Reversal Agents for Non-Vitamin K Oral Anticoagulants: Practice Revolution?

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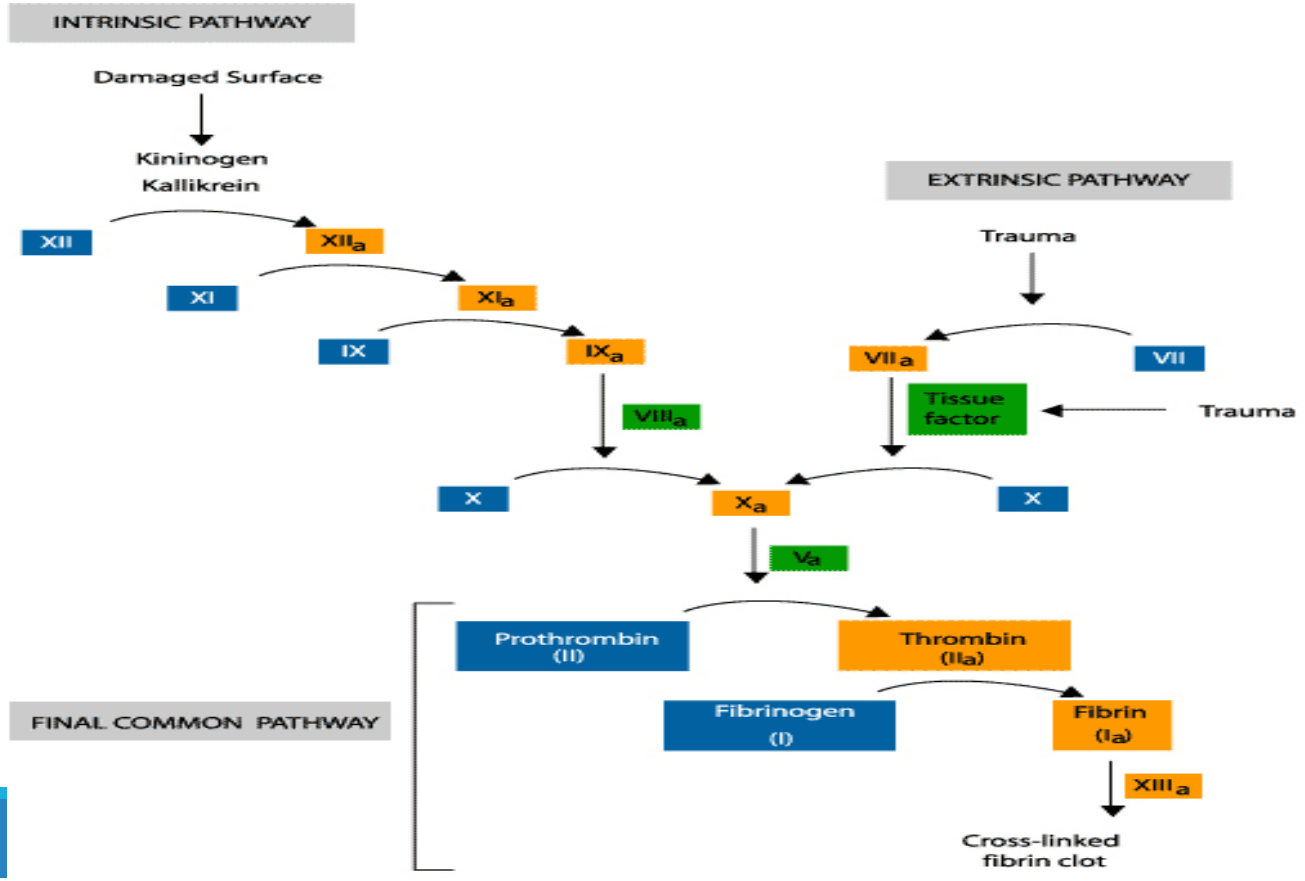
Objectives

- Discuss the evidence for use of idarucizumab, andexanet alfa, and ciraparantag for the emergent reversal of non-vitamin K oral anticoagulants

- Assess appropriate patient selection and safety considerations for targeted anticoagulation reversal of non-vitamin K oral anticoagulants

Direct Oral Anticoagulants (DOACs)



Bombeli T, et al. *Br J Anesth* 2004;93(2):275-87

Indications & Recommendations for DOACs

Indication	Dabigatran	Apixaban	Endoxaban	Rivaroxaban
Treatment of acute DVT/PE	X	X	X	X
Secondary prevention of DVT/PE	X	X		X
VTE prevention in total hip and knee replacement surgeries	X*	X		X
Risk reduction of stroke or systemic embolism in nonvalvular atrial fibrillation	X	X	X*	X

- 2016 CHEST Venous Thromboembolism (VTE) Guidelines recommend for patients without cancer, the use of dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (Grade 2B)
- 2014 AHA/ACC Atrial Fibrillation Guidelines recommend warfarin (Level of Evidence A), dabigatran (Level of Evidence B), apixaban (Level of Evidence B), or rivaroxaban (Level of Evidence B)

Craig T, et al. *Circulation* 2014;130(23):2017-104
Kearon C, et al. *CHEST* 2016;149(2):315-352

Bleeding Risk of DOACs in Comparison to Warfarin in Atrial Fibrillation

Study	Anticoagulants	Major Bleed (% Per Year)	Intracranial Bleed (% Per Year)	Gastrointestinal Bleed (% Per Year)
RE-LY	Dabigatran 150mg BID vs Warfarin	3.11 vs 3.66	0.3 vs 0.75	1.51 vs 1.02
ARISTOTLE	Apixaban 5mg BID vs Warfarin	2.13 vs 3.09	0.33 vs 0.8	0.76 vs 0.86
ENGAGE AF-TIMI 48	Endoxaban 60mg Daily vs Warfarin	2.75 vs 3.43	0.39 vs 0.85	1.51 vs 1.23
ROCKET AF	Rivaroxaban 20mg Daily vs Warfarin	3.6 vs 3.4	0.5 vs 0.7	2.4 vs 1.5

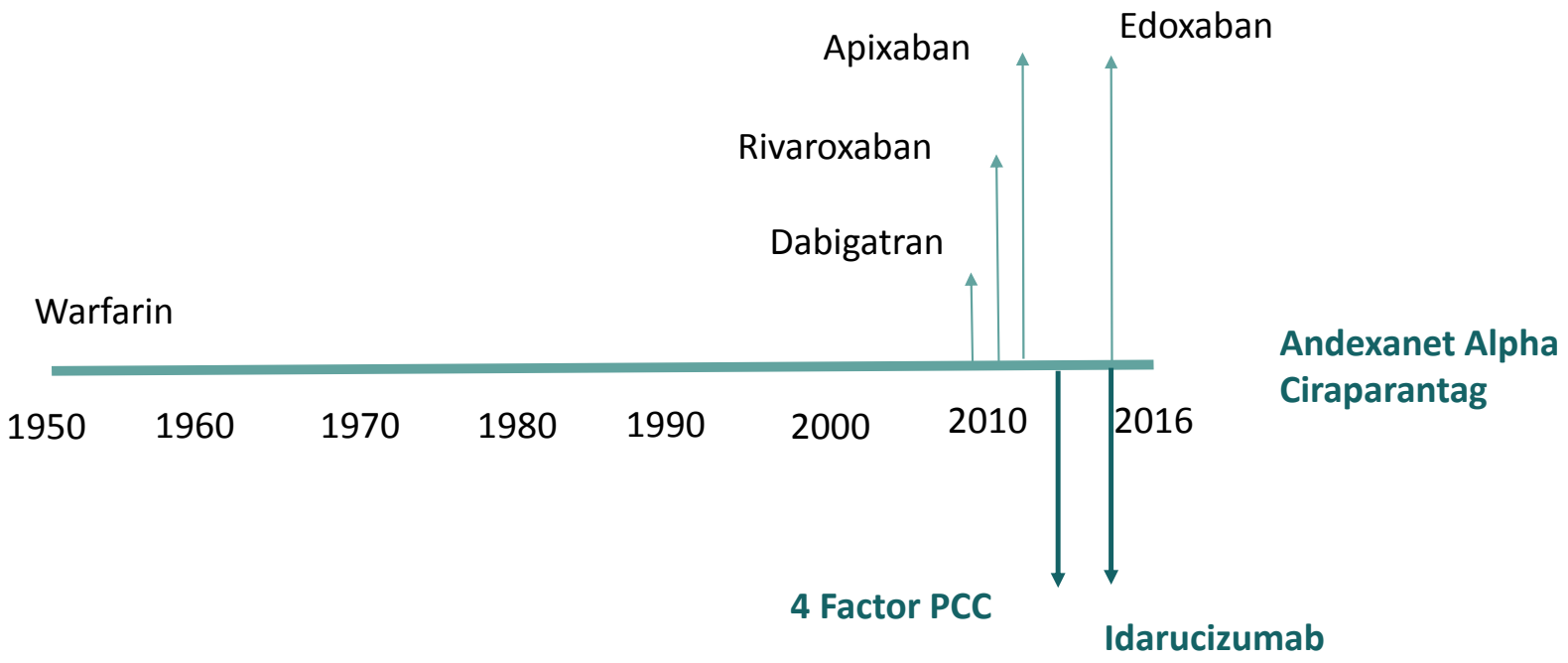
Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104
Patel MR, et al. *N Engl J Med* 2011;365:883-91
Connolly SJ, et al. *N Engl J Med* 2009;361:1139-51
Granger CB, et al. *N Engl J Med* 2011;365:981-98

Kinetics of DOACs

Anticoagulant	Time to Peak (Hours)	Half Life (Hours)	Renal Clearance	Effect of AKI on Clearance
Dabigatran	1 -2	12 – 17	80%	++++
Apixaban	3 – 4	~12	27%	+
Endoxaban	1 – 2	10 – 14	50%	+++
Rivaroxaban	2 – 4	5 – 9	36%	++

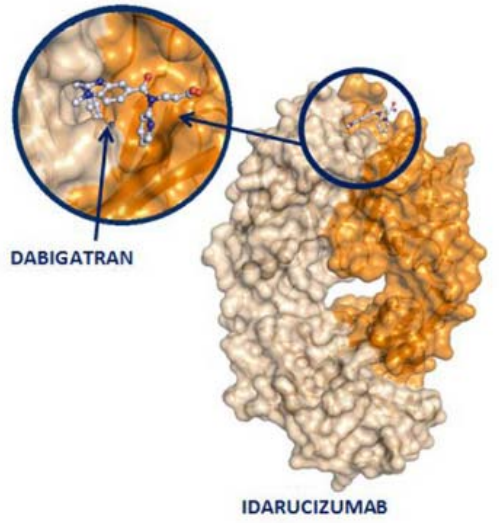
Dabigatran package insert. Boehringer Ingelheim. Ridgefield, CT 06877. 2015.
Apixaban package insert. Pfizer Inc. New York, NY 08543. July 2016.
Edoxaban package insert. Daiichi Sankyo Inc. Tokyo, Japan. 2015
Rivaroxaban package insert. Janssen Pharm. Titusville, NJ 08560. 2011

Reversal Agents for Direct Oral Anticoagulants



Idarucizumab for Reversal of Dabigatran

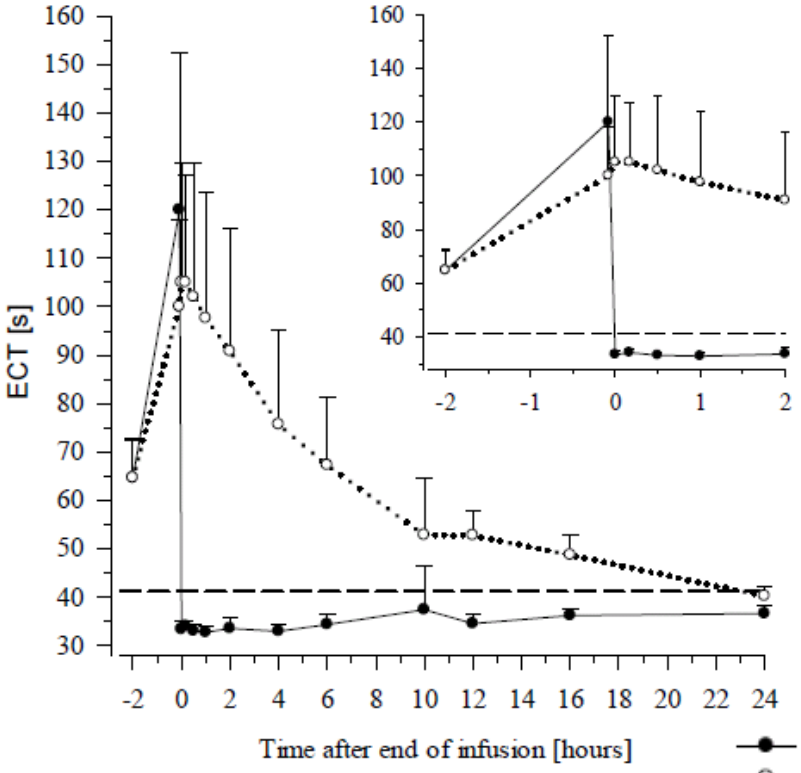
- Monoclonal antibody fragment
- Affinity for dabigatran is 350 times higher than thrombin
- Neutralize dabigatran's anticoagulant effect

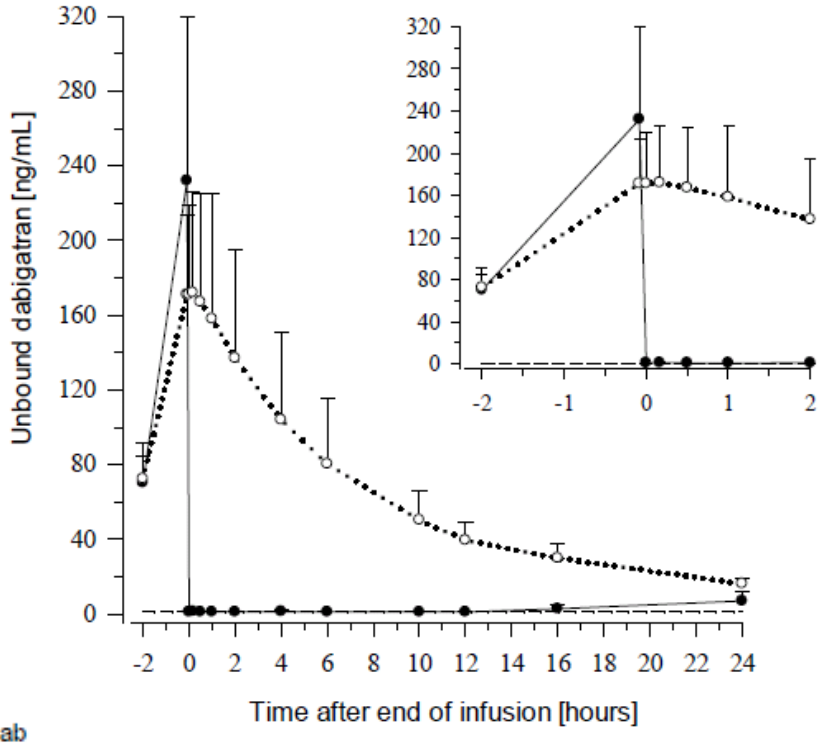


Idarucizumab is in late-stage development and has not yet been approved for clinical use

Idarucizumab Package. Boehringer Ingelheim Pharm Inc. Ridgefield, CT 06877. 2015

Phase Ib Idarucizumab Trial





Dabigatran etexilate + Idarucizumab
dabigatran etexilate + Placebo
Lower limit of quantification = 1 ng/mL

Glund S, et al. *Lancet* 2015;386:680-90
Idarucizumab Package. Boehringer Ingelheim Pharm Inc. Ridgefield, CT 06877. 2015.

RE-VERSE AD Phase III Trial

- Ongoing, multicenter, prospective cohort study

Cohort A	• Overt, uncontrolled, life-threatening bleeding
Cohort B	• Required surgery or other invasive procedures that could not be delayed for 8 hours and required normal hemostasis

- Study Treatment
  - 5 grams IV of Idarucizumab administered as two 2.5 gram IV doses separated no more than 15 minutes apart.

RE-VERSE AD Patient Characteristics

Characteristic	Group A (N = 51)	Group B (N = 39)	Total (N = 90)
Age, Median (range), yr	77 (43 – 93)	76 (56 – 93)	76.5 (48 – 93)
Weight, Median (range), kg	71 (42 – 128)	73 (50 – 116)	72 (42 – 128)
CrCl, Mean (SD), mL/min	59 ± 33	65 ± 36	62 ± 35
Dose of dabigatran, no (%)			
-150mg PO BID	14 (27)	15 (38)	
-110mg PO BID	34 (67)	24 (62)	
Time since last dose, Median, hr	15.2	16.6	15.4
Type of bleeding, no (%)			
-Intracranial	18 (35)	-	18 (35)
-Trauma-related	9 (18)	-	9 (18)
-Gastrointestinal	20 (39)	-	20 (39)
-Other	11 (22)	-	11 (22)

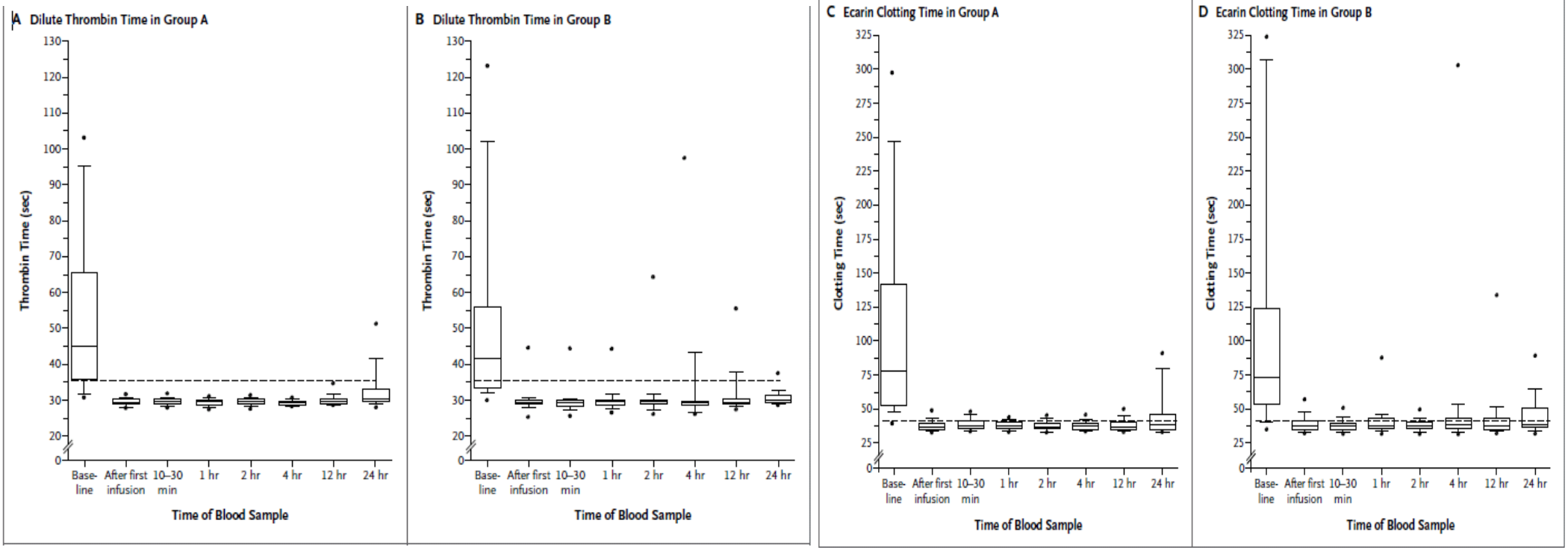
Pollack CV, et al. *N Eng J Med* 2015;373:511-20

Primary Outcome: Maximum Percentage of Reversal of Dabigatran

- Percentage Reversal = $\left(\frac{\text{Pre-dose Result} - \text{Minimum Post-Dose Result}}{\text{Per-dose Result} - \text{Upper Limit of Normal}}\right) \times 100$

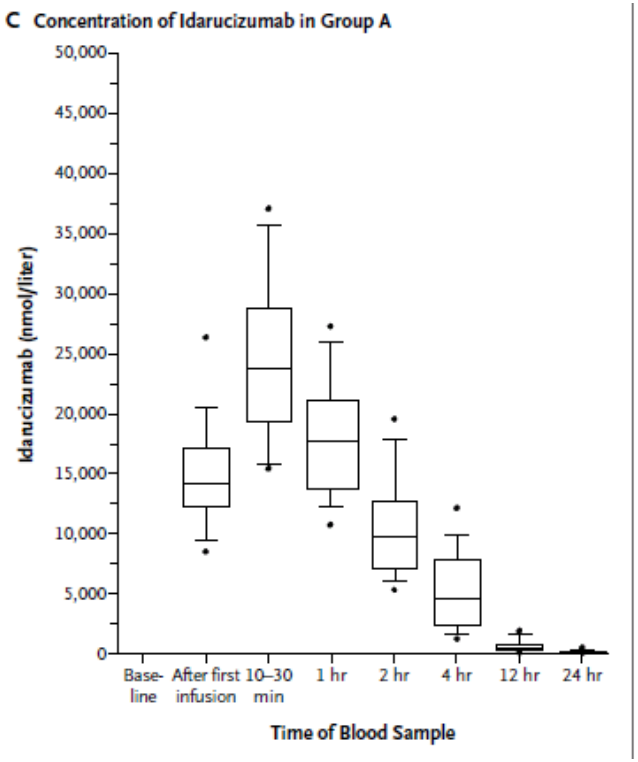
Characteristic	Group A (N = 51)	Group B (N = 39)	Total (N = 90)
Elevated dTT at baseline, No. (%)	40 (78)	28 (71)	68 (76)
Elevated ECT at baseline, No. (%)	47 (92)	34 (87)	81 (90)

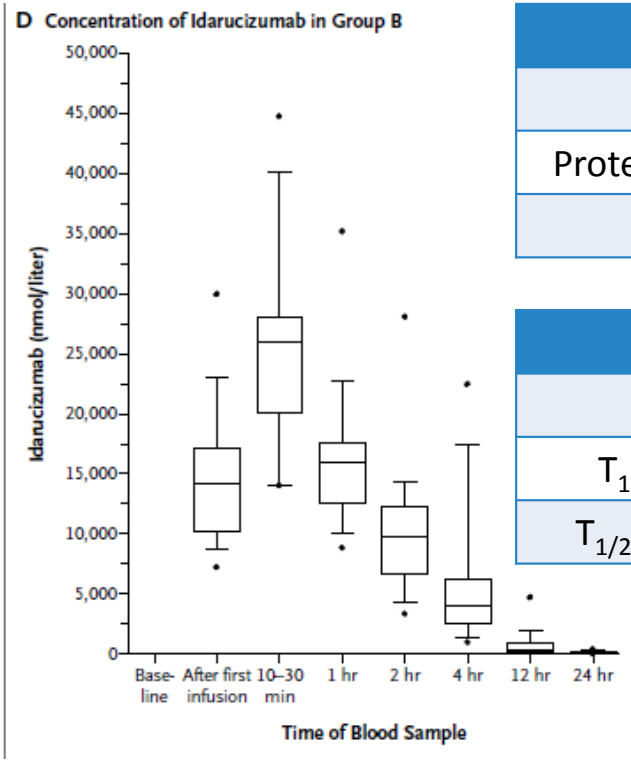
Primary Outcome: Maximum Percentage of Reversal of Dabigatran



Pollack CV, et al. *N Eng J Med* 2015;373:511-20

Unbound Dabigatran and Idarucizumab Concentration





Dabigatran	
V_d	50 – 70 L
Protein Binding	30%
$T_{1/2}$	12 – 28 hr

Idarucizumab	
V_d	8.9 L
$T_{1/2}$ Initial	47 min
$T_{1/2}$ Terminal	10.3 hr

Pollack CV, et al. *N Eng J Med* 2015;373:511-20

Idarucizumab Clinical Outcomes

Characteristic	Group A (N = 38)	Group B (N = 36)
Cessation of bleeding, Median, hr	11.4	
Normal Intraoperative hemostasis, No (%)		33 (92%)

- Overall, 18 of the 90 patients enrolled died within 30 days
- 65% of patients in Group A and 44% in Group B required blood products
- 5 patients experienced thromboembolic event post Idarucizumab administration
  - 1 patient within 72 hours
  - 4 patients between 7 and 26 days

Pollack CV, et al. *N Eng J Med* 2015;373:511-20

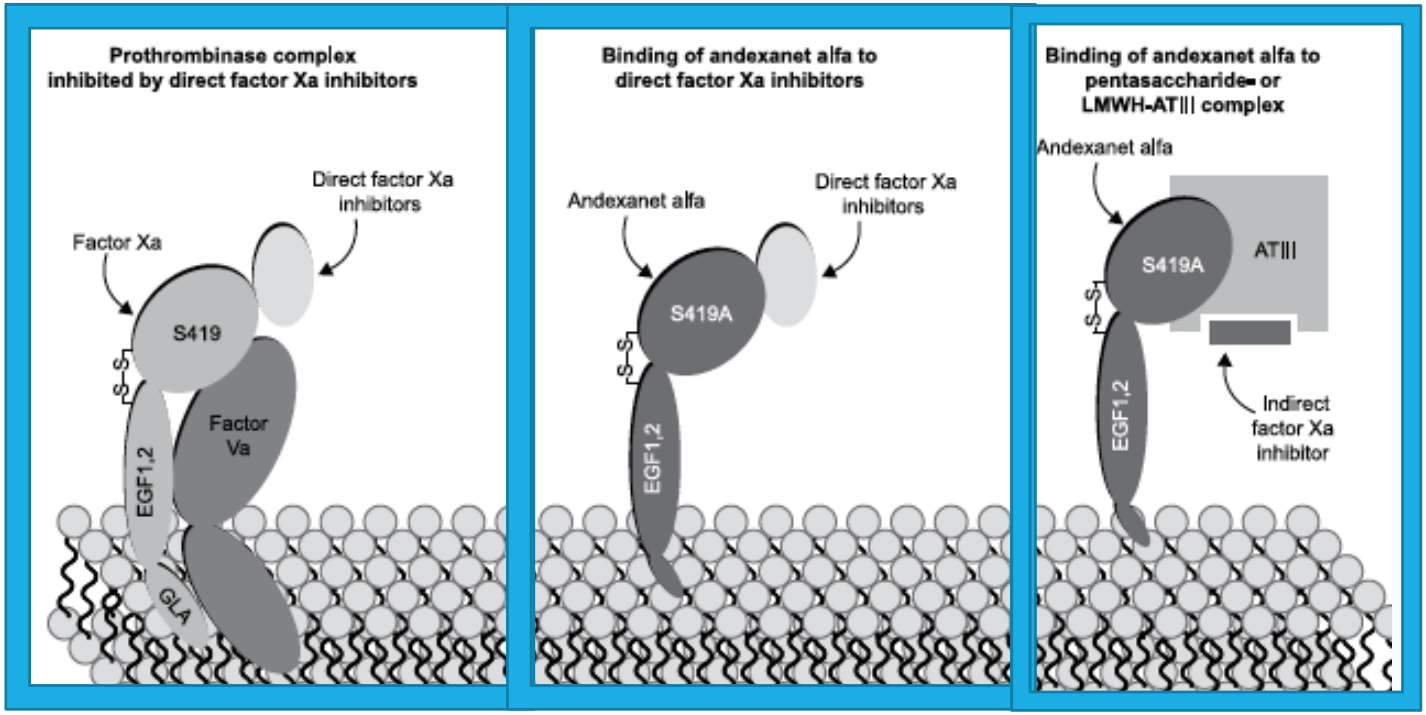
Idarucizumab (Praxbind®)

- FDA approved humanized monoclonal antibody fragment indicated for reversal of dabigatran anticoagulation effect for
  - Emergency surgery or urgent procedures
  - In life-threatening or uncontrolled bleeding
- Dose of 5 grams IV once
- Risk of serious adverse reactions in patients with hereditary fructose intolerance

Idarucizumab Package. Boehringer Ingelheim Pharm Inc. Ridgefield, CT 06877. 2015

Andexanet Alfa for the Reversal of Factor Xa Inhibitors

- Andexanet Alfa is a modified recombinant version of Factor Xa



Am J Health Syst Pharm 2016; 73(suppl 2):S27-48

ANNEXA-A and ANNEXA-R Studies

- Randomized, double-blind, placebo-controlled studies of andexanet alfa in healthy volunteers

ANNEXA-A

- Part 1: 400 mg IV Bolus
- Part 2: 400 mg IV Bolus followed by 4 mg/min IV for 2 hours

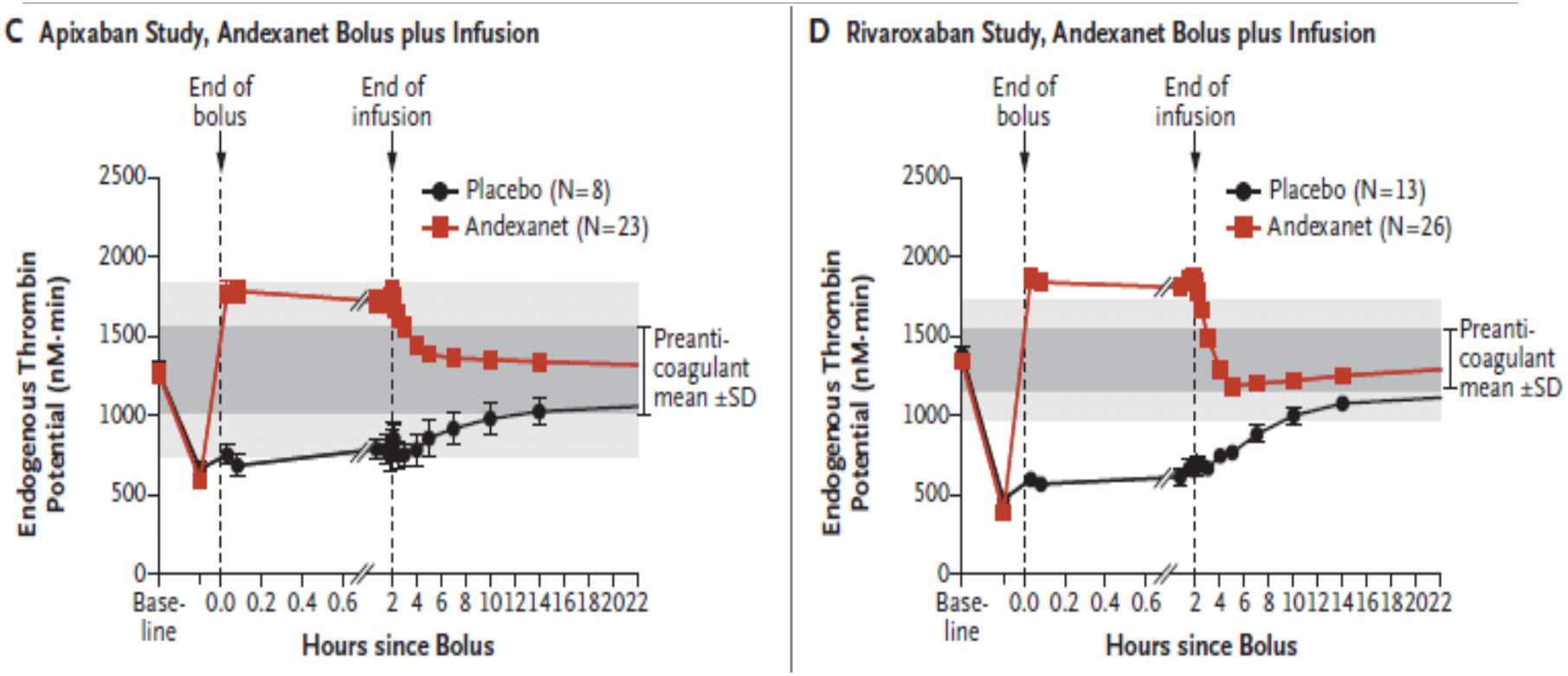
ANNEXA-R

- Part 1: 800 mg IV Bolus
- Part 2: 800 mg IV bolus followed by 8 mg/min IV for 2 hours

	Apixaban				Rivaroxaban			
	Part 1		Part 2		Part 1		Part 2	
	Andexanet	Placebo	Andexanet	Placebo	Andexanet	Placebo	Andexanet	Placebo
N	24	9	23	8	27	14	26	13
% Change in anti-Xa activity (SD)	-93.9 (1.7)	-20.7 (8.6)	-92.3 (2.8)	-32.7 (5.6)	-92.2 (10.7)	-18.4 (14.7)	-96.7 (1.8)	-44.8 (11.7)

Siegal D, et al. *N Engl J Med* 2015;373:2413-24

ANNEXA-A and ANNEXA-R Results



Siegal D, et al. *N Eng J Med* 2015;373:2413-24

ANNEXA-4 Study

- Ongoing, multicenter, prospective, open-label, single-group study of andexanet alfa in patients with acute major bleeding

Acute Major Bleed
Potentially life-threatening acute overt bleeding with sx of hemodynamic compromise
Acute overt bleeding associated with a decrease in Hgb of at least 2 g/dL
Acute symptomatic bleeding in a critical area or organ

or

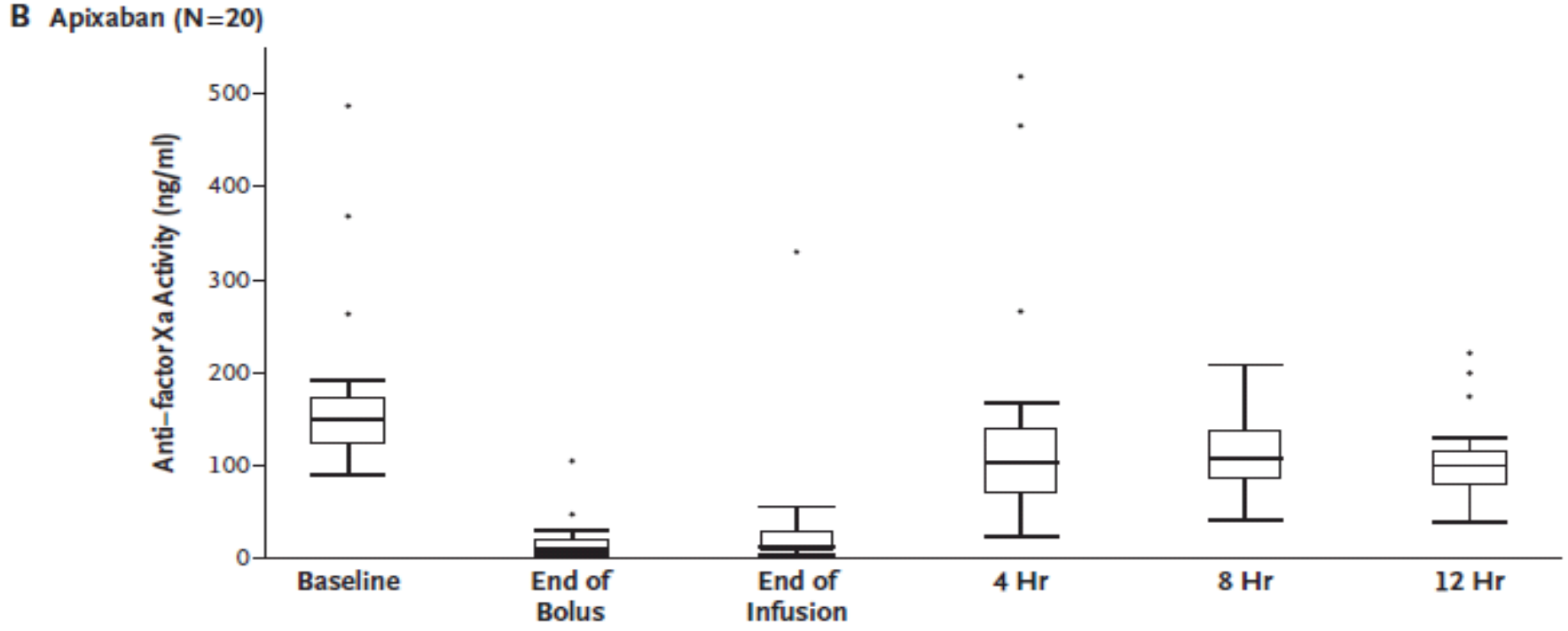
Apixaban or rivaroxaban given < 7 hours prior

- 800 mg IV bolus over 15 – 30 minutes followed by 960 mg IV infusion over 2 hours

ANNEXA-4 Patient Characteristics

Characteristic	Safety Group (N = 67)	Efficacy Group (N = 47)
Age, Mean ± SD, yr	77.1 ± 10	77.1 ± 10.1
Anticoagulant, no		
-Apixaban	31	20
-Rivaroxaban	32	26
-Enoxaparin	4	1
Time since last dose, Mean, hr	12.1 (A), 12.8 (R), 10.8 (E)	11 (A), 12 (R), 13.1 (E)
Type of bleeding, no (%)		
-Intracranial	28 (42)	20 (43)
-Gastrointestinal	33 (49)	25 (53)
-Other	6 (9)	2 (4)

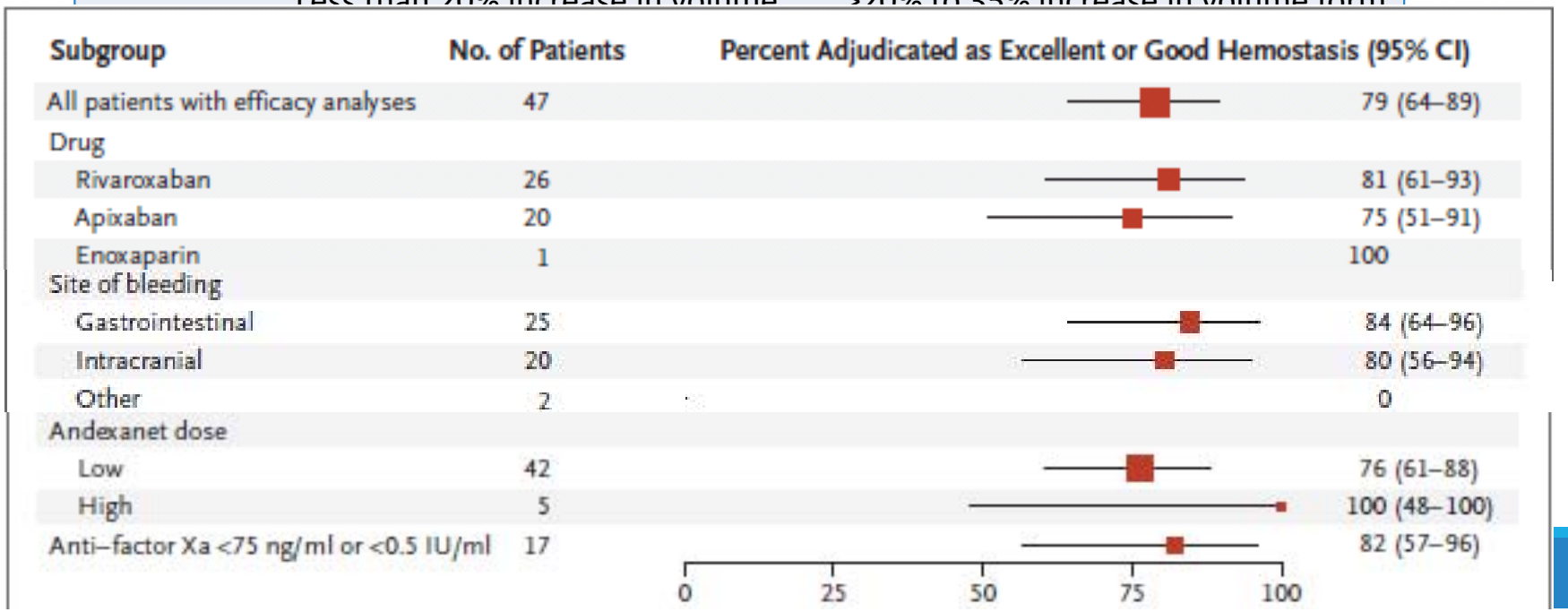
Andexanet Alfa Effect on Anti-Xa Activity



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	149.7	10.3	12.5	103.0	107.1	100.2
Percent Change (95% CI)		−93 (−87 to −94)	−92 (−85 to −94)	−30 (−23 to −46)	−28 (−19 to −38)	−31 (−27 to −41)

Hemostatic Efficacy with Andexanet Alfa at 12 Hours

N = 47	"Excellent Hemostasis"	"Good Hemostasis"	"Poor or No Hemostasis"
Total	31 (66%)	6 (13%)	9 (19%)
	Less than 20% increase in volume	>20% to 35% increase in volume form	



Andexanet Alfa Safety

- No infusion reactions
- No antibodies to Factor Xa or X and no neutralizing antibodies

Thromboembolic Events within 30 days

- 12 (18%) patients
- 1 MI, 5 CVA, 7 DVT, and 1 PE

Death within 30 days

- 10 (15%) patients

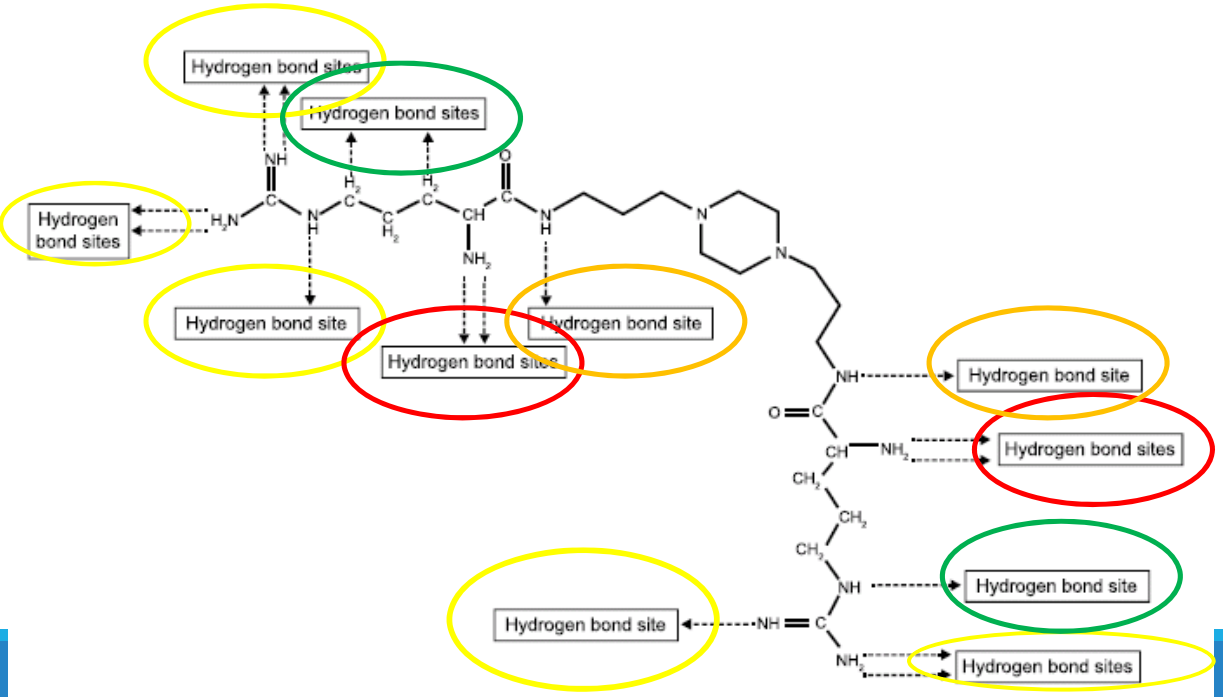
Andexanet Alfa FDA Approval

- February 2016 – Portola Pharmaceuticals submitted Biologics License Application with FDA
  - Trade Name: AndexXa™
  - Indication: Patients treated with direct (apixaban, edoxaban, rivaroxaban) or indirect (enoxaparin) Factor Xa Inhibitors when reversal is needed due to life-threatening or uncontrolled bleeding
  - FDA designated Breakthrough Therapy

- August 2016 – FDA issued a Complete Response Letter
  - Requested provide additional data to support the inclusion of edoxaban and enoxaparin in the label

Is Ciraparantag the Ultimate Reversal Agent?

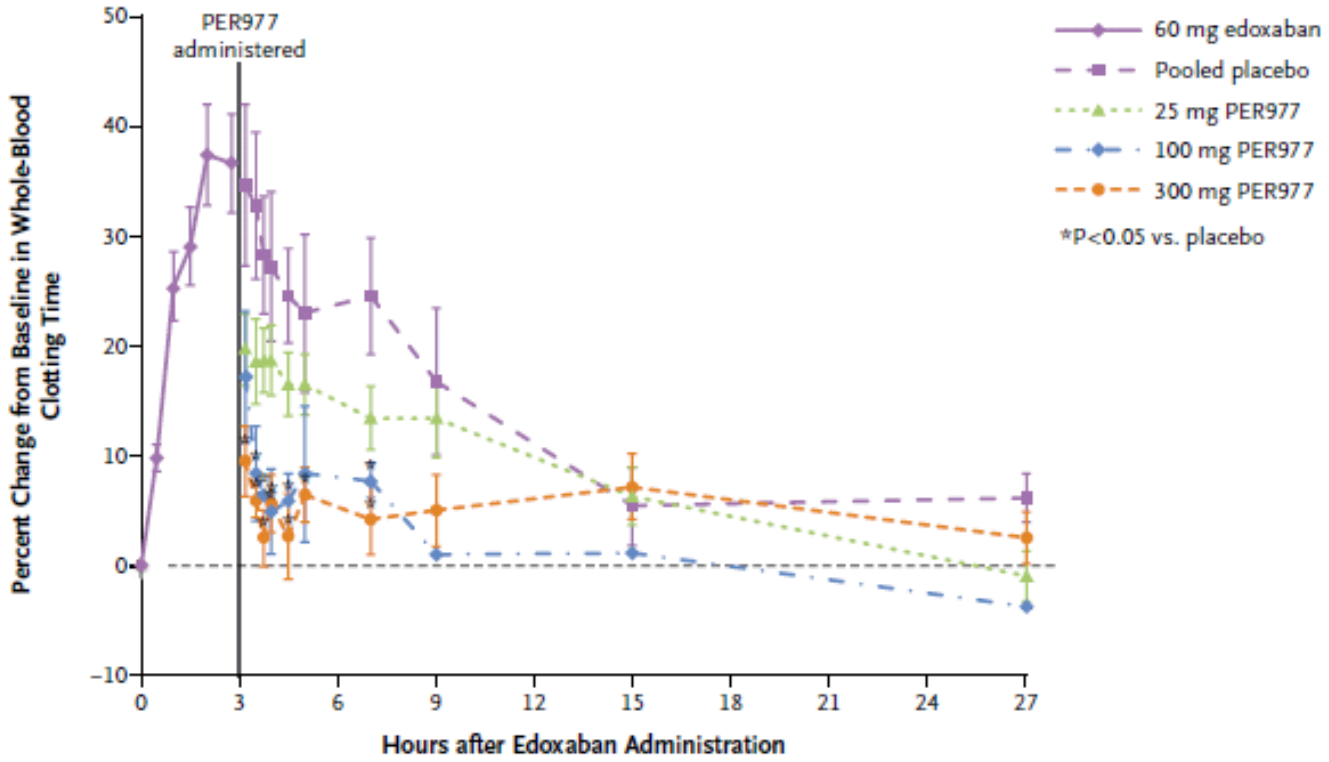
- PER977 is a synthetic, small molecule designed reverse DOACs and heparins.
- Exerts reversal activity through forming non-covalent bonds



Color	Anticoagulants
Yellow	Edoxaban, Dabigatran, Rivaroxaban
Green	Dabigatran, Rivaroxaban, Apixaban
Red	Dabigatran, Rivaroxaban
Orange	Edoxaban, Apixaban

Smyth et al. *Am J Health-Syst Pharm.* 2016; 73(suppl 2):S27-48

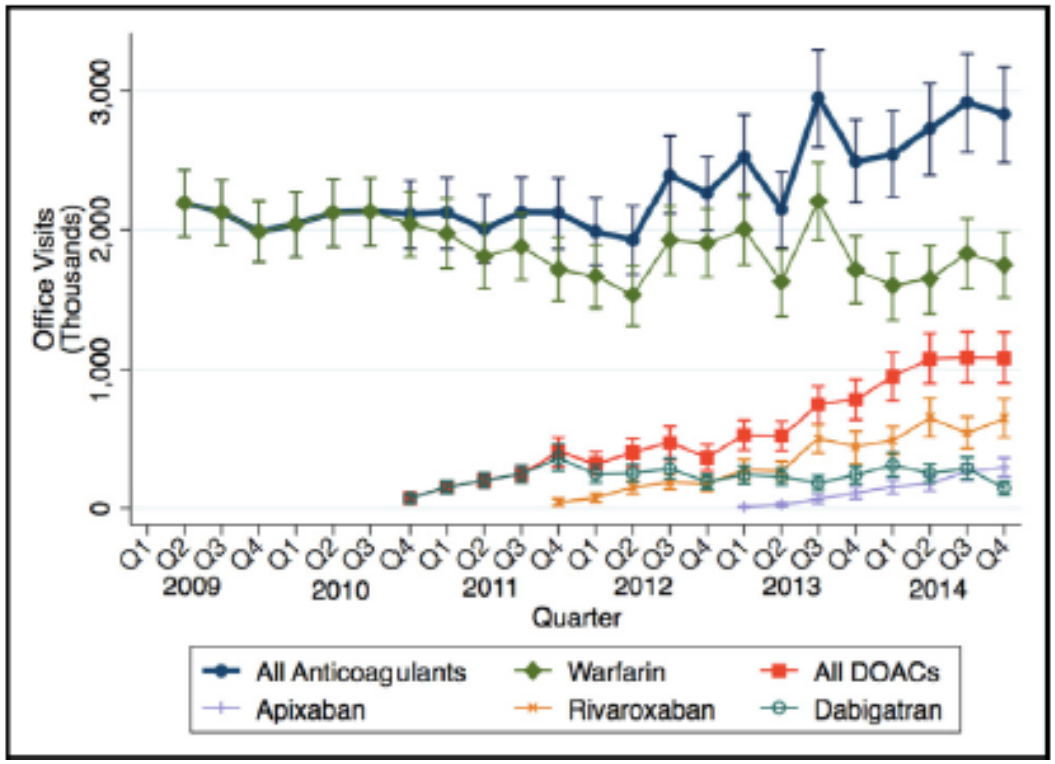
Ciraparantag Effects in Healthy Volunteers



DOAC Emergent Reversal Agents

Medication	Structure	Mechanism of Action	Targets	Time to Response	Duration (hours)	Unanswered Questions
Idarucizumab	Humanized monoclonal antibody Fragment	Noncompetitive binding	Dabigatran	Immediate	12-24	-Future lab assessment for patient selection. -Clinical impact of rise of anticoagulant concentration after immediate reversal.
Andexanet Alfa	Variant protein decoy Factor Xa	Competitive binding	Oral direct Factor Xa Inhibitors, LMWH	Immediate	4	
Ciraparantag	Small synthetic molecule	Form hydrogen bonds	Dabigatran, Oral direct Factor Xa Inhibitors, LMWH, heparin	Immediate	24	-Anticoagulant required within 24 hours.

DOAC Prescribing Patterns



Barnes GD, et al. *The Am J of Med* 2015; 128: 1300-5

Conclusion

- Idarucizumab, andexanet alfa, and ciraparantag all have the ability to reverse the anticoagulation effect of certain DOACs without being prothrombotic.

- The clinical significance of the rise in anticoagulation activity 12 hours after idarucizumab and 4 hours after andexanet alfa administration has yet to be determined.

- The patient selection for emergent reversal of DOACs currently involves severity of hemorrhage assessment, renal function assessment, and assessment of the time since last dose of the DOAC.

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