Clinical Controversies in DOAC Reversal

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NewYork-Presbyterian Hospital/Weill Cornell Medical Center

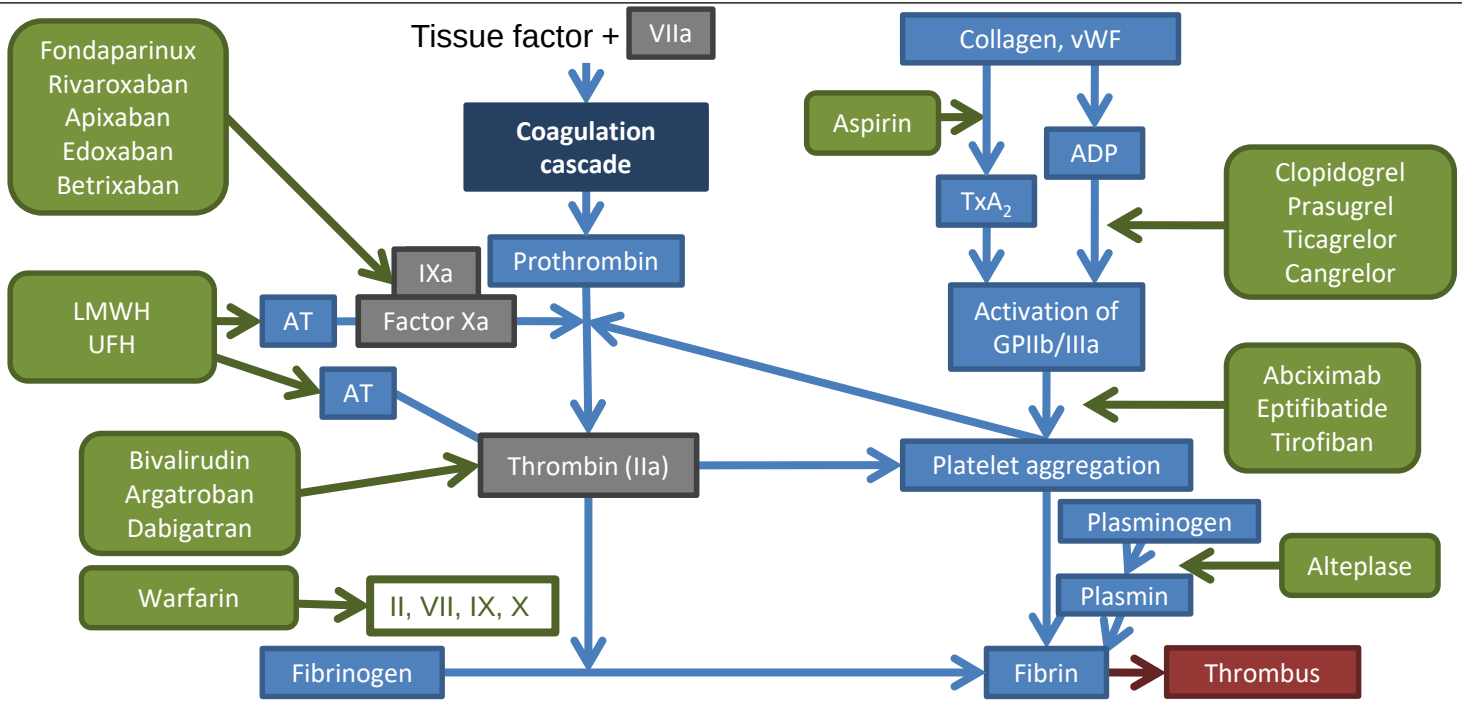
Pharmacist Objectives

- Identify the pharmacologic options for reversal of DOAC-associated life threatening bleeds
- Compare and contrast the role of concentrated factors versus antidotes
- Review the literature supporting the dosing of and indications of reversal agents

Technician Objectives

- Recognize the pharmacologic options for the management of critical bleeds
- Describe the importance of timely preparation of pharmacologic reversal agents in life-threatening bleeds
- Identify indications for reversal agent administration

Coagulation Cascade and Platelet Activation Pathways



LMWH: low molecular weight heparin; UFH: unfractionated heparin; AT: antithrombin; vWF: von Willebrandt factor TxA_2: thromboxane A2; ADP: adenosine diphosphate

Van de Weft F. *Circulation* 2011;123:1834.

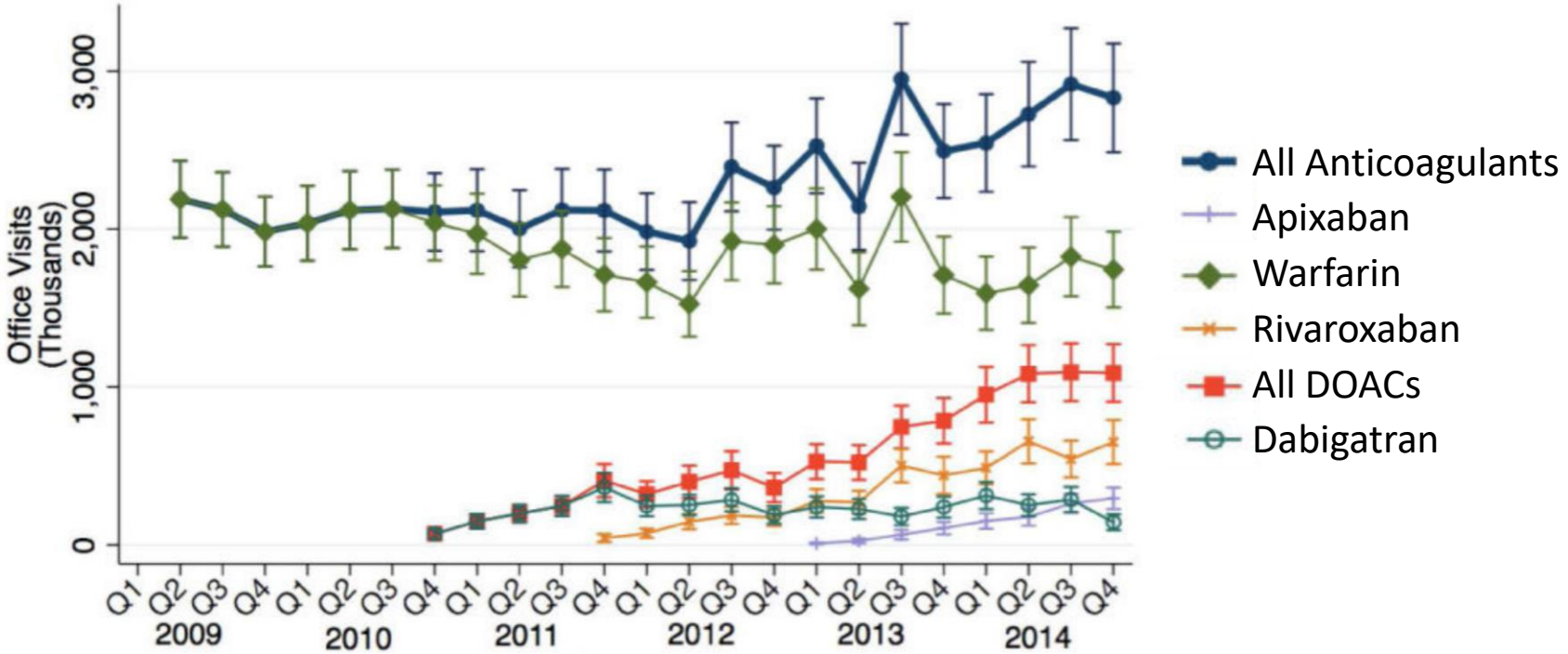
DOAC vs Warfarin-Associated Bleeds

Outcome	Dabigatran 110 mg vs. warfarin Hazard ratio (95% CI)	Dabigatran 150 mg vs. warfarin Hazard ratio (95% CI)	Rivaroxaban vs. warfarin Hazard ratio (95% CI)	Apixaban vs. warfarin Hazard ratio (95% CI)
Stroke or systemic embolism	0.90 (0.74–1.10)	0.65 (0.52–0.81)	0.88 (0.75–1.03)	0.79 (0.66–0.95)
Major bleeding	0.80 (0.70–0.93)	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.69 (0.60–0.80)
Intracranial hemorrhage	0.30 (0.19–0.45)	0.41 (0.28–0.60)	0.67 (0.47–0.93)	0.42 (0.30–0.58)
All-cause mortality	0.91 (0.80–1.03)	0.88 (0.77–1.00)	0.92 (0.82–1.03)	0.89 (0.80–0.99)

- Dabigatran, rivaroxaban, and apixaban all shown to have decreased risk of intracranial hemorrhage vs warfarin

Mantha S, et al. *Clin Pharmacol Ther* 2013;93(1):68-77.

National Trends in Ambulatory Oral Anticoagulant Use



Barnes GD, et al. *Am J Med* 2015;128(12):1300-1305.e2.

Direct Acting Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Mechanism of Action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability (%)	3-7	66-100	50	62	34
Prodrug	Yes	No	No	No	No
Protein Binding (%)	35	>90	87	55	60
Half-life (hours)	12-17	5-9	8-15	10-14	19-27
Route of Elimination	80% renal	33% renal	25% renal	50% renal	11% renal
Pgp Substrate	Yes	Yes	Yes	Yes	Yes
CYP3A4 Substrate	No	Yes	Yes	Minimal	No

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Smythe MA, et al. *Pharmacotherapy* 2013;33(11):1223-45.
Tummala R, et al. *Int J Cardiol* 2016;214:292-8.
Dabi A, et al. *Crit Care Res Pract* 2018;4907164.

Cessation of DOACs for Expected Procedures

Drug	Renal Function (CrCl)	Estimated half-life (hours)	Hold Time (hours)	
			Low Bleeding Risk Surgery	High Bleeding Risk Surgery
Dabigatran	>80	14	28-42	57-70
	>50-70	17	34-51	68-85
	30-49	19	38-57	76-95
	15-29	28	56-84	112-140
	<15	Unknown	Consider transition to warfarin/UFH	
Rivaroxaban	>80	8	16-24	32-40
	30-79 CrCl ~35	9	18-27 Do not reverse	36-45 Reverse
Last dose 30 hours ago	15-29	10	20-30	40-50
	<15	Unknown	Consider transition to warfarin/UFH	
Apixaban	>50	7-8	14-24	28-40
	15-49	17-18	34-54	68-90
	<15	Unknown	Consider transition to warfarin/UFH	

Burnett AE, et al. *J Thromb Thrombolysis* 2016;41:206-32.

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Effect of DOACs on Coagulation Tests and Assays

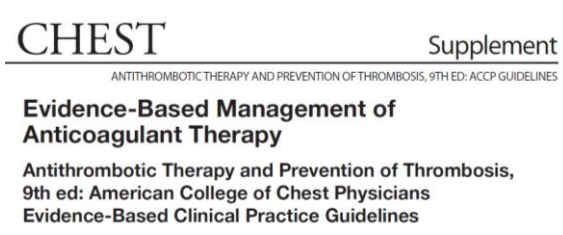
Assay	Dabigatran	Factor Xa Inhibitors
aPTT	Qualitative (normal does not rule out effect)	Not useful
PT	Not suitable in therapeutic concentrations	Qualitative
Chromogenic anti-factor Xa assay	N/A	Quantitative (if calibrated to specific agent)
dTT	Quantitative	N/A
TT	Qualitative (overly sensitive)	N/A
ECT	Quantitative	N/A

dTT = dilute thrombin time; TT = thrombin time; ECT = ecarin clotting time

Conway SE, et al. *Pharmacotherapy* 2017;37(2):236-48.

Guideline Recommendations

CHEST 2012

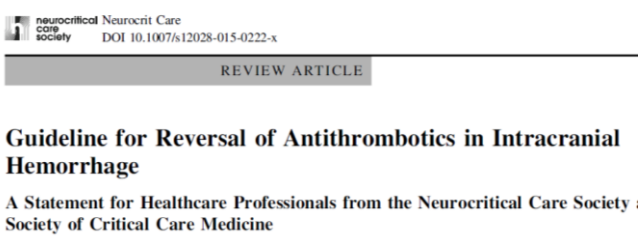

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Evidence-Based Management of Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

NCS/SCCM 2016


neurocritical care society Neurocrit Care

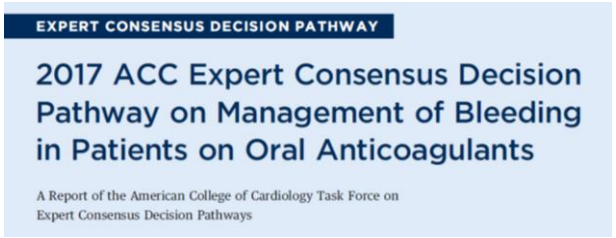
DOI 10.1007/s12028-015-0222-x

REVIEW ARTICLE

Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

A Statement for Healthcare Professionals from the Neurocritical Care Society : Society of Critical Care Medicine

ACC Consensus Statement 2017


EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

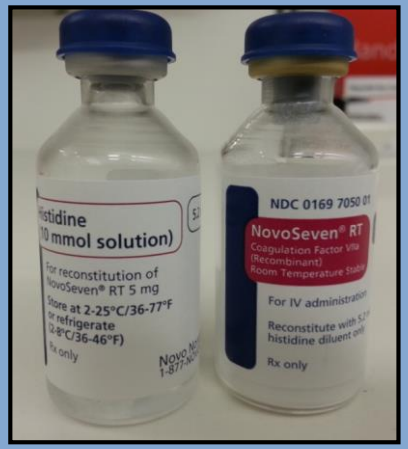
- Many published prior to availability of new agents
- Conflicting recommendations
- Low quality of evidence guiding recommendations

Reversal and Hemostatic Agents

- Prothrombin Complex Concentrates (PCCs)
  - 3F-PCC (Profilnine®, Bebulin®)
  - 4F-PCC (Kcentra®)
  - 4F-aPCC (FEIBA®)
- Idarucizumab (Praxbind®)
- Andexanet alfa/coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa®)

Concentrated Factors

Recombinant factor VIIa (rFVIIa)

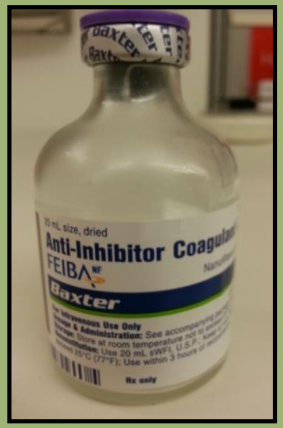


rFVIIa

Prothrombin Complex Concentrates (PCC)

- 3-factor (factors II, IX, X)
- 4-factor (factors II, VII, IX, X)
- Activated 4-factor (factors II, VIIa, IX, X)

3-Factor PCC



4-Factor aPCC

Prothrombin Complex Concentrates Available in the US

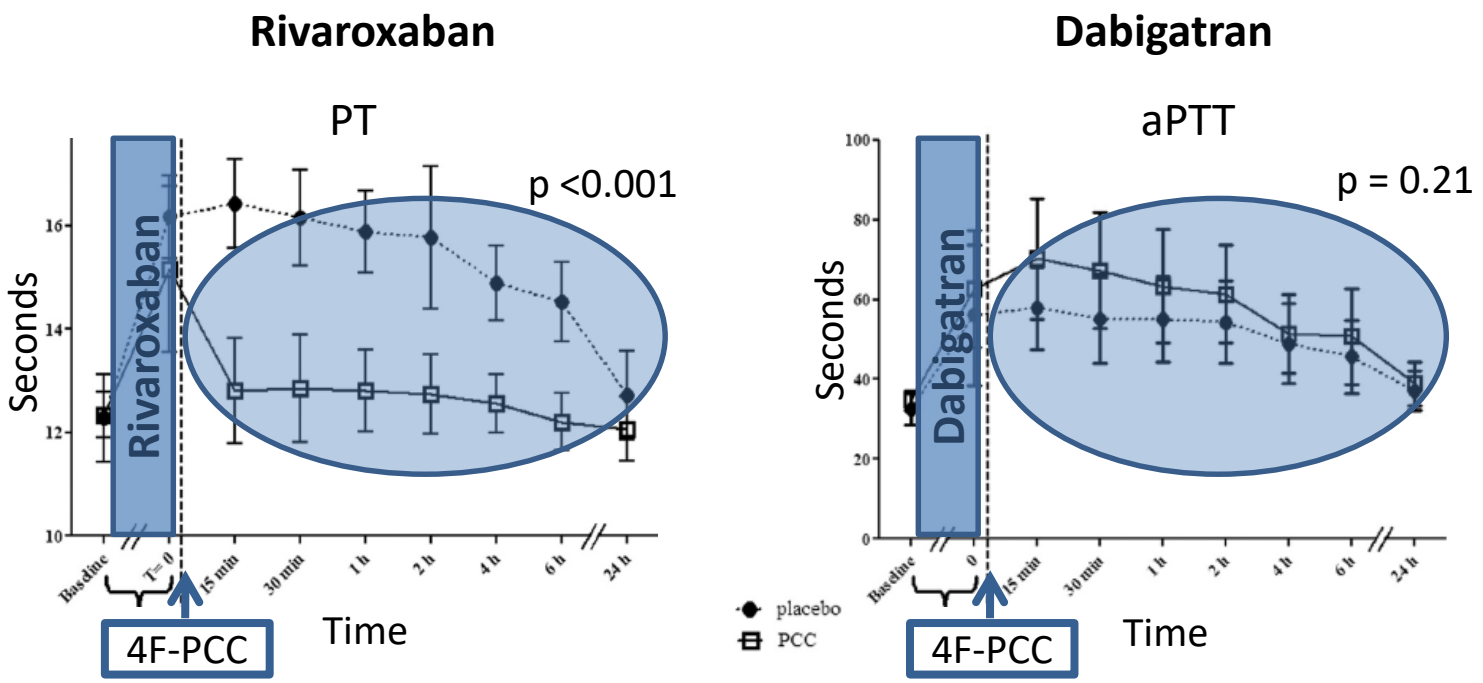
	Factors Covered (International Units relative to Factor IX)[1]			
	II	VII	IX	X
3- Factor PCCs				
Profilnine®	148	11	100	64
Bebulin® VH[3]	120	13	100	100
4- Factor PCCs				
Kcentra®[3]	118	70	100	152
Activated 4- Factor PCCs[2]				
FEIBA®	✓	✓	✓	✓

[1]Approximate values; exact potency of factors varies per vial
[2]Dose based on units of factor VIII bypassing activity, factor VII is activated
[3]Contains heparin

Sorenson B, et al. *Crit Care* 2011;15:201.
Nitzki-George D, et al. *Ann Pharmacother* 2013;47:841-55.

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi



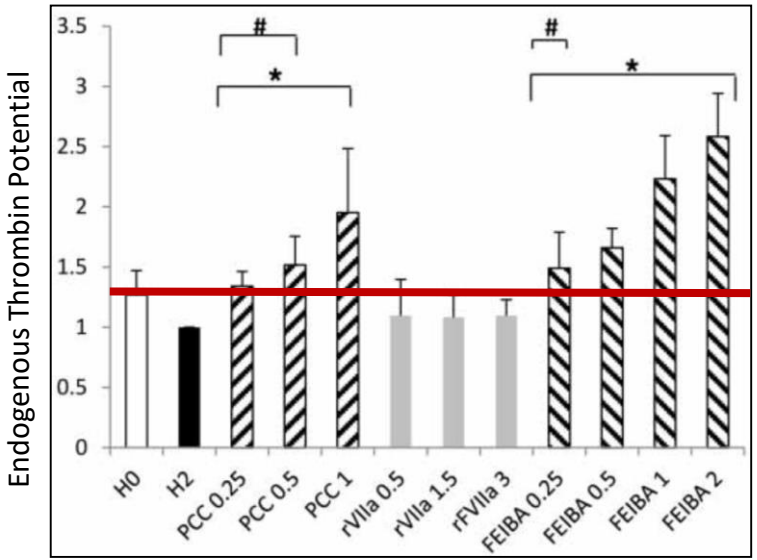
50 units/kg PCC reversed the anticoagulant effect of rivaroxaban but had no effect on dabigatran

Erenberg ES, et al. *Circulation* 2011;124:1573-9.

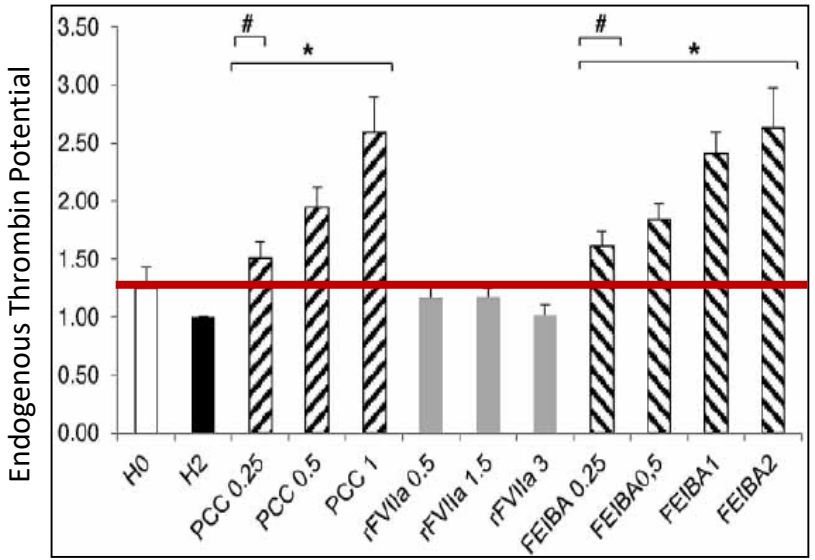
Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban

A randomised crossover *ex vivo* study in healthy volunteers

Rivaroxaban



Dabigatran



In vitro 4F-PCC and 4F-aPCC (FEIBA) increased endogenous thrombin potential after rivaroxaban and dabigatran

Marlu R, et al. *Thromb Haemost* 2012;108:217-24.

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PCC for Major Bleeding on Factor Xa Inhibitors

Apixaban- or Rivaroxaban-associated major bleed
N = 66 (36 ICH)

↓

4F-PCC 2,000 units

Outcome	4F-PCC
Good hemostasis	65% (67% ICH)
Moderate hemostasis	20% (17% ICH)
Thromboembolism (day 0-7)	3%
Thromboembolism (day 8-30)	5%

- 4F-PCC for factor Xa inhibitors was associated with 85% good/moderate hemostasis and 8% thrombosis within 30 days

Schulman S, et al. *Thromb Haemost* 2018;118:842-51.

PCC for Major Bleeding on Factor Xa Inhibitors

Apixaban- or Rivaroxaban-associated major bleed
N = 84 (59 ICH)

↓

4F-PCC 1,500-2,000 units
(Median: 2000 units; 26.5 units/kg)

Outcome	4F-PCC
Hemostasis	69.1% (72.9% ICH)
Thrombosis	3% (5% ICH)

- 4F-PCC for factor Xa inhibitors was associated with 69% hemostasis and 3% thrombosis within 30 days

Majeed A, et al. *Blood* 2017;130(15):1706-1712.

PCC for Major Bleeding on Factor Xa Inhibitors

DOAC-associated major bleed or surgical reversal
N = 42 (25 rivaroxaban, 13 apixaban, 4 dabigatran)

↓

4F-PCC 25 units/kg

Outcome	4F-PCC
Hemostasis	78.9%
Thromboembolism within 14 days	7.1%
Thromboembolism (Bleeding)	5.6%
Thromboembolism (Surgery)	16.7%

- 4F-PCC for DOACs was associated with 79% hemostasis and 7% thrombosis within 14 days

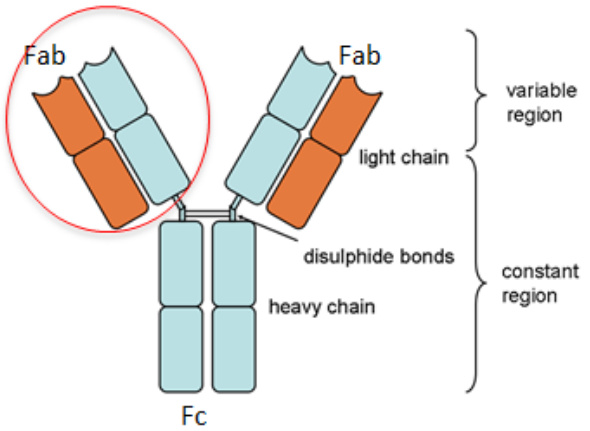
Santibanez M, Lin L, Lesch CA, Berger K. *J Crit Care* 2018;48:183-90.

PCC Considerations

- Dosing
  - Weight based vs flat dosing
- Product selection
  - 3F- vs 4F- vs a4F-PCC
  - Heparin-containing products
- True thrombosis and hemostasis rates for DOACs unknown

Idarucizumab (Praxbind®)

FDA-approved	• October 2015
MOA	• Humanized monoclonal antibody fragment that binds to dabigatran w/ 350 x higher affinity than the binding affinity of dabigatran to thrombin
Dose	• 2.5 g/50 mL x 2 doses *Total dose is always 5 g*
Administration	• Spike vial & hang each vial as 2 min bolus
Warnings/ADE	• Hypersensitivity reactions • Re-elevation of coagulation parameters • Thromboembolic risk?



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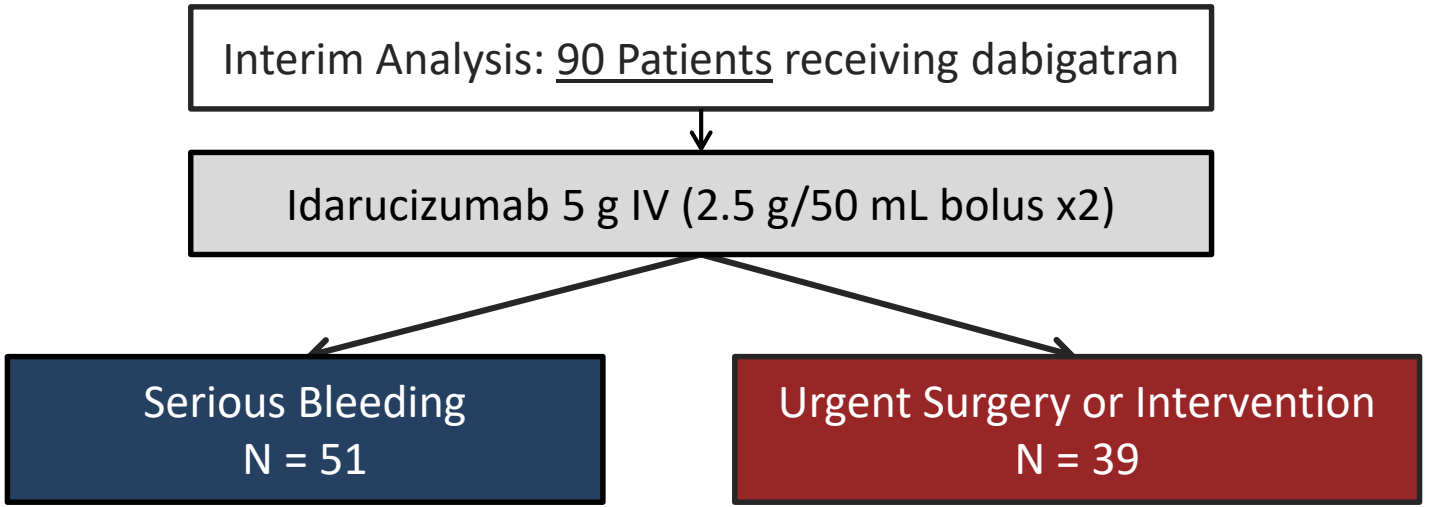
ORIGINAL ARTICLE

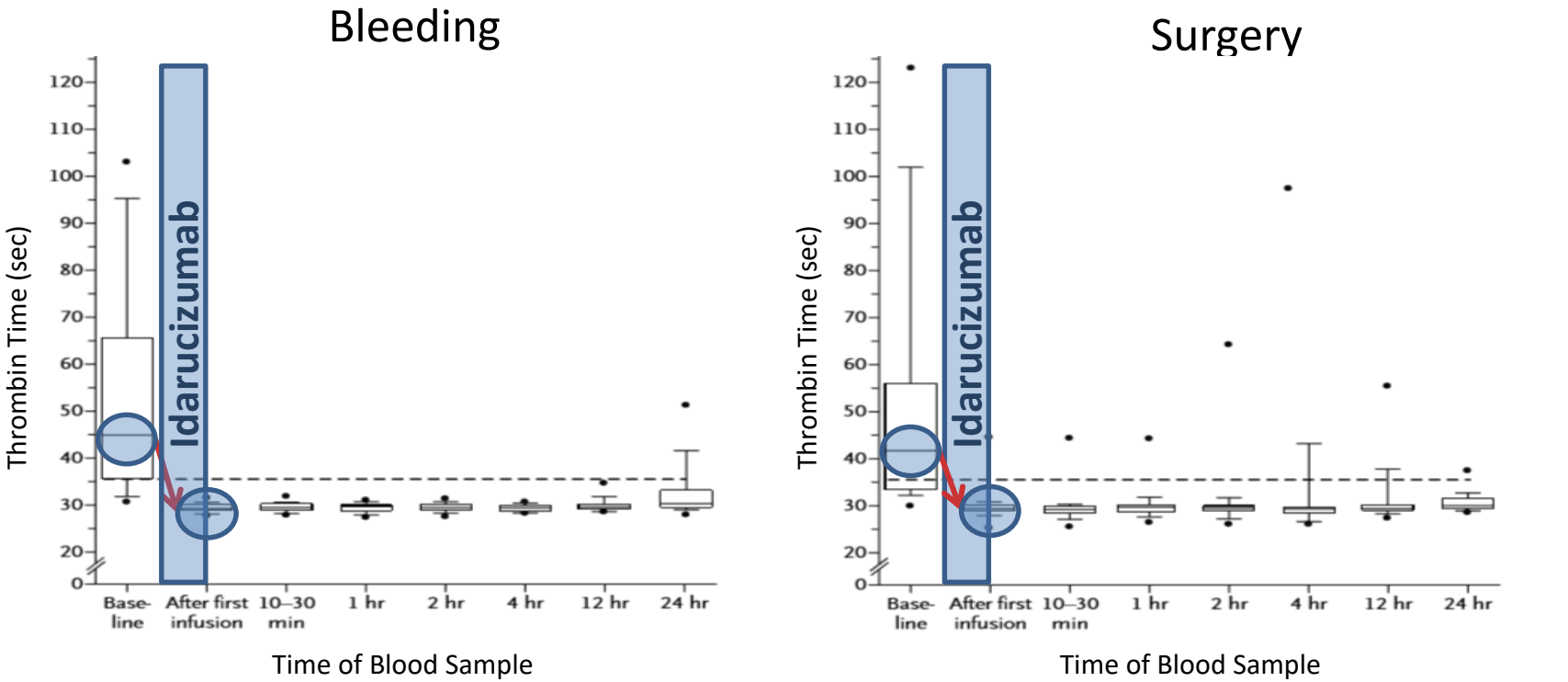
Idarucizumab for Dabigatran Reversal



- Reversed anticoagulant activity of dabigatran in 88-98% of patients

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

Dilute Thrombin Time



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

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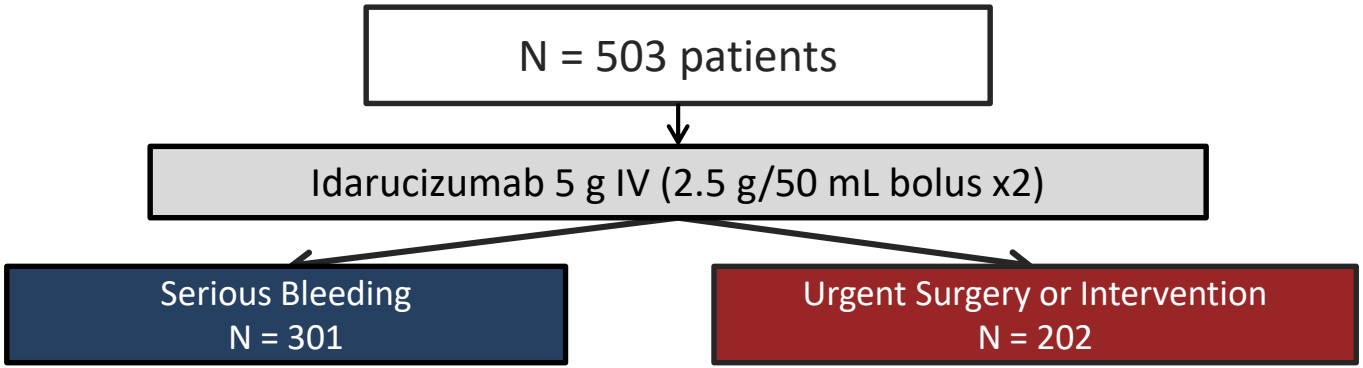
ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis



- Hemostasis at 24 hours: 67.7% (203 evaluable patients)
  - Median time to cessation of bleeding: 2.5 hours (from 11.4 hours in interim analysis)
- Median time to initiation of procedure: 1.6 hours
- Thrombotic events within 30 days: 4.8% (from 5.6% in interim analysis)

Pollack Jr CV, et al. *N Engl J Med* 2017;377:431-41.

Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

Oral Direct Thrombin Inhibitors (DTI)

- Stop agent
- Assess exposure (last dose, renal function)
- Reversal of DTI and Xa inhibitors guided by bleed, not labs
- Activated charcoal if ingestion ≤2 hours

Idarucizumab (Praxbind) 5 g if dabigatran administered within 3-5 half-lives and no renal failure

Frontera JA, et al. *Neurocrit Care* 2016;24(1):6-46.

Idarucizumab Considerations

- Idarucizumab vs PCC
  - Time to hemostasis?
  - Ongoing bleeding: Re-dose idarucizumab vs PCC
- Renal failure
  - Hemodialysis (renal replacement therapy) vs re-dosing

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-015-0222-x

REVIEW ARTICLE

Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

Direct Thrombin Inhibitors (DTI)

(8) In patients with dabigatran-associated intracranial hemorrhage who have already been treated with idarucizumab, PCC, or aPCC, with ongoing evidence of clinically significant bleeding, we suggest consideration of redosing idarucizumab and/or hemodialysis. (Conditional recommendation, low-quality evidence)

Frontera JA, et al. *Neurocrit Care* 2016;24(1):6-46.

Dabigatran Reversal in Renal Failure

- Dabigatran is primarily renally eliminated
- Idarucizumab has a short half-life which may lead to rebound increases in dabigatran levels (shown in REVERSE-AD trial)
- Patients presenting with renal dysfunction may be at a higher risk for rebound
- Use of idarucizumab in patients with renal impairment has only been described in case reports

Awesat J, et al. *Thromb Res* 2018;169:120-2.
Marino KK, et al. *Pharmacotherapy* 2016;36:e160:5.
Pollack Jr. CV, et al. *N Engl J Med* 2017;377:431-41.

Idarucizumab in Patients With and Without Renal Dysfunction

- Compared idarucizumab in patients with renal dysfunction (RD) (CrCl <30 mL/min) and no RD (NRD)

	Renal Failure (N= 10)	No Renal Failure (N= 12)	p-value
Age, median (IQR)	85 (74-92)	85 (80-90)	0.84
Time since last dose of dabigatran			
Unknown	7 (70)	7 (58)	--
> 12 hrs	2 (20)	3 (25)	--
< 12 hrs	1 (10)	1 (8)	--
Indication			
GI	7 (70)	6 (50)	0.61
Trauma	2 (20)	1 (8)	0.86
Other*	1 (10)	3 (25)	0.72
Emergent GI Surgery	0 (0)	2 (17)	0.54

*1 intramuscular hematoma, 2 pulmonary hemorrhage, and 1 subdural hemorrhage

Der Nigoghossian C, Chacko J, Park Y, Berger K. *Crit Care Med* 2019;47(1):419 (abstract #880).

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Idarucizumab Data and Clinical Outcomes

	Renal Failure (N= 10)	No Renal Failure (N= 12)	p-value
# Idarucizumab doses given, %			
0.5	20	0	0.19
1	60	100	0.03
2*	20	0	0.19
> 15 min between doses	2/8 (25)	1/12 (8.3)	0.7
Thrombotic events**, %	0	0	1
Hospital length of stay, days, median	7	5	0.97
Admission to ICU, %	70	58	0.90
Mortality during hospitalization, %	40	8	0.21

*One patient received 1.5 doses initially and then an extra 0.5 dose the next day;**Thrombotic event during hospitalization or within 90 days

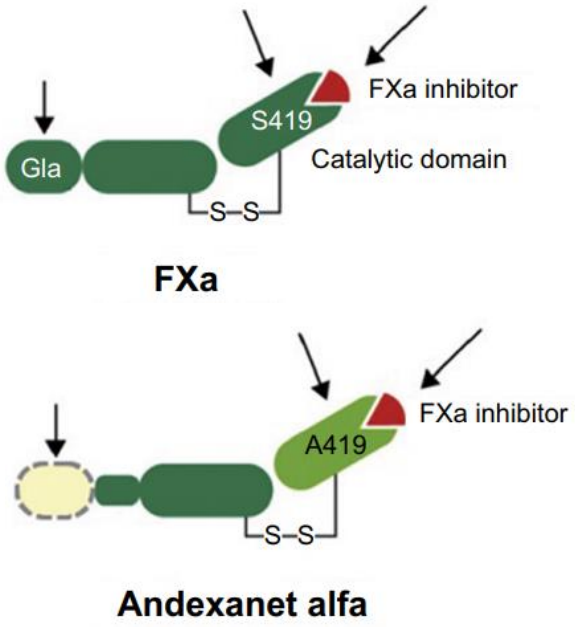
- Patients with RD had a higher number of idarucizumab dose deviations, including repeat dosing
- Patients with RD should be closely monitored for potential rebound bleeding after idarucizumab administration

Dabigatran Reversal Summary

- Idarucizumab 5 g IV
- ?PCC/aPCC 25-50 units/kg
- Concomitant Vitamin K not necessary
- Time to reversal dependent on renal function
- Consider baseline coagulation labs, but don’t wait to administer
  - Thrombin time and aPTT helpful to assess drug exposure
- Monitor for rebound bleeding with renal failure
  - Hemodialysis (renal replacement therapy) if access readily available

Andexanet alfa (Coagulation factor Xa (recombinant), inactivated-zhzo), Andexxa®

FDA-Approved	• May 2018
MOA	• Modified, recombinant, inactive factor Xa
Dose	• 400-800 mg bolus + 4-8 mg/min infusion x2 hours
Onset	• Rapid
Half-life	• PK half-life: 5-7 hours in PI • PD half-life: 1 hour
Adverse Reactions	• Thrombotic events (10%, 34/352 patients) • Infusion related reactions (<0.01%, 2/352 patients) • Symptoms mild to moderate in severity



Kaatz S, et al. *J Blood Med* 2017;8:141-9.

Andexanet Dosing

- Dosing depends on drug reversed, dose of Xa inhibitor, and time since last dose

Dose*	Bolus	Infusion
Low Dose	400 mg (30 mg/min)	4 mg/min x120 min
High Dose	800 mg (30 mg/min)	8 mg/min x120 min

Factor Xa Inhibitor	Last Dose	<8 hours or Unknown	≥8 hours
Rivaroxaban	≤10 mg	Low dose	Low dose
	>10 mg/Unknown	High dose	
Apixaban	≤5 mg	Low dose	
	>5 mg/Unknown	High dose	

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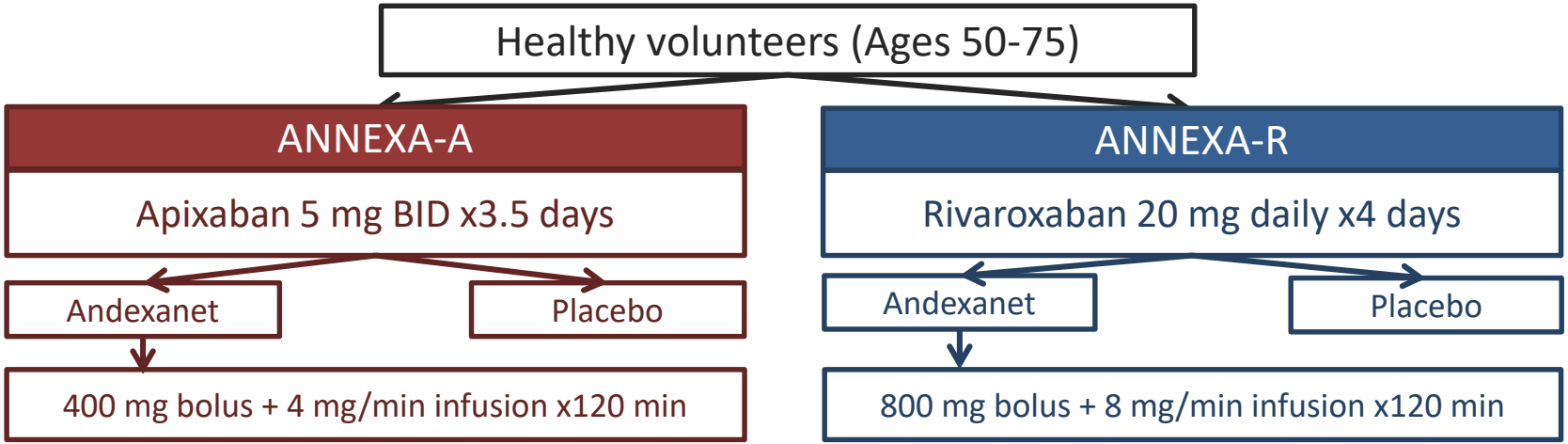
ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

ANEXXXA-A and ANNEXA-R

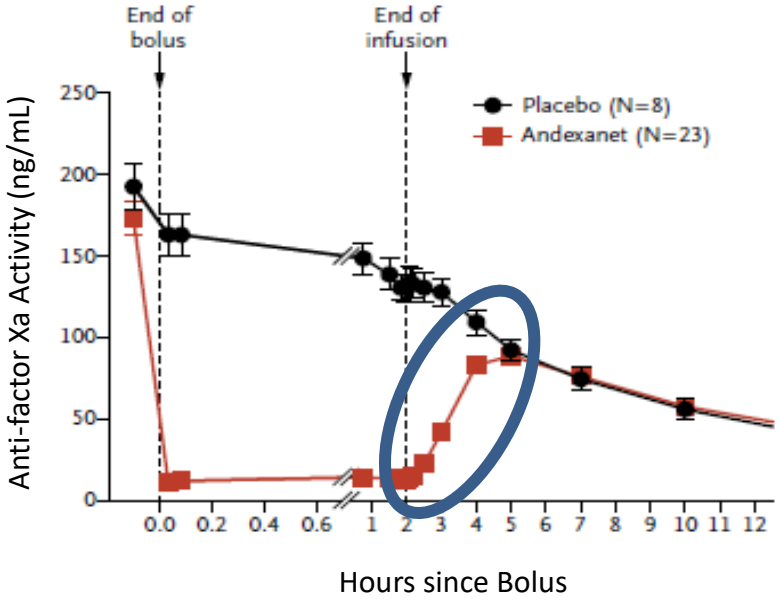


- ≥80% reversal of anti-factor Xa activity: 100% vs 0% (p <0.001)
- No serious adverse events and no thrombotic events reported

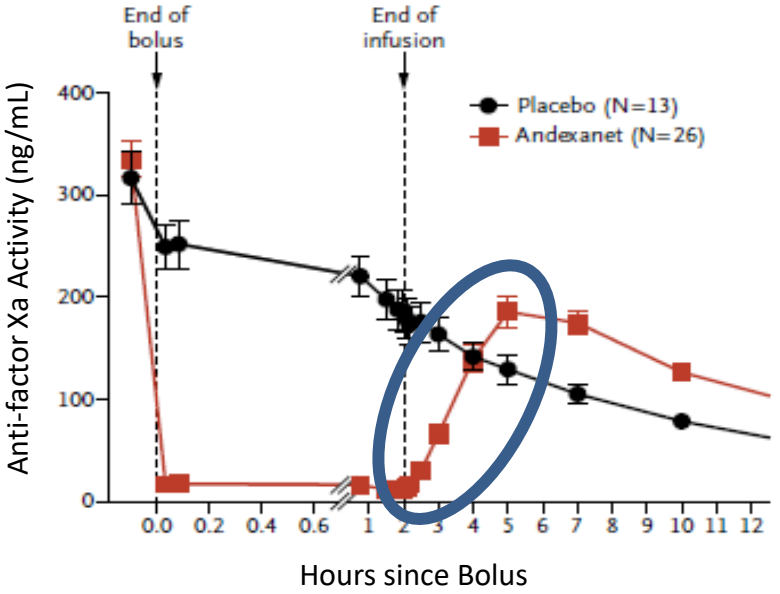
Siegal DM, et al. *N Engl J Med* 2015;373:2413-24.

Anti-factor Xa Activity

ANNEXA-A (Apixaban)



ANNEXA-R (Rivaroxaban)



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

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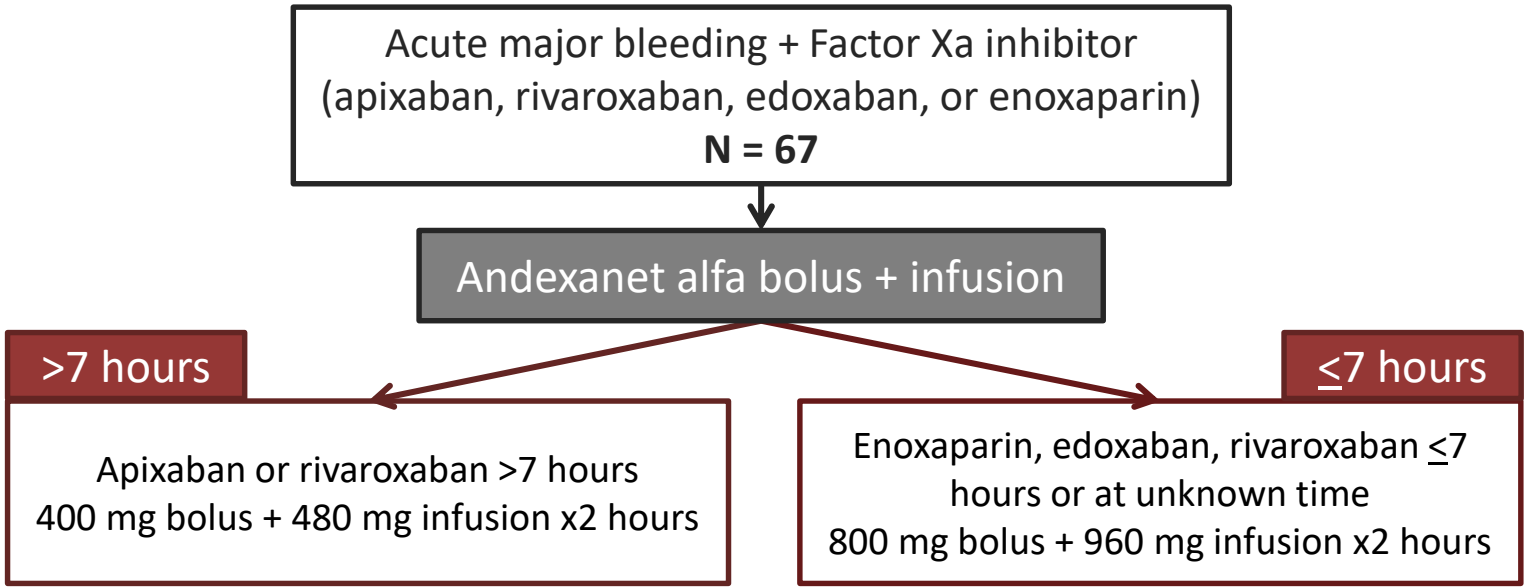
ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

ANEXXXA-4 Interim Report



Connolly SJ, et al. *N Engl J Med* 2016;375:1131-41.

Key Exclusion Criteria

- Planned surgery within 12 hours
- ICH and GCS <7
- ICH hematoma volume >60 mL
- Thrombosis within 2 weeks
- Use of PCC, rFVIIa, or plasma within previous 7 days

ICH = intracerebral hemorrhage; GCS = Glasgow Coma Scale; PCC = prothrombin complex concentrate; rFVIIa = recombinant factor VIIa

Connolly SJ, et al. *N Engl J Med* 2016;375:1131-41.

Clinical Outcomes

Outcome	
Efficacy Population (N = 47; 18 ICH)	
Overall Hemostasis*	79%
ICH*	80%
Safety Population (N = 67)	
Thrombosis	18%

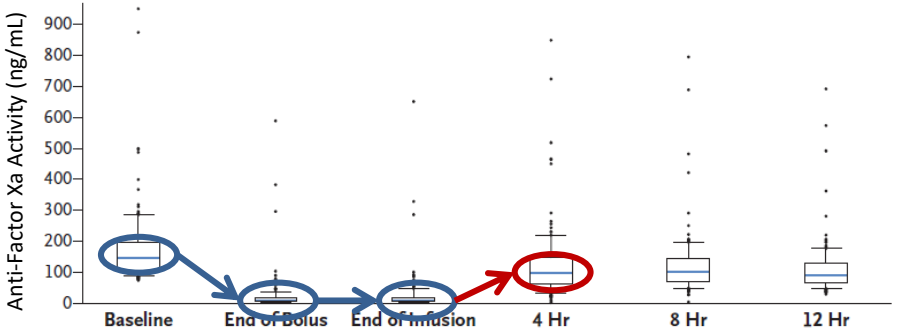
*Excellent or good hemostasis 12 hours after andexanet infusion; ICH = intracerebral hemorrhage

Connolly SJ, et al. *N Engl J Med* 2016;375:1131-41.

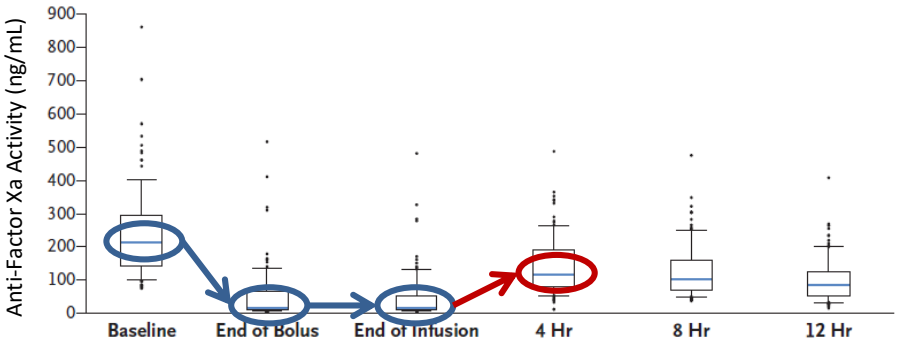
Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

ANEXXXA-4 Full Study

Apixaban



Rivaroxaban



Median Anti-Factor Xa Activity (ng/mL)

	Apixaban (n = 134)	Rivaroxaban (n = 100)
Baseline	149.7	211.8
End of Infusion	11.5	16.5
4 hours post-infusion	↑ 97.2	↑ 121.7

Connolly SJ, et al. *N Engl J Med* 2019;380:1326-35.

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Outcomes

Outcome	Interim Analysis N = 90	Full Cohort N = 352
Efficacy Population	n = 47; 18 ICH	n = 249; 98 ICH
Overall Hemostasis*	79%	82%
ICH*	80%	80%
Safety Population	n = 67	n = 352
Thrombosis	18%	10%

*Excellent or good hemostasis 12 hours after andexanet infusion; ICH = intracerebral hemorrhage

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Connolly SJ, et al. *N Engl J Med* 2016;375:1131-41.
Connolly SJ, et al. *N Engl J Med* 2016;375:1131-41.

Time To Andexanet

Factor Xa Inhibitor	Time to Andexanet* (hours)	Safety Population (N = 352)	Efficacy Population (N = 254)
Rivaroxaban	Time from last dose	12.3[1]	12[2]
	Time from hospitalization	4.7[1]	4.7[3]
Apixban	Time from last dose	12.1[4]	11.6[5]
	Time from hospitalization	4.5[4]	4.7[5]

*Data presented as mean; [1]n = 123; [2]n = 96; [3]n = 97; [4]n = 189; [5]n = 130

Connolly SJ, et al. *N Engl J Med* 2019;380:1326-35.

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Phase 4 RCT: Andexxa vs Usual Standard of Care in ICH

Detailed Description:

This is a randomized, multicenter clinical trial designed to determine the efficacy and safety of andexanet compared to usual care in patients presenting with acute intracranial hemorrhage within 12 hours of symptom onset and within 15 hours of taking an oral factor Xa inhibitor. The study will use a prospective, randomized, open label (PROBE) design. The primary efficacy outcome will be adjudicated by a blinded Endpoint Adjudication Committee. To support the adjudication of hemostatic efficacy, a blinded Imaging Core Laboratory will review all available scans. Approximately 440 patients are planned to be enrolled in the study.

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	440 participants
Allocation:	Randomized
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase 4 Randomized Clinical Trial of Andexanet Alfa [Andexanet Alfa for Injection] in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor
Actual Study Start Date :	January 18, 2019
Estimated Primary Completion Date :	March 1, 2023
Estimated Study Completion Date :	November 1, 2023

ClinicalTrials.gov Identifier: NCT03661528

Andexanet Considerations

- FDA-approved for apixaban- and rivaroxaban-associated life threatening bleeding
- Not studied for emergent surgery
- Options if last dose >18 hours
- Options for continued bleeding or subsequent surgery
- ?Use after PCC/aPCC
- 2-bag vs 1-bag

Case

- 71 year old, 130kg female on edoxaban for stroke prevention in atrial fibrillation
- Presents to the ED with acute onset headache and right sided weakness → CT head: ICH
- What is/are the most appropriate agent(s) for reversal of her bleed?
  - ~~Vitamin K~~
  - ***PCC**
  - ~~Dialysis~~
  - ***Activated charcoal*** (depending on timing of last dose)
  - ***Andexanet alfa*** (theoretically works)
  - ~~Nothing; watch and wait as edoxaban has no reversal agent~~

Case

- 71 year old, 130kg female on edoxaban for stroke prevention in atrial fibrillation
- Presents to the ED with acute onset headache and right sided weakness → CT head: ICH
- What baseline labs are needed prior to administration of PCC?
  - PT/INR
  - aPTT
  - SCr
  - TT
  - Thromboelastography with ROTEM or TEG
  - No labs required

Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

Oral Factor Xa Inhibitors

- Stop agent
- Assess exposure (last dose, renal function)
- Reversal of DTI and Xa inhibitors guided by bleed, not labs
- Activated charcoal if ingestion ≤2 hours

4F-PCC or aPCC if factor Xa inhibitor administered within 3-5 half-lives or in the context of liver failure

Frontera JA, et al. *Neurocrit Care* 2016;24(1):6-46.

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy

Recommendation 18a

For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel *suggests* using *either* 4-factor PCC administration as an addition to cessation of oral direct Xa inhibitor *or* cessation of oral direct Xa inhibitor alone (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.

Recommendation 18b

For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel *suggests* using coagulation factor Xa (recombinant), inactivated-zhzo in addition to cessation of oral direct Xa inhibitor rather than no coagulation factor Xa (recombinant), inactivated-zhzo (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** This recommendation does not apply to non–life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.

Witt DM, et al. *Blood Adv* 2018;2(22):3257-91.

ASH Recommendations Explained

Conclusions and research needs for this recommendation. Based on the absence of data for the comparator, very low certainty evidence from 1 observational study, and the extremely high cost of the intervention, the panel could not come to a unanimous decision. Voting resulted in a conditional recommendation for administration of coagulation factor Xa (recombinant), inactivated-zhzo, primarily based on the evidence for direct Xa inhibitor reversal and biological plausibility of preventing worsening of bleeding for widely used anticoagulants, the direct Xa inhibitors, using a specific reversal agent. Whether coagulation factor Xa (recombinant), inactivated-zhzo is associated with excess thromboembolism is unknown. This recommendation does not apply to non–life-threatening bleeding, because the cost likely outweighs potential benefit.

Witt DM, et al. *Blood Adv* 2018;2(22):3257-91.

American Journal of Hematology AJH

CRITICAL REVIEW | Free Access

Reversal of Direct Oral Anticoagulants: Guidance from the Anticoagulation Forum

Apixaban & Rivaroxaban

Guidance statement 3:

In patients with rivaroxaban-associated or apixaban-associated major bleeding in whom a reversal agent is warranted (see Guidance statement 1), we suggest treatment with andexanet alfa dosed according to the US FDA label (Table 2). If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units.

Edoxaban & Betrixaban

Cuker A, et al. *Am J Hematol* 2019 [Epub ahead of print].

Andexanet vs PCC

	Connolly	Schulman	Santibanez	Allison	Tao	Majeed
N	352	66	42	31	43	84
Drug	Andexanet	4F-PCC	4F-PCC	4F-PCC	4F-PCC	4F-PCC
Dose	Bolus + infusion	2000 units	25 units/kg	35 units/kg	25-50 units/kg	1500-2000 units
Hemostasis	82%	65%	79%	84%	93%	69%
Thrombosis	10%[2]	8%[2]	7%[1]	0*	2.1%[1]	4%[2]

*Assessed until discharge, median length of stay was 7 days; [1] = 14 days; [2] = 30 days

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Connolly SJ, et al. *N Engl J Med* 2019;380:1326-35.
Schulman S, et al. *Thromb Haemost* 2018;118:842-51.
Santibanez M, et al. *J Crit Care* 2018;48:183-90.
Allison TA, et al. *J Intensive Care Med* 2018 [Epub ahead of print].
Tao J, et al. *J Intensive Care* 2018;6:34.
Majeed A, et al. *Blood* 2017;130:1706-12.

Factor Xa Inhibitor Reversal Summary

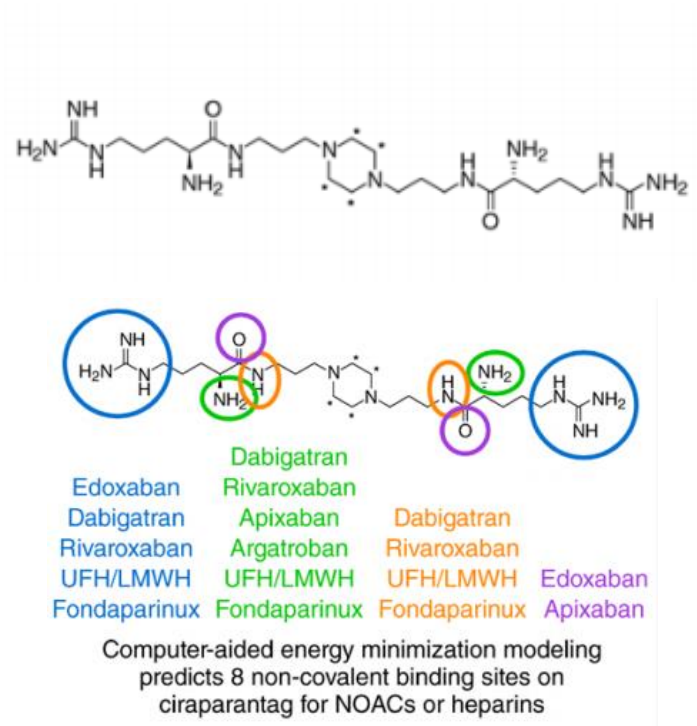
- All factor Xa inhibitors (bleeding or surgery)
  - PCC/aPCC 25-50 units/kg
- Apixaban/rivaroxaban-associated bleeding
  - Andexanet alfa bolus + infusion
  - PCC/aPCC 25-50 units/kg
- Concomitant Vitamin K not necessary
- Consider baseline coagulation labs, but don’t wait to administer

Praxbind vs Andexxa

	Idarucizumab (Praxbind)	Andexanet alfa (Andexxa)
Mechanism	Monoclonal antibody	Factor Xa decoy protein
Specific vs Class Effect	Specific to dabigatran	Likely works on all factor Xa inhibitors
FDA-approved for Bleeding	Yes	Yes
FDA-approved for Surgery	Yes	No
Administration	IV push	Bolus (13-26 min), then 2 hour infusion
Number of vials	2	5-18
Reconstitution	No	Yes
Dose dependent on DOAC dose?	No	Yes
Dose dependent on time since last DOAC dose?	No	Yes
Rebound	None to delayed	Anti-factor Xa levels ↑ within 4 hours
Cost	$3500	$25,000-50,000

Ciraparantag (aripazine, PER 977)

MOA	• Small synthetic molecule that binds to oral anticoagulants and heparin via noncovalent hydrogen bonds
Target	• Factor Xa inhibitors • Dabigatran • UFH, LMWH
Dose	• 100-300 mg IV bolus



Computer-aided energy minimization modeling predicts 8 non-covalent binding sites on ciraparantag for NOACs or heparins

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Mo Yoonsun. *Pharmacotherapy* 2015;35:201.
Ansell JE, et al *N Engl J Med* 2014;371:2141-2.
Ruff CT, et al. *Circulation* 2016;134:248–261.

Reversal Agent Targets

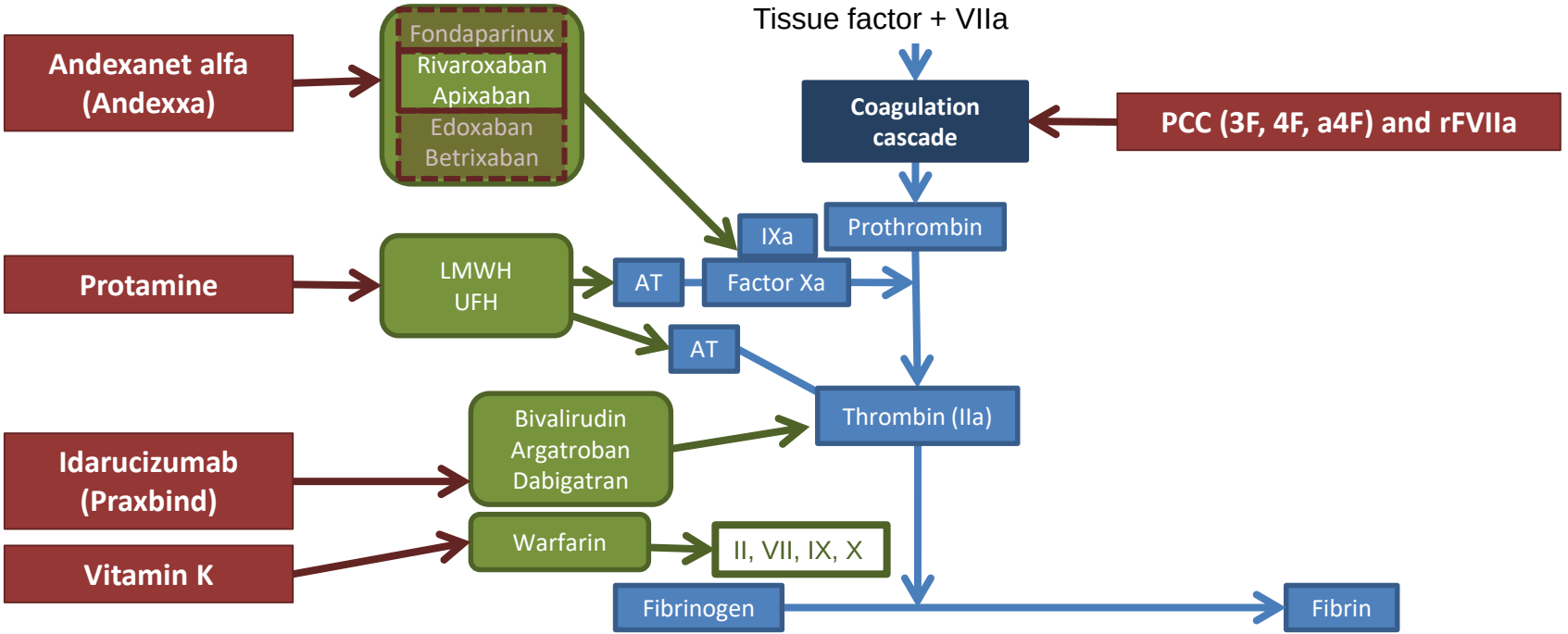
Anticoagulant	Pharmacologic Class	Idarucizumab	Andexanet alfa	Ciraparantag
Apixaban	Xa	N/A	FDA-approved ✓	✓
Dabigatran	IIa	✓	N/A	✓
Edoxaban	Xa	N/A	✓	✓
Rivaroxaban	Xa	N/A	FDA-approved ✓	✓
UFH	Heparin	N/A	N/A	✓
LMWH	Heparin	N/A	Enoxaparin ✓	✓
Fondaparinux	Xa	N/A	Unknown	✓
Warfarin	VKA	N/A	N/A	N/A

Xa = factor Xa inhibitor; IIa = factor IIa inhibitor; UFH = unfractionated heparin; LMWH = low-molecular weight heparin; VKA = vitamin K antagonist

X = active reversal agent; N/A = no activity

Costin J, et al. *Postgrad Med* 2014;126(7):19-24.

Targeted Reversal



LMWH: low molecular weight heparin; UFH: unfractionated heparin; AT: antithrombin

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Van de Weft F. *Circulation* 2011;123:1834.
Mo Yoonsun. *Pharmacotherapy* 2015;35:201.

Cost of Reversal Agents

Reversal Agent	Cost	Unit	Approximate Dose	Approximate Cost/Dose[1]
3F-PCC (Profilnine®)	$673	500 unit vial	25-50 units/kg	$2600-4700
4F-PCC (Kcentra®)	$884	500 unit vial	25-50 units/kg	$3500-6000
aPCC (FEIBA®)	$1080	500 unit vial	25-50 units/kg	$4000-7500
Idarucizumab (Praxbind®)	$3500	Two 2.5 g vials	5 g	$3500
Andexanet alfa (Andexxa®)	$2750	100 mg vial	400-800 mg bolus, 4-8 mg/min x2 hours	$24,750-49,500

[1] Based on 70 kg patient

Andexxa® Reimbursement and Replacement

- NTAP: Up to $14,062.50 (50% of low dose acquisition cost)
- Andexxa® Replacement Credit Program
  - Replacement credit of vials which are prepared for a **labeled indication**, yet not administered because **patient has expired/coded or refused treatment**
  - Submit Portola Replacement Credit Program form within 30 days and product within 60 days
  - *Replacement credit on a case-by-case basis at the sole discretion of Portola
  - *No credit if ANY portion of the product has been administered
  - *Retain all original product packaging, including intact vials

NTAP = New Technology Add on Payment

Unanswered Questions

- PCCs
  - Superiority of 3F- vs 4F- vs aPCC
  - Re-dosing in DOACs (when, how much)
  - Weight based vs flat dosing
- Targeted agents
  - Idarucizumab/andexanet alfa +/- PCC/aPCC
  - Extended infusion andexanet alfa/Re-dosing idarucizumab
  - Utility of targeted agent after PCC
- Laboratory assessments
  - Role of ROTEM/TEG, anti-factor Xa levels

Key Points

- Idarucizumab and andaxanet FDA-approved under accelerated review
  - Approval based on low quality data (single arm, interim analyses)
- PCC/aPCC recommended for DOAC reversal in clinical guidelines
  - Mostly retrospective and observational studies
  - Most guidelines published prior to antidote availability

Learning Assessment #1

- Which of the following is true of idarucizumab?
  A. Monoclonal antibody with a targeted class-effect against direct thrombin inhibitors
  B. Factor II decoy meaning it is structurally similar to factor II, but is enzymatically inactive
  C. Available as a kit of two 2.5 g vials where 1 or 2 doses may be used for reversal, depending on the severity of the bleed
  D. First FDA-approved antidote for a direct-acting oral anticoagulant

Learning Assessment #2

- Which of the following would be the most ideal candidate for andexanet? Assume all patients took their last dose this morning.
  A. 33 yo M on apixaban going for elective surgery
  B. 84 yo F on rivaroxaban who presents with an acute intracerebral hemorrhage
  C. 62 yo M on betrixaban who presents with an acute subdural hematoma
  D. 55 yo F on rivaroxaban who requires an emergent cholecystectomy
  E. 49 yo M on apixaban with an acute subdural hematoma planned for neurosurgical hematoma evacuation

Learning Assessment #3

- RJ is a 64 year old man on rivaroxaban for a DVT diagnosed 2 months ago. He presents with the worst headache of his life and is found to have an acute aneurysmal subarachnoid hemorrhage. The plan is to take him to the OR for aneurysm clipping. Which of the following options would be the most appropriate agent for reversal of his bleed?
  A. Vitamin K
  B. 4F-PCC
  C. Andexanet
  D. Idarucizumab
  E. Supportive care alone

Clinical Controversies in DOAC Reversal

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