOSTATIQUE

Rapide
Totale
Soutenue