Anticoagulation Reversal – Use of Specific Reversal Agents

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Objectives

- Summarize clinical controversies surrounding the use of reversal agents (antidotes) for anticoagulation reversal

- Explain the advantages and disadvantages associated with using reversal agents (antidotes) as the primary treatment approach for anticoagulation reversal

I do not have any financial conflicts of interest related to this presentation

Outline

- Brief overview of available anticoagulant reversal agents
- Review available literature and guideline recommendations
- Compare and contrast the use of PCC vs. specific antidotes for DOAC related bleeding

Reversal Options for DOAC Bleeding

- Plasma derived products
  - Fresh frozen plasma
  - Prothrombin complex concentrate (PCC)
    - 3 and 4 factor products
- Specific antidotes
  - Idarucizumab
  - Andexanet alfa

Available Reversal Antidotes

	Idarucizumab	Andexanet alfa
Anticoagulant(s) Reversed	Dabigatran	Factor Xa inhibitors
Chemical Structure	Humanized monoclonal antibody fragment	Recombinant human factor Xa variant (decoy)
Mechanism of Action	Binds dabigatran and metabolites with affinity 350x greater than thrombin	Binds and sequesters factor Xa inhibitors
Pharmacokinetics/ Pharmacodynamics	Onset: 2-5 minutes Half-life: 47 mins, 10.3 hours (terminal) Duration: ~ 24 hours Elimination: Urine	Onset: 1-2 minutes Half-life: 6 hours (terminal) Duration: 1-2 hours
Dosing	5 grams IV - Give as 2 separate 2.5 mg doses 15 minutes apart	400-800 mg IV bolus, then 4-8 mg/min infusion for 2 hours
Monitoring	Bleeding and/or thrombosis Coagulation parameters	Bleeding and/or thrombosis Anti-xa levels

Idarucizumab

REVERSE-AD Trial Idarucizumab for Dabigatran Reversal – Full Cohort Analysis	
Design	Multicenter, prospective, open-label study
Patients	Adults patients receiving dabigatran • Group A - patients with uncontrollable or life-threatening bleeding • Group B – patients undergoing surgery that could not be delayed for at least 8 hours No major exclusions
Intervention	5 grams IV idarucizumab (no placebo) • Second dose allowed if continued bleeding
Primary Outcome	Maximum percent reversal of the anticoagulant effect of dabigatran, assessed with diluted thrombin time or ecarin clotting time
Secondary Outcomes	Adverse events (thrombosis, hypersensitivity)

Pollack CV, et al. *N Engl J Med* 2015;373.
Pollack CV, et al. *N Engl J Med* 2017;377.

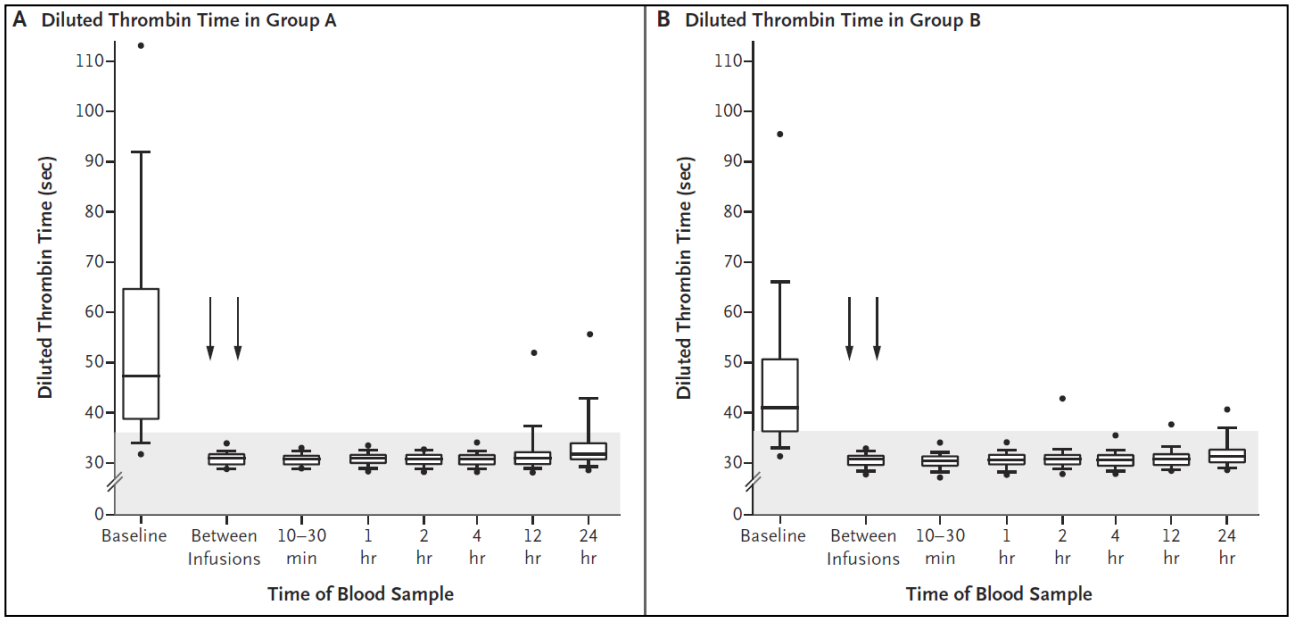
Idarucizumab

REVERSE-AD Trial		
Table 1. Baseline Characteristics		
	Group A (n=301)	**Group B (n=202)**
Age (median, range)	79 (24-96)	77 (21-96)
Indication, n (%) Atrial fibrillation Venous thromboembolism Other	 288 (95.7) 5 (1.7) 3 (1)	 190 (94.1) 4 (2) 5 (2.5)
Time since last dose, hours (median, range)	14.6 (1.5-90.4)	18 (2.6-105.8)
Elevated ECT or DTT at baseline, n (%)	276 (91.7)	185 (91.6)

ECT = ecarin clotting time
DTT = diluted thrombin time

Pollack CV, et al. *N Engl J Med* 2017;377

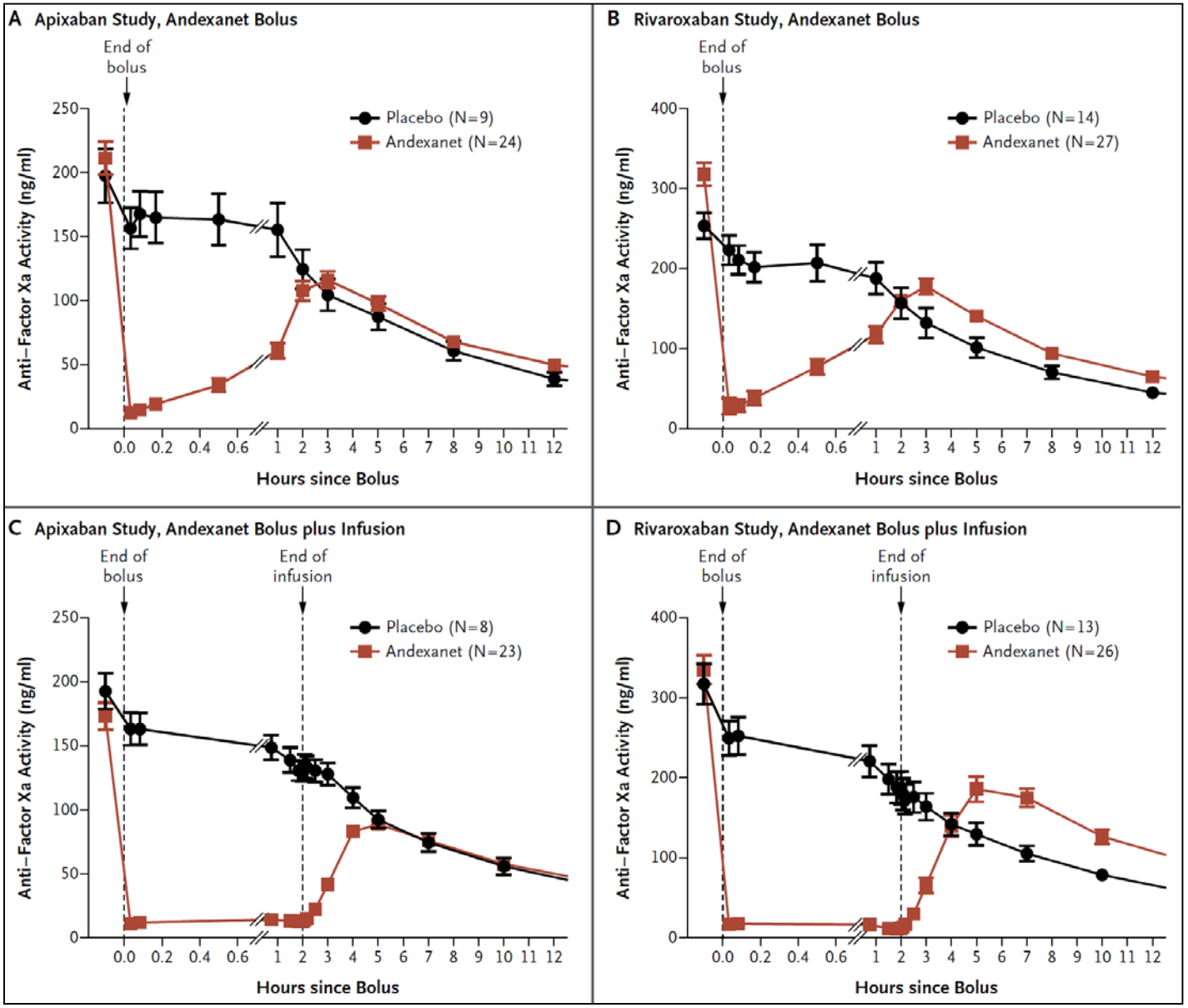
Idarucizumab



- Clinical outcome – cessation of bleeding within 24 hours
  - 134/203 (67.7%) in group A
  - 184/197 (93.4%) in group B
- Mortality (30 days)
  - 13.5% in group A vs. 12.6% in group B
- Thrombosis (90 days)
  - 6.3% group A vs. 7.4% group B
- Serious Adverse Event (5 days)
  - 23.3% of patients

Pollack CV, et al. *N Engl J Med* 2017;377.

Andexanet alfa (ANNEXA-A/R Trial)



Siegal DM, et al. *N Engl J Med* 2015;373.

Andexanet alfa

ANNEXA-4 Trial Andexanet alfa for acute major bleeding associated with factor Xa inhibitors	
Design	Multicenter, prospective, open-label, singe group study
Patients	63 Centers in North American and Europe • Adults patients who received apixaban, rivaroxaban, edoxaban, or enoxaparin within the past 18 hours, AND • Acute major bleeding (life threatening, hemoglobin drop > 2 g/dl, bleeding in a critical organ) Exclusion – surgery planned within 12 hours, ICH + GCS < 7, recent thrombosis, expected survival < 30 days
Intervention	Andexanet 400-800 mg IV bolus, then 4-8mg/min infusion • If last dose > 7 hours ago or unknown, low dose used
Primary Outcome	Change in anti-Xa activity Clinical hemostasis efficacy during the first 12 hours
Secondary Outcomes	Adverse events (thrombosis, infusion reactions, immune) Mortality

ICH = Intracranial hemorrhage
GCS = Glasgow Coma Scale

Connolly SJ, et al. *N Engl J Med* 2019;380.

Andexanet alfa

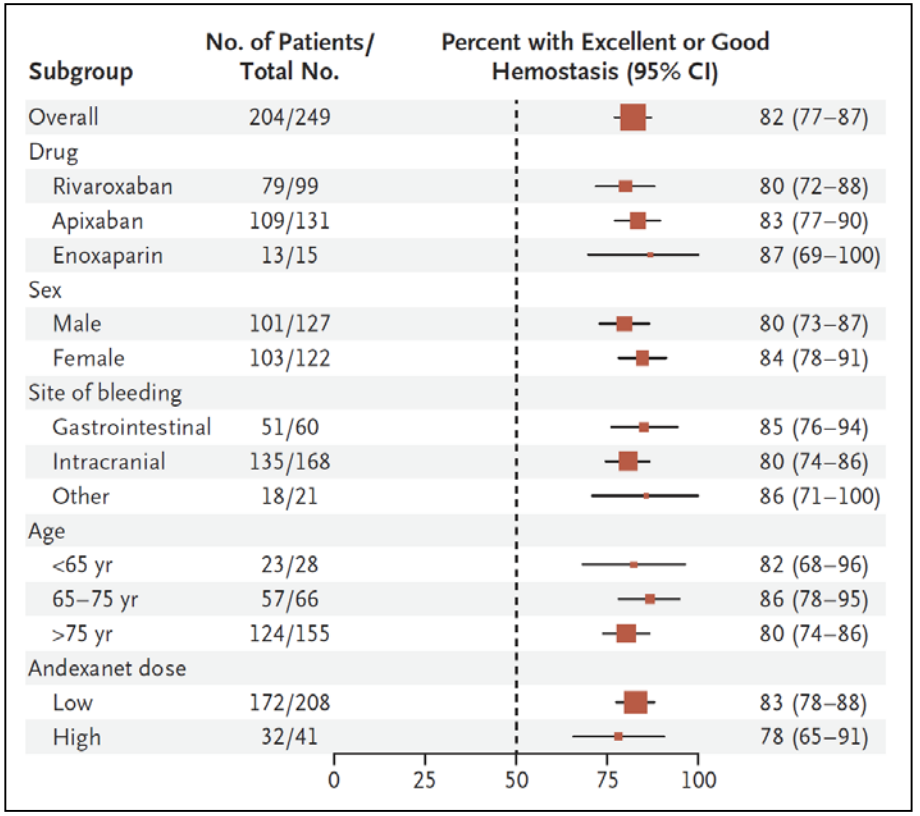
ANNEXA-4 Trial		
Table 1. Baseline Characteristics		
	Safety Population (n=352)	**Efficacy Population (n=254)**
Age (mean, standard dev.)	77.4 ± 10.8	77.1 ± 11.1
Indication, n (%)		
Atrial fibrillation	280 (80)	201 (79)
Venous thromboembolism	61 (17)	46 (18)
Other	11 (3)	7 (3)
Time from hospitalization till dose, hours (mean)		
Apixaban	4.5 ± 3.6	4.7 ± 4.0
Rivaroxaban	4.7 ± 3.1	4.7 ± 3.4
Factor Xa inhibitor used, n (%)		
Rivaroxaban	128 (36)	100 (39)
Apixaban	194 (55)	134 (53)
Enoxaparin	20 (6)	16 (6)
Edoxaban	10 (3)	4 (2)
Type of bleeding, n (%)		
Gastrointestinal	90 (26)	62 (24)
Intracranial	227 (64)	171 (67)
Other	35 (10)	21 (8)

Connolly SJ, et al. *N Engl J Med* 2019;380.

Andexanet alfa

ANNEXA-4 Results	Baseline	End of bolus	End of infusion	4 hours	8 hours	12 hours
Rivaroxaban anti-Xa (median, % change baseline)	211.8	14.2 (-92%)	16.5 (-90%)	121.7 (-42%)	101.4 (-48%)	85.5 (-62%)
Apixaban anti-Xa (median, % change baseline)	149.7	11.1 (-92%)	11.5 (-92%)	97.2 (-32%)	104.6 (-34%)	91.2 (-39%)

Safety Outcome (30 days)	Safety Population (n=352)
Thrombotic Event, n (%)	34 (10)
Event before restart anticoagulant	26 (7)
Event after restart anticoagulant	8 (2)
Death within 30 days, n (%)	49 (14)
Restart anticoagulant (yes), n (%)	220 (62)



Connolly SJ, et al. *N Engl J Med* 2019;380.

Direct Comparison of PCC vs. Specific Reversal Agents?

So What Do The Experts Say?

Guideline Recommendations

- 2016 Neurocritical Care Society and SCCM Statement
  - Factor Xa inhibitors – Suggest 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure (conditional rec, low-quality evidence)
  - Direct thrombin inhibitors – Suggest 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred, if Idarucizumab is not available (conditional rec, low-quality evidence)

- 2016 ESC Atrial Fibrillation Guidelines
  - For severe or life threatening bleeding, consider specific antidote or PCC if no antidote available.

- 2018 CHEST Atrial Fibrillation Guidelines
  - For serious bleeding, give DOAC specific reversal agent or PCC if reversal agent is not available

Frontera JA, et al. *Neurocrit Care* 2016;24.
Kirchhof P, et al. *European Heart Journal* 2016;37(38).
Lip GY, et al. *Chest* 2018;154(5).

Guideline Recommendations

- 2017 ACC Consensus Document on Management of Bleeding
  - For severe bleeding with dabigatran, recommend idarucizumab. If not available, consider 4F-PCC or aPCC 50 units/kg IV
  - For severe bleeding with Factor Xa inhibitors, recommend 4F-PCC 50 units/kg

- 2019 Guidance From Anticoagulation Forum
  - For severe bleeding with dabigatran, recommend idarucizumab. If not available, suggest treatment with aPCC 50 units/kg
  - For severe bleeding with Factor Xa inhibitors, recommend Andexanet. If not available, suggest treatment with four factor PCC 2000 units

- 2019 AHA/ACC/HRS Atrial Fibrillation Focused Update
  - Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure **(I B-NR)**
  - Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life threatening or uncontrolled bleeding **(IIa B-NR)**

Tomaselli GF, et al. *J Am Coll Cardiol* 2017;70.
Cuker A, et al. *Am J Hematol*2019;94.
January CT, et al. *Circ* 2019;140.

PCC – The Good, the Bad, the Ugly

- Good data for warfarin related bleeding
- Readily available, lower drug acquisition cost
- Compared to FFP, much less volume with administration

PCC – The Good, **the Bad, the Ugly**

- Lack of evidence in “real” patients
  - 8/17 studies in healthy volunteers
  - 2/17 studies were prospective, major bleeds (37 patients)
- Most studies used different endpoints
  - Only 4 studies evaluated clinical hemostasis
- Which product do we use? What dose?
  - 3 factor vs. 4 factor
  - Weight based vs. fixed dose
- “Low” rates of thromboembolism (3-9%)
  - Difficult to truly assess with small sample sizes

A Few Clinical Conundrums

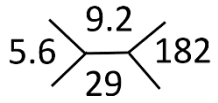
- Repeat dosing
  - What guides decision to re-dose?
- Obese patients
  - Fixed dose ok?
- Restarting anticoagulation
  - Thrombosis occurred in patients who did not have anticoagulation restarted (30 days)

Back to the Patient Case

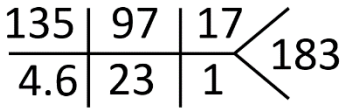
- 63-year-old female patient with metastatic endometrial cancer presents with intractable vomiting and progressive headache
- CT head shows 40mm right parietal intra-parenchymal hemorrhage with ventricular extension
- History of DVT, on rivaroxaban 20 mg daily (last dose 11 hours ago)

1. Does this qualify as a severe, life threatening bleed?
2. Do we need any other information to make a decision?
3. What intervention should be choose? (Drug, dose)

Complete Blood Count (CBC)



Chemistry Panel



- PO_4: 3.4 mg/dL
- Magnesium: 1.4 mg/dL
- Ca: 11.5 mg/dL

Other

- Tbili: 0.4 mg/dL
- Alk phos: 61 International units/L
- ALT: 19 International units/L
- AST: 28 International units/L
- Alb: 3.7 g/dL
- PT: 17.7 seconds
- INR: 1.43
- aPTT: 30.7 seconds

Learning Assessment Question

- Which of the following anticoagulants have commercially available reversal agents?

A. Dabigatran

B. Rivaroxaban

C. Apixaban

D. All of the above

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A. Delay in restarting anticoagulation

B. Faster correction of coagulation effects of medication

C. Volume of drug being administered

D. All of the above

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Rebuttal/Closing Thoughts

- Should be used in severe, life threatening bleeds
  - Can bleeding be stopped with other measures first?
  - Cost significant, but urgent need
- Better data in “real” patients
  - Most of studies with PCC/aPCC are in healthy volunteers/retrospective studies
  - Guidelines recommend specific reversal agents first
- Accepted drug selection and dosing with antidotes
  - Consider when to restart anticoagulation to minimize thrombosis

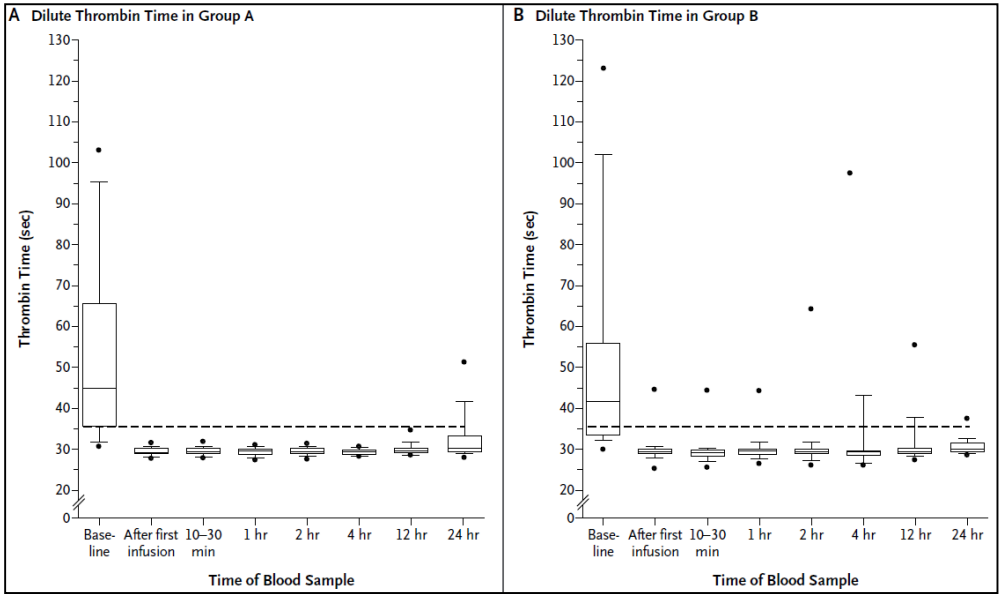
Idarucizumab

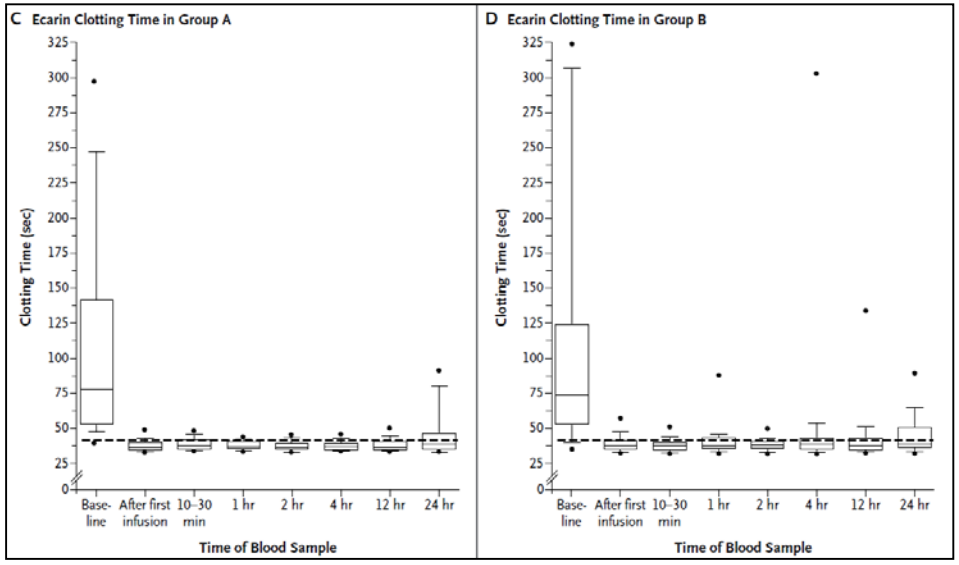
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.





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