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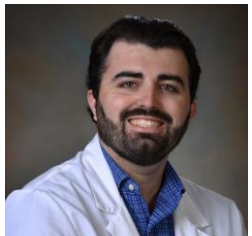
Who's the Real Alfa? Andexanet Alfa vs. 4F-PCC for DOAC Reversal

A presentation for HealthTrust Members

May 23, 2024



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Learning Objectives

- Recall the mechanisms of action of four-factor prothrombin complex concentrate (4F-PCC) and andexanet alfa
- Identify the outcomes of studies utilizing 4F-PCC and andexanet alfa for direct oral anticoagulant (DOAC) reversal
- Describe the pros and cons of 4F-PCC and andexanet alfa use in DOAC reversal

Abbreviations & Definitions

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4F-PCC- Four-Factor Prothrombin Complex Concentrate
AA – Andexanet Alfa
AC – Anticoagulation
ACC – American College of Cardiology
AF – Atrial Fibrillation
AWP – Average Wholesale Price
CAD – Coronary Artery Disease
DOAC – Direct Oral Anticoagulants
FXa – Factor Xa
GCS – Glasgow Coma Scale
GIB – Gastrointestinal Bleeding
ICH – Intracranial Hemorrhage
ICP – Intracranial Pressure
IPH – Intraparenchymal Hemorrhage
ISTH – International Society on Thrombosis and Hemostasis
IV – Intravenous
IU – International Units
Kg – Kilograms
PAD – Peripheral Artery Disease
SBP – Systolic Blood Pressure
TE – Thromboembolic Events
VTE – Venous Thromboembolism

Background

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	MOA	Onset	Half-life	Elimination
Apixaban	Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of free and clot-bound FXa	3 to 4 hours	~ 12 hours	Urine (~27% as parent drug); feces (biliary and direct intestinal excretion)
Rivaroxaban	Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of FXa	2 to 4 hours	5 to 9 hours	Urine (66% primarily via active tubular secretion; feces
Edoxaban	Inhibits free FXa and prothrombinase activity and inhibits thrombin-induced platelet aggregation	1 to 2 hours	10 to 14 hours	Urine (primarily unchanged); renal clearance: ~50% of total clearance
Dabigatran	A specific, reversible, direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin	1 to 2 hours	12 to 17 hours	Primarily in urine

Source: Lexicomp. Lexi.com. 2024.

Background

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Common Indications for DOACS

- Non-valvular atrial fibrillation
- Venous thromboembolism
- VTE prophylaxis after hip/knee replacement
- PAD, CAD, VTE prophylaxis in medical patients (Rivaroxaban)

Anticoagulation Risk

- Excessive bleeding that may be life-threatening
  - Traumatic
  - Non-traumatic
  - Medication errors

Source: Tomaselli, G, et al. J Am Coll Cardiol. 2021.

Background

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DOAC Related Bleeding

- Incidence of major bleeding with the use of DOACs is about 3-4% of patients per year
- ICHs comprise about 13% of all major bleeds in DOAC-treated patients
- More than 900 ICH cases are associated with factor Xa inhibitors each month in the United States
- ICHs account for up to 45% of all DOAC-related bleeding deaths

Source: Greenberg, S, et al. AHA/ASA. Stroke. 2022.

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When is anticoagulation reversal indicated?

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The ACC recommends reversal of anticoagulation for patients experiencing a "major" bleeding event

What is considered a "major" bleed?

Source: Tomaselli, G, et al. J Am Coll Cardiol. 2021.

Background

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Major Bleeding: One or more of the following factors

- Involves a critical site
- Leads to hemodynamic instability
- Leads to a ≥2 g/dl hemoglobin decline, or requires ≥2 units of red blood cell transfusion

Hemodynamic instability

- SBP < 90 mmHg or need for vasopressors to achieve SBP ≥90 mmHg
- A decrease in SBP >40 mm Hg, or orthostatic blood pressure changes (systolic blood pressure drop of 20 mmHg or diastolic blood pressure drop of 10 mmHg upon standing)
- Continuous invasive measurement of mean arterial pressure with a value <65 mmHg
- End organ hypoperfusion

Source: Tomaselli, G, et al. J Am Coll Cardiol. 2021.

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Critical Sites

- ICH
- CNS hemorrhage
- Pericardial tamponade
- Airway
- Hemothorax
- Intra-abdominal bleeding
- Retroperitoneal hemorrhage
- Intramuscular
- Intra-articular

Source: Tomaselli, G, et al. J Am Coll Cardiol. 2021.

Background

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Intracranial hemorrhage

- Epidural
- Subdural
- Subarachnoid
- Intraparenchymal

Leads to:

- Accumulation of blood within the cranial vault
- Hematoma formation/expansion
- Increase in ICP
- Brain tissue damage

Source: Tomaselli, G, et al. J Am Coll Cardiol. 2021.

Background

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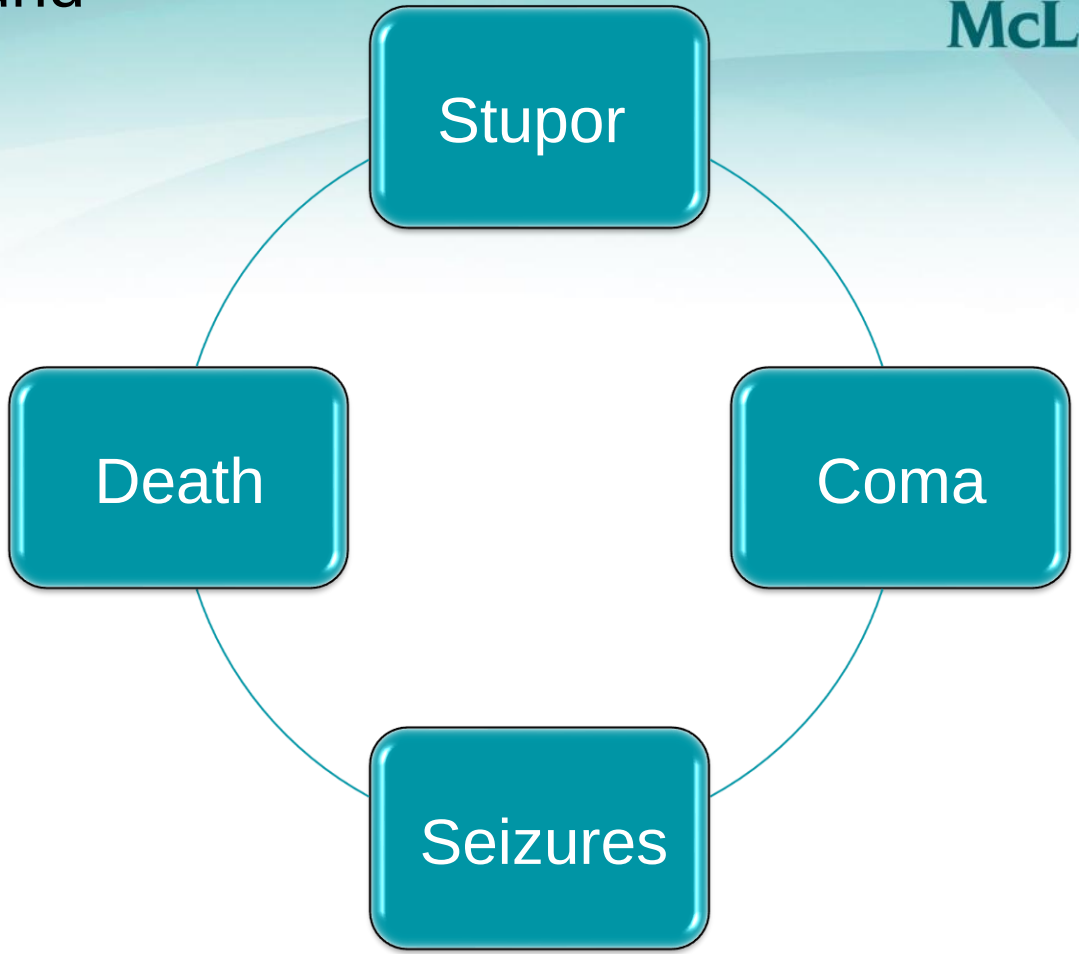

Background

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Reversal Agents

- Andexanet alfa
- PCC (3 and 4 factor, activated/unactivated)
- Recombinant factor VIIa
- Fresh frozen plasma
- Idarucizumab (Dabigatran)

Background – Andexanet Alfa

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	MOA	Onset/Duration	Half-life	Use (Approved)	Cost (AWP)
Andexanet Alfa (Andexxa)	Binds and sequesters the factor Xa inhibitors rivaroxaban and apixaban, increases tissue factor-initiated thrombin generation	2 to 5 minutes; Anti-factor Xa activity increases to levels seen in patients receiving placebo ~2 hours after infusion completion	~ 4 hours; elevation of tissue factor-initiated thrombin generation occurs within 2 minutes and is sustained for at least 22 hours after administration	Reversal of apixaban or rivaroxaban in those experiencing life-threatening or uncontrolled bleeding	$3,000 per each 200 mg vial

Source: Lexicomp. Lexi.com. 2024.

Background – Andexanet Alfa

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Low dose

- 400 mg IV bolus
  - ~30 mg/minute
- Followed within 2 minutes by an IV infusion of 4 mg/minute for up to 120 minutes
- $13,200

High dose

- 800 mg IV bolus
  - ~30 mg/minute
- Followed within 2 minutes by an IV infusion of 8 mg/minute for up to 120 minutes
- $26,400

Source: Lexicomp. Lexi.com. 2024.

Background – Andexanet Alfa

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Andexanet alfa Dose Based on Apixaban or Rivaroxaban Dose			
Factor Xa Inhibitor	**Factor Xa Inhibitor Last Dose**	**Timing of Factor Xa Inhibitor Last Dose Before Andexanet alfa Initiation**	
		<8 Hours or Unknown	**≥8 Hours**
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg or unknown	High dose	

Source: Lexicomp. Lexi.com. 2024.

Background – 4F-PCC

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	MOA	Onset/Duration	Half-life	Use (Off-label)	Cost (AWP)
4F-PCC (Balfaxar; Kcentra)	Provides an increase in the levels of the vitamin K-dependent coagulation factors (II, VII, IX, and X) with the addition of protein C and protein S	Rapid; significant affects within 30 minutes	Dependent upon factor/protein	Life-threatening bleeding associated with direct factor Xa inhibitors	$3.78 per each unit (Balfaxar); $3.58 per each unit (Kcentra); Institutional – $1.32 per each unit (Balfaxar)

Dosing:

- IV: 2,000 units once or 25 to 50 units/kg once
- $2,640

Source: Lexicomp. Lexi.com. 2024.

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Who's the Real Alfa? Andexanet Alfa versus 4F-PCC for DOAC reversal

ANNEXA-A and ANNEXA-R

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ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

Methods

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Study Design

- Randomized
- Double-blind
- Placebo-controlled
- ANNEXA-A
  - Apixaban 5 mg twice daily for 3.5 days
  - 3 hours post dose, andexanet was administered
- ANNEXA-R
  - Rivaroxaban 20 mg once daily for 4 days
  - 4 hours after the last dose, andexanet was administered

Criteria

- Healthy adults 50 to 75 years of age

Primary Outcome

- Percent change in anti factor Xa activity

Source: Deborah, S, et al. N Engl J Med 2015;373:2413-24

Methods

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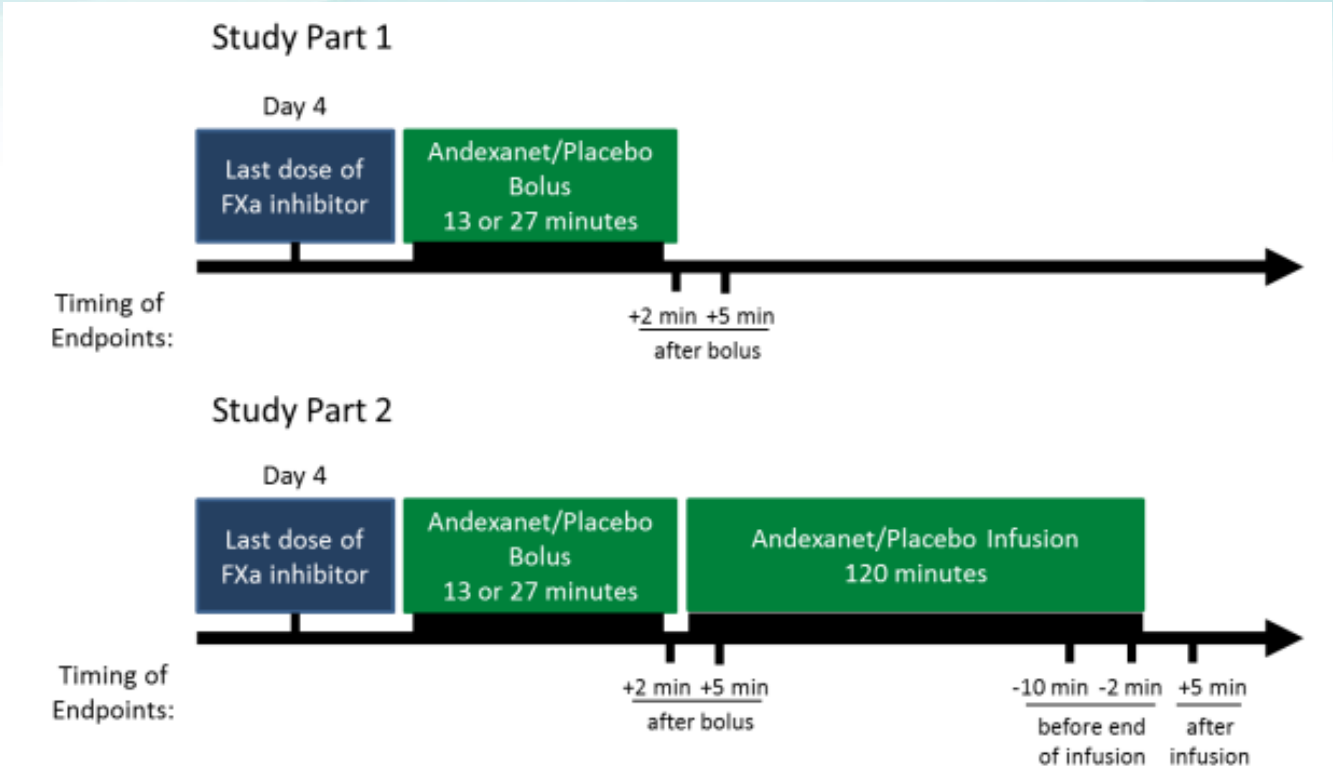

Source: Deborah, S, et al. N Engl J Med 2015;373:2413-24

Patient Population

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~58 years

60% male

85% caucasian

~27 m^2

Source: Deborah, S, et al. N Engl J Med 2015;373:2413-24

Patient Population

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101 to receive andexanet

- 48 apixaban
- 53 rivaroxaban

44 to receive placebo

- 17 apixaban
- 27 rivaroxaban

Source: Deborah, S, et al. N Engl J Med 2015;373:2413-24

Results

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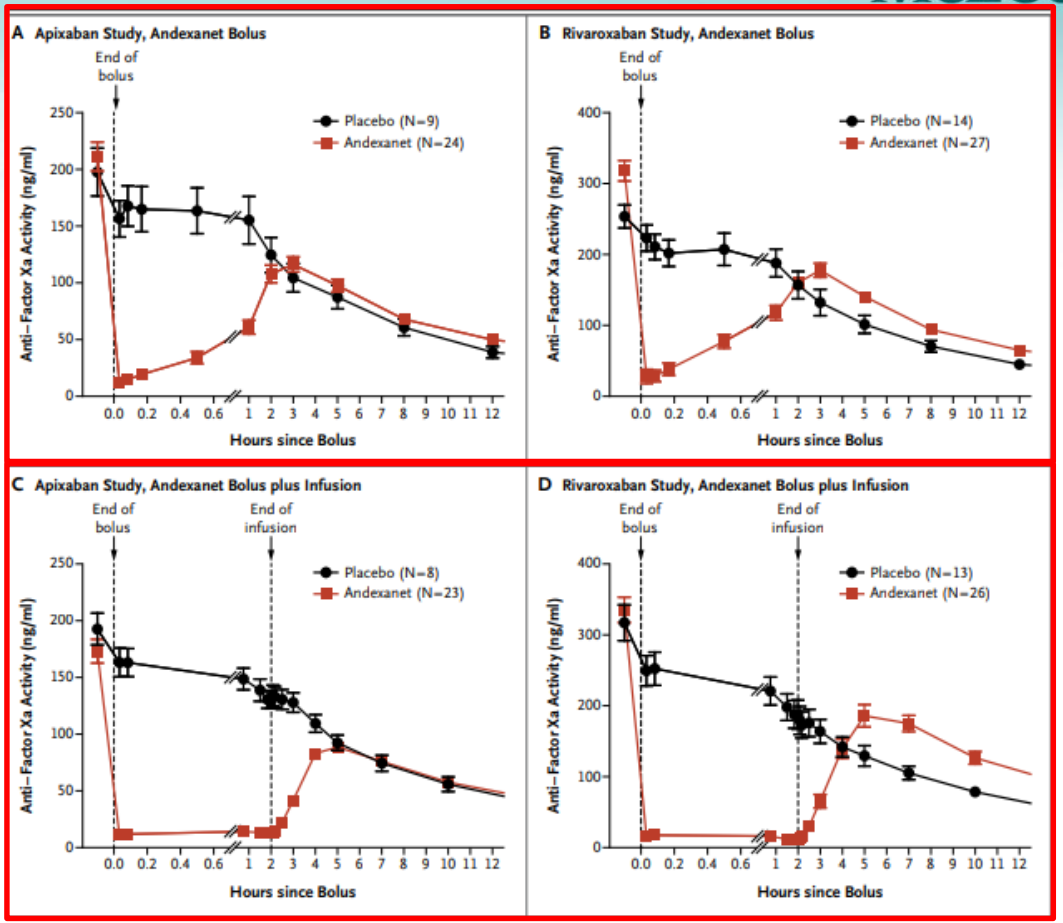

Source: Deborah, S, et al. N Engl J Med 2015;373:2413-24

Results

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	Apixaban				Rivaroxaban			
	Part 1 bolus only		Part 2 bolus+infusion		Part 1 bolus only		Part 2 bolus+infusion	
	Andexanet	Placebo	Andexanet	Placebo	Andexanet	Placebo	Andexanet	Placebo
N	24	9	23	8	27	14	26	13
Primary Endpoint								
Mean change (SD) in anti-FXa activity from baseline to nadir post-bolus (Part 1) or post-infusion (Part 2)	-198.7 (60.8)	-42.5 (24.5)	-160.6 (49.3)	-63.2 (18.1)	-292.2 (75.9)	-46.5 (42.2)	-324.5 (89.2)	-143.4 (58.8)
% change (SD) in anti-FXa activity	-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)
p-value % change (vs. placebo)	<0.001		<0.001		<0.001		<0.001	

Source: Deborah, S, et al. N Engl J Med 2015;373:2413-24

Limitations

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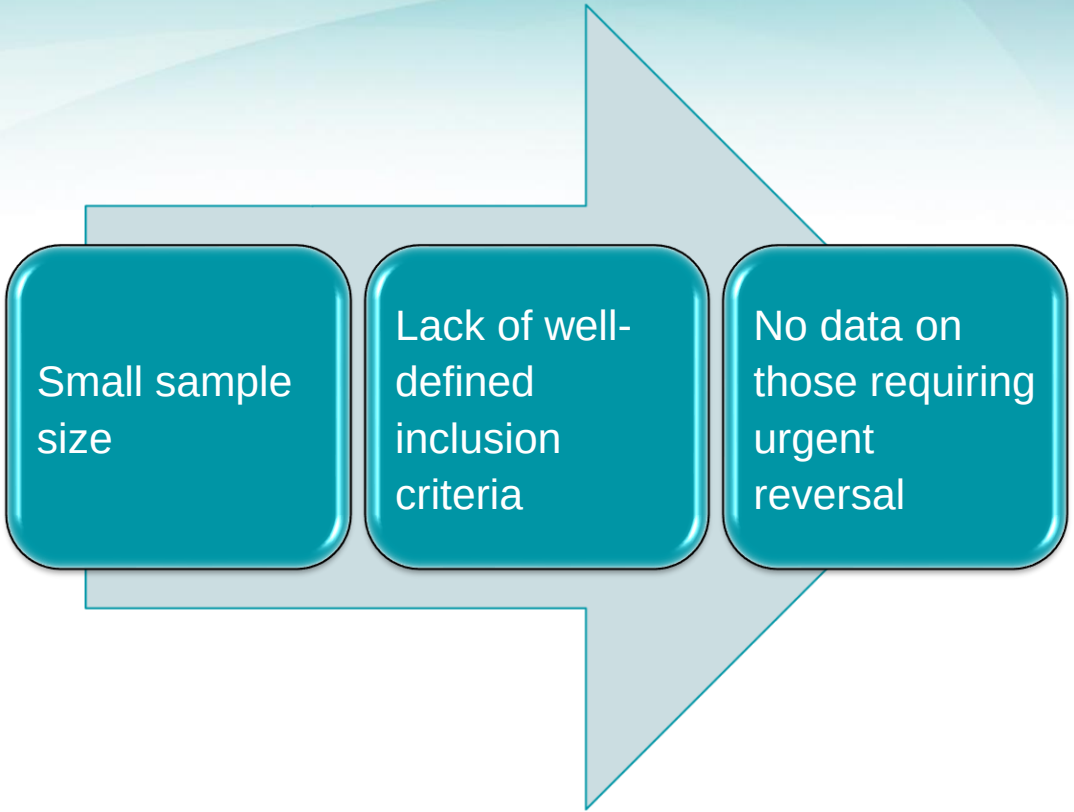

Source: Deborah, S, et al. N Engl J Med 2015;373:2413-24

Author's Conclusions

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Andexanet rapidly restored factor Xa activity, thrombin generation, and reduced unbound factor Xa inhibitor concentrations
Andexanet was not associated with safety concerns or thrombotic events

Source: Deborah, S, et al. N Engl J Med 2015;373:2413-24

ANNEXA-4

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ORIGINAL ARTICLE

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

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

Methods

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Study Design

- Multi-center, prospective, open-label, single-group
- Apixaban or rivaroxaban (>7 hours prior for rivaroxaban)
  - Andexanet 400 mg bolus followed within 2 minutes by an IV infusion of 4 mg/minute for up to 120 minutes
- Enoxaparin, edoxaban, or rivaroxaban (≤ 7 hours or at an unknown time for all)
  - Andexanet 800 mg bolus followed within 2 minutes by an IV infusion of 8 mg/minute for up to 120 minutes

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

Methods

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Inclusion Criteria

- 18+
- Acute major bleeding
- Within 18 hours received any dose of apixaban, rivaroxaban, or edoxaban
- Enoxaparin at a dose of 1 mg/kg

Exclusion Criteria

- Planned surgery within 12 hours
- ICH with GCS < 7
- Hematoma volume >60 mL
- Expected survival < 1 month
- TE in prior 2 weeks
- Use of other AC/blood products in prior 7 days

Co-Primary Outcomes

- Percent change from baseline in anti–factor Xa activity
- Percentage of patients with excellent or good hemostatic efficacy

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

Patient Population

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~77 years	53% male	87% caucasian
~27 m^2	80% afib	55% apixaban
36% rivaroxaban	64% IC	26% GI

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

Patient Population

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352 patients enrolled

- All in the safety population
- 254 qualified for the efficacy population
  - Baseline anti–factor Xa activity ≥ 75 ng/mL and confirmed major bleeding

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

Results

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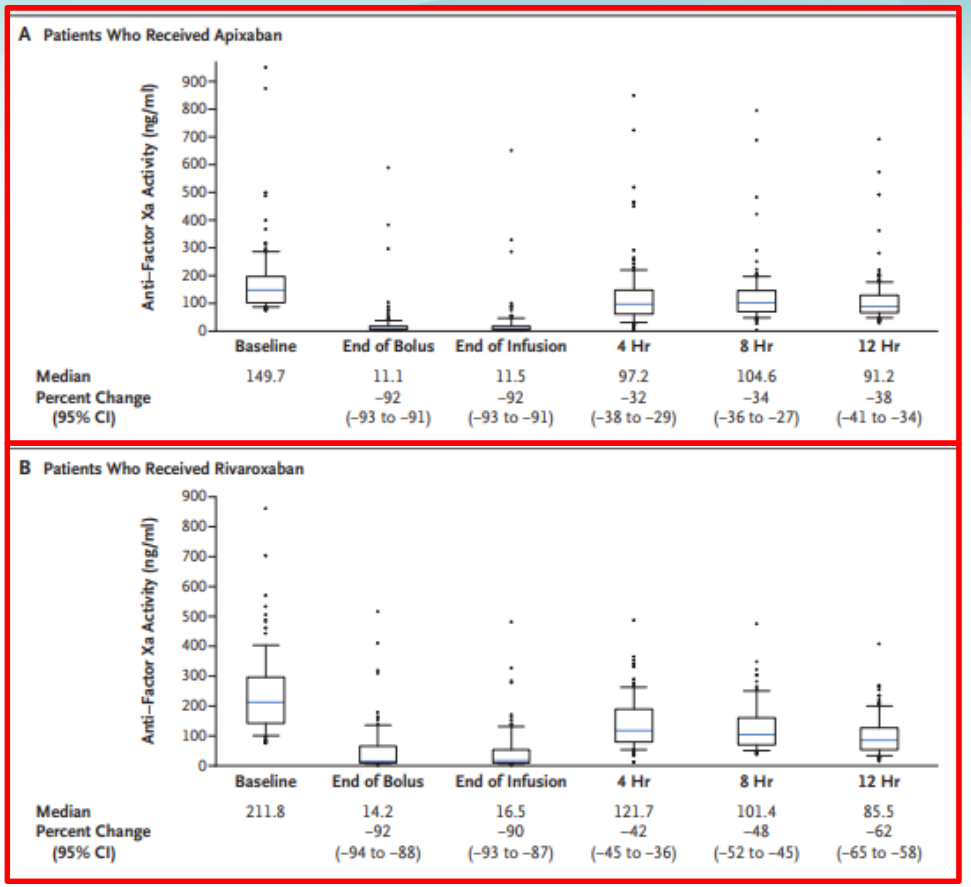

Source: Connolly, M, et al. N Engl J Med 2019;380:1326-35

Results

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Subgroup	No. of Patients/ Total No.	Percent with Excellent or Good Hemostasis (95% CI)
Overall	204/249	82 (77–87)
Drug		
Rivaroxaban	79/99	80 (72–88)
Apixaban	109/131	83 (77–90)
Enoxaparin	13/15	87 (69–100)
Sex		
Male	101/127	80 (73–87)
Female	103/122	84 (78–91)
Site of bleeding		
Gastrointestinal	51/60	85 (76–94)
Intracranial	135/168	80 (74–86)
Other	18/21	86 (71–100)
Age		
<65 yr	23/28	82 (68–96)
65–75 yr	57/66	86 (78–95)
>75 yr	124/155	80 (74–86)
Andexanet dose		
Low	172/208	83 (78–88)
High	32/41	78 (65–91)

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

Results

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Table 2. Timing of Thrombotic Event and Restarting of Anticoagulation.*

Variable	Safety Population (N=352)			
	Total	<6 Days after Bolus	6–14 Days after Bolus	15–30 Days after Bolus
	number of patients (percent)			
≥1 Thrombotic event within 30 days†	34 (10)	11	11	12
Myocardial infarction	7	6	1	0
Ischemic stroke or stroke of uncertain classification	14	5	6	3
Transient ischemic attack	1	0	0	1
Deep-vein thrombosis	13	1	5	7
Pulmonary embolism	5	1	0	4
Death within 30 days‡	49 (14)	8	21	20
Cardiovascular cause	35	7	15	13
Noncardiovascular cause	12	1	5	6
Uncertain cause	2	0	1	1
Restart of any anticoagulation§	220 (62)	145 (41)	46 (13)	29 (8)
Thrombotic event before restart¶	26 (7)			
Thrombotic event after restart	8 (2)			
Restart of oral anticoagulation‖	100 (28)	31 (9)	37 (11)	32 (9)
Thrombotic event before restart¶	34 (10)			
Thrombotic event after restart	0			

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

Limitations

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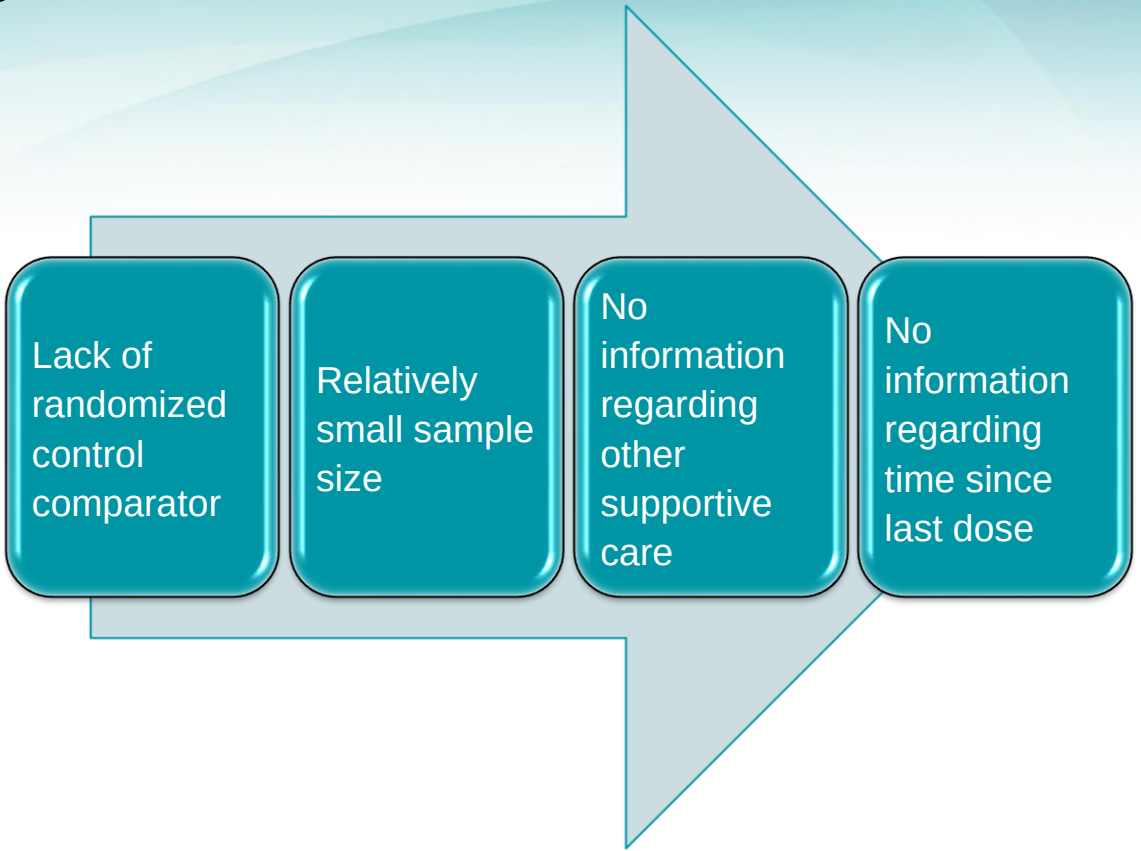

Source: Connolly, M, et al. N Engl J Med 2019;380:1326-35

Author's Conclusions

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Andexanet markedly reduced anti–factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours

Rapid specific reversal of factor Xa inhibition with andexanet, may improve clinical outcomes

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

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UPRATE

Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study

Ammar Majeed,[1-4] Anna Ågren,[1,3] Margareta Holmström,[1,3] Maria Bruzelius,[1,3] Roza Chaireti,[3,5,6] Jacob Odeberg,[1,3,7] Eva-Lotta Hempel,[1,3] Maria Magnusson,[6,8,9] Tony Frisk,[10] and Sam Schulman[11,12]

Methods

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Study Design

- Multi-center, prospective, observational, cohort study
- 1,500 IU PCC for body weight < 65 kg
- 2,000 IU PCC for body weight > 65 kg
- An additional dose was allowed at the discretion of the treating physician
- This protocol was based on an approximation of a PCC dose equivalent to 25 IU/kg

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Methods

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Criteria

- Inclusion
  - Acute and active major bleeding while on rivaroxaban or apixaban
  - Last dose < 24 hours
- Exclusion
  - Receival of other hemostatic agents prior to PCC (rFVIIa or activated PCC)

Primary Outcome

- Hemostatic effectiveness

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Patient Population

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75 years	57% male	75 kg
75% afib	~70% ICH	~16% GIB

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Patient Population

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84 participants

- 39 apixaban
- 45 rivaroxaban

Median time since last dose

- 12.5 hours

Median time to PCC administration

- 6 hours

Median dose

- 2,000 IU or 26.7 IU/kg
- 3 patients received a second dose

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Patient Population

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Transfusion of red blood cell concentrates

- Before PCC administration: 12 (14.3%)
- After PCC administration: 18 (21.4%)

Plasma

- Before PCC administration: 5 (5.9%)
- After PCC administration: 8 (9.5%)

Platelets

- After PCC administration: 10 (11.9%)

Tranexamic acid

- 56 (66.7%)

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Results

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Table 3. Outcome of bleeding management with PCCs

	Apixaban		Rivaroxaban	
	Effective	Ineffective	Effective	Ineffective
Bleeding location, n (%)				
ICH	21 (72.4)	8 (27.6)	22 (73.3)	8 (26.7)
GI	3 (60.0)	2 (40.0)	5 (62.5)	3 (37.5)
Visceral	0 (0.0)	2 (100.0)	1 (33.3)	2 (66.7)
Genitourinary	1 (50.0)	1 (50.0)	2 (100.0)	0 (0.0)
Musculoskeletal	1 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)
Hemoglobin drop, n (%)	2 (33.3)	4 (66.7)	3 (37.5)	5 (62.5)
Any invasive procedure, n (%)				
None	17 (68.0)	8 (32.0)	23 (74.2)	1 (25.0)
Craniotomy	5 (71.4)*	2 (28.6)	6 (100.0)*	0 (0.0)
Gastroscopy	3 (75.1)†	1 (25.0)	1 (33.3)†	2 (66.7)
Embolization	0 (0.0)	2 (100.0)	1 (50.0)*	1 (50.0)
Fasciotomy	1 (100.0)*	0 (0.0)	0 (0.0)	0 (0.0)
Laparotomy	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)
Thoracotomy	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Length of hospital stay, d, median (IQR)	7.0 (3.0-15.0)	4.5 (2.0-7.0)	9.0 (4.0-16.0)	2.5 (2.0-5.0)
Discharge destination, n (%)				
Home	14 (93.3)	1 (6.7)	10 (90.9)	1 (9.1)
Rehabilitation facility	7 (63.6)	4 (36.4)	13 (92.9)	1 (7.1)
Other hospital	2 (66.7)	1 (33.3)	1 (100.0)	0 (0.0)
Deceased	3 (33.3)	6 (66.7)	5 (35.7)	9 (64.3)
Unknown	0 (0.0)	1 (100.0)	1 (33.3)	2 (66.7)
Total	26	13	32	13

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Results

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Table 4. Characteristics of patients with thromboembolic events after treatment with PCCs

Age, y	Sex	Anticoagulant	Dose	Indication	Bleeding	PCC dose, IU (IU/kg)	Thromboembolism	Timing from PCC, d	Outcome
80	Female	Rivaroxaban	20 mg × 1	SPAF	ICH	1500 (29)	Stroke	10	Discharged. Died after 112 d of new stroke.
71	Female	Apixaban	5 mg × 2	SPAF	ICH	2000 (27)	Stroke	5	Died after 18 d from ICH.
73	Male	Rivaroxaban	20 mg × 1	SPAF	ICH	2000 (27)	Suspected PE*	15	Died after 16 d from ICH.

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Limitations

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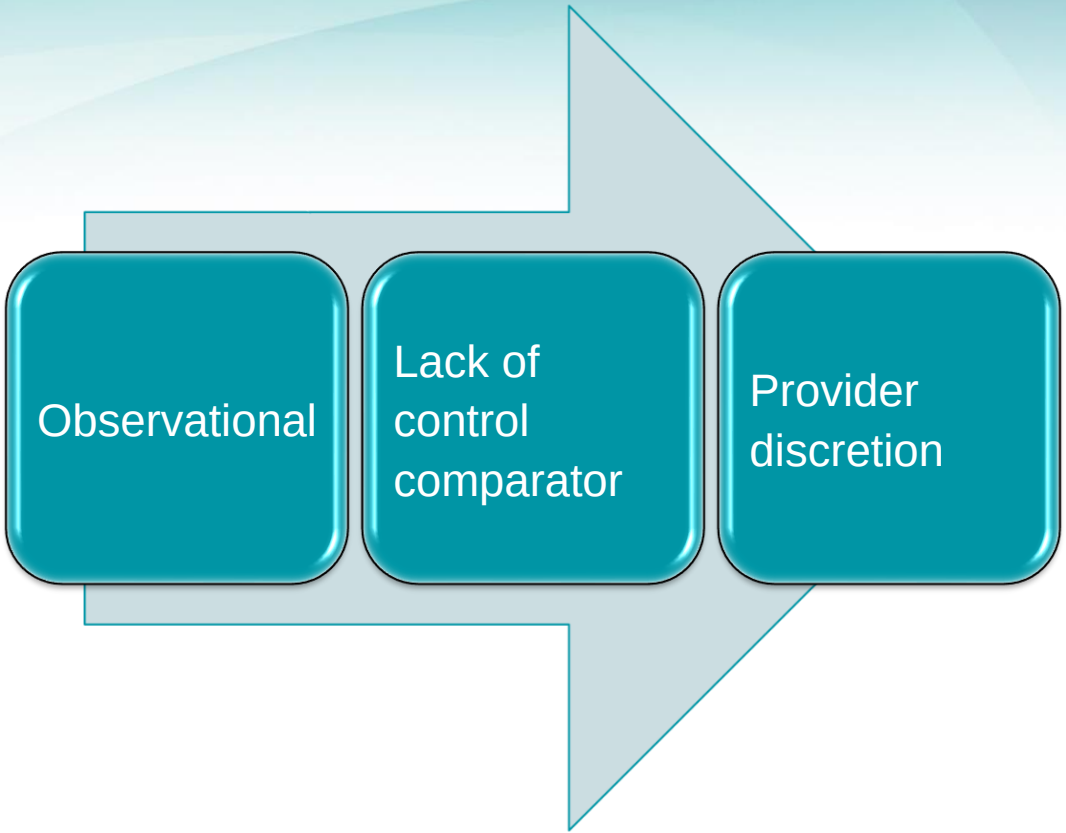

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Author's Conclusions

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The majority of patients treated with 4F-PCC achieved effective bleeding control, with few observed TEs

Based on the results, authors suggest giving patients an initial 4F-PCC dose of 2,000 IU, which may be repeated if the effect is suboptimal

Source: Ammar, M, et al. Blood. 2017;130(15):1706-1712

Pham, H, et al. 2022.

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Evaluation of andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhages

Haithuy Pham, PharmD [a,*], Whitney Gibson Medford, PharmD, BCCCP [c,f], Spencer Horst, PharmD, BCPS [b], Melissa Levesque, PharmD, BCCCP [c], David Ragoonanan, PharmD, BCCCP [c], Christine Price, PharmD [d], Harold Colbassani, MD [d], Keaton Piper, MD [c], Keith Chastain, MSQA, CMBB, CQE [e]

Methods

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Study Design

- Multi-center, retrospective, chart review
- Andexanet dosed according to product labeling
- 4F-PCC 50 units/kg (Max 5,000 units) for one dose

Inclusion Criteria

- 18+
- Taking apixaban or rivaroxaban prior to admission
- Radiographical evidence of ICH
- Received Andexanet or 4F-PCC for reversal

Primary Outcome

- Excellent hemostasis (ISTH)

Source: Pham, H, et al. Am J Emerg Med 2022;(55):38–4

Patient Population

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~79 years

~59% male

~79% caucasian

~ 80 kg

~80% afib

~74% apixaban

~62% IPH

109 patients

- Andexanet 47
- 4F-PCC 62

Source: Pham, H, et al. Am J Emerg Med 2022;(55):38–4

Results

McLeod Health

Table 3
Primary outcomes.

Hemostasis Scale	Andexanet alfa ($N = 38$)	4F-PCC ($N = 58$)	Difference with 95% CI	p	Adjusted p*
Excellent	27 (71.1)	41 (70.7)	0.4 (−18.2–18.9)	1	0.654
Good	4 (10.5)	5 (8.6)	1.9 (−10.2–14.0)	0.737	0.921
Poor	7 (18.4)	12 (20.7)	−2.3 (−18.4–13.9)	1	0.667

Source: Pham, H, et al. Am J Emerg Med 2022;(55):38–4

Results

McLeod Health

Table 4
Secondary outcomes.

Outcome	Andexanet alfa (N = 47)	4F-PCC (N = 62)	Difference with 95% CI	p	Adjusted p*
% Change in hemorrhage volume from baseline to 12–24 h after reversal treatment	0 [−0.17–0.24)	0 [−0.021–0.29]	0 (−0.058–0.00)	0.439	0.601
Thromboembolism event	4 (8.5)	6 (9.7)	−1.2 (−12.0–9.7)	1	0.973
Myocardial infarction	1 (2.1)	0 (0.0)	2.1 (−2.0–6.3)	0.431	
Stroke	0 (0.0)	0 (0.0)	0 (*–*)	1	
Deep vein thrombosis	3 (6.4)	5 (8.1)	−1.7 (−11.4–8.1)	1	
Pulmonary embolism	0 (0.0)	1 (1.6)	−1.6(−4.7–1.5)	1	
Inpatient mortality	16 (34.0)	13 (21.0)	13.1(−3.8–30.0)	0.134	0.283
Total cost of reversal treatment ($)	$23,602 [$23,602–$23,602]	$6692 [$5950–$7649]	$16,910 ($16,082–$17,022)	0.000	

Source: Pham, H, et al. Am J Emerg Med 2022;(55):38–4

Results

McLeod Health

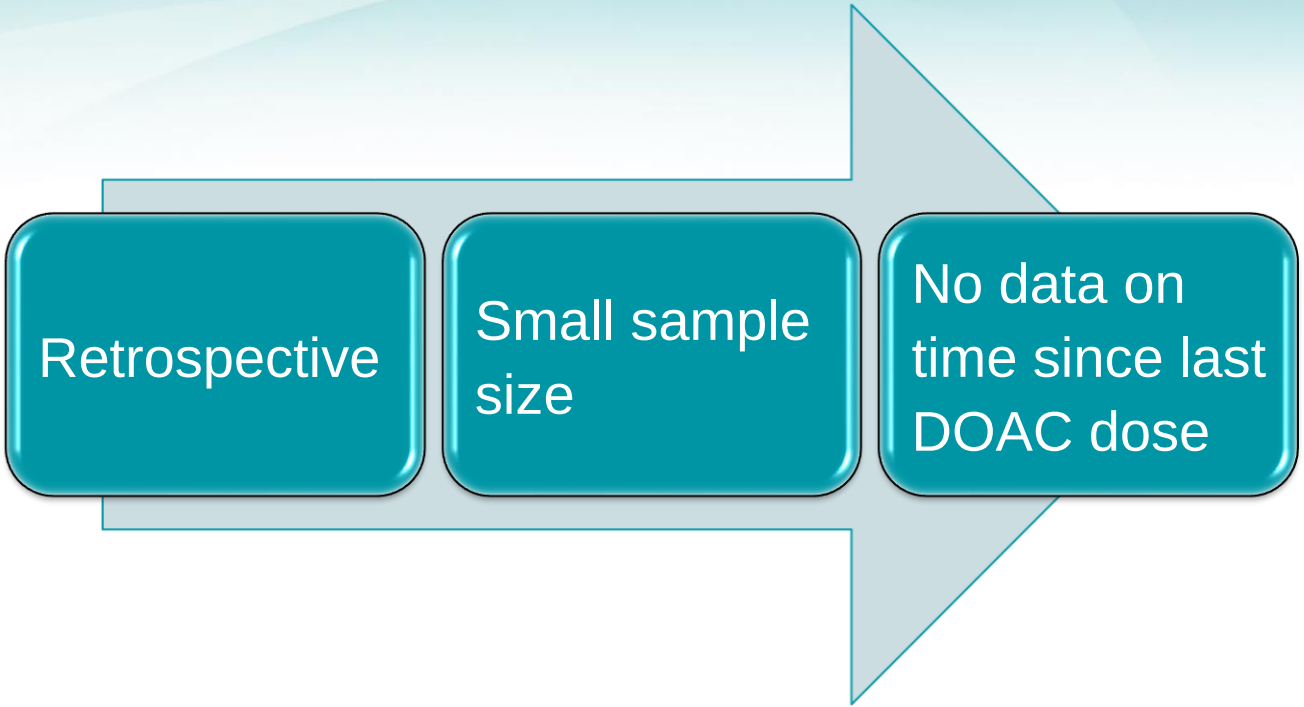
Table 5
Other Data of Interest

Other Data of Interest	Andexanet alfa ($N = 47$)	4F-PCC ($N = 62$)	Difference with 95% CI
Time between order and administration of reversal agent (minutes)	70 [55–87]	43 [31–61.5]	27 (9.0–41.1)
Additional transfusion			
RBC concentrate	1 (2.1)	3 (4.8)	−2.7 (−9.5–4.0))
Plasma	1 (2.1)	3 (4.8)	−2.7 (−9.5–4.0)
Platelets	2 (4.3)	11 (17.7)	−13.5 (−24.6–-2.4)
Vitamin K	2 (4.3)	3 (4.8)	−0.6 (−8.4–7.3)

Source: Pham, H, et al. Am J Emerg Med 2022;(55):38–4

Limitations

McLeod Health



Source: Pham, H, et al. Am J Emerg Med 2022;(55):38–4

Author's Conclusions

McLeod Health

No significant difference was found in efficacy or safety between Andexanet and 4F-PCC. There is insufficient evidence to recommend one reversal agent over the other for patients with ICHs associated with the use of apixaban/rivaroxaban

Source: Pham, H, et al. Am J Emerg Med 2022;(55):38–4

Gomez, A, et al. 2021.

McLeod Health

Meta-Analysis of Reversal Agents for Severe Bleeding Associated With Direct Oral Anticoagulants

Antonio Gómez-Outes, MD, PhD, MSc,[a] Pau Alcubilla, MD,[b] Gonzalo Calvo-Rojas, MD, PhD,[b,c] Ana Isabel Terleira-Fernández, MD, PhD,[d,e] Mª Luisa Suárez-Gea, PharmD, PhD,[a] Ramón Lecumberri, MD, PhD,[f,g] Emilio Vargas-Castrillón, MD, PhD[d,e]

Methods

McLeod Health

Study Design

- Meta-analysis of 60 studies
- 4,735 patients
  - 4F-PCC (n = 2,688)
  - Andexanet (n = 936)

Criteria

- Inclusion
  - Studies evaluating 4F-PCC, idarucizumab, or andexanet
  - Severe/uncontrolled bleeding associated with DOAC use
- Exclusion
  - Case-series with <10 patients
  - Not indicated to treat major bleeding

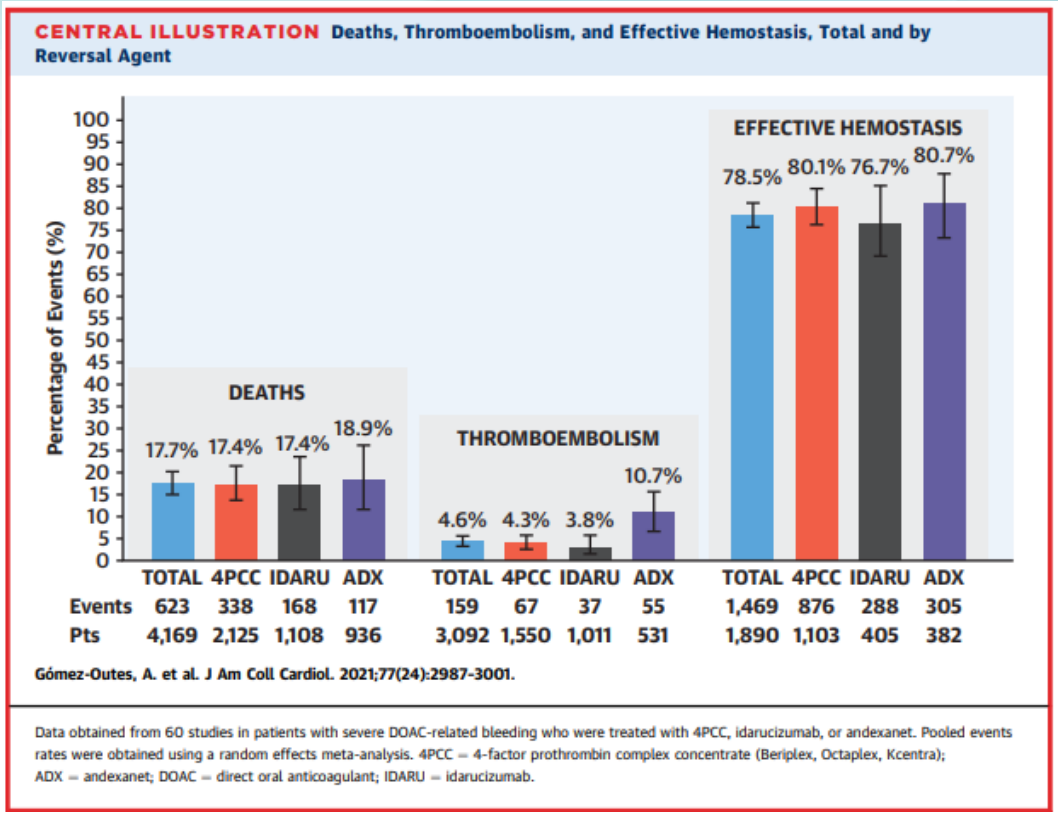
Outcomes

- All-cause mortality
- Effective hemostasis
- TEs

Source: Gomez, A, et al. J Am Coll Cardiol 2021;77:2987–3001

Results

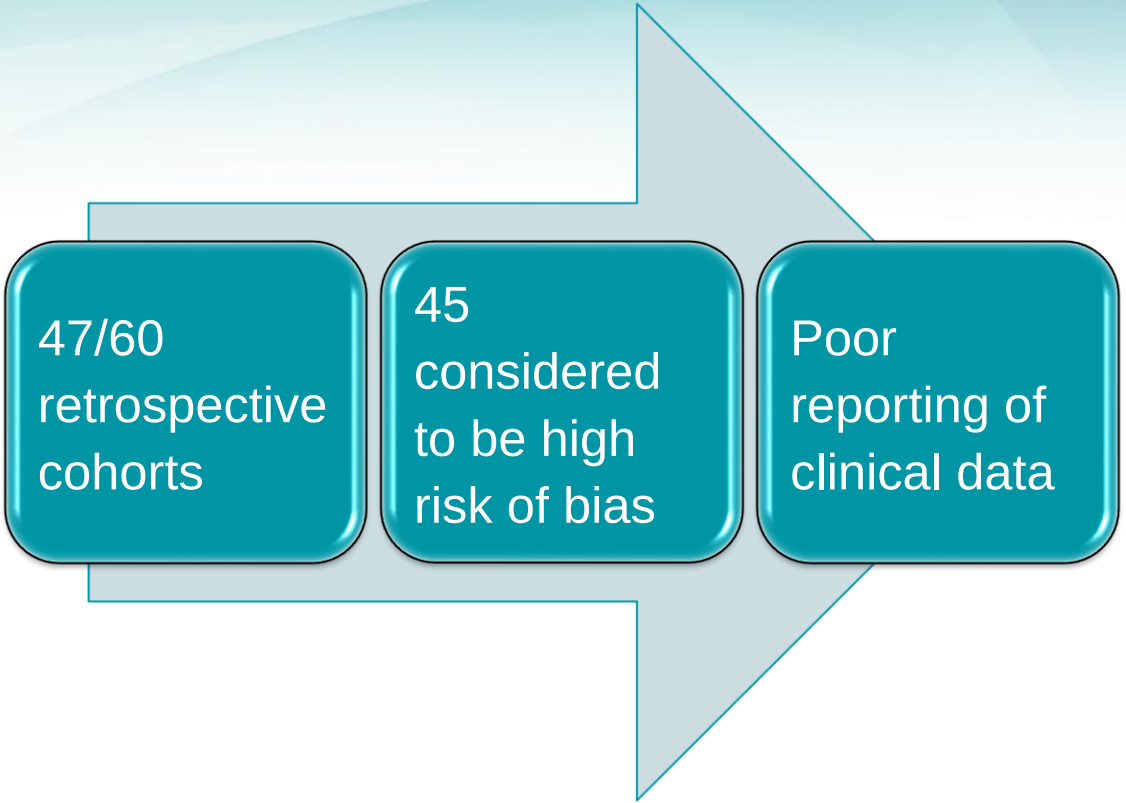
McLeod Health



Source: Gomez, A, et al. J Am Coll Cardiol 2021;77:2987–3001

Limitations

McLeod Health



Source: Gomez, A, et al. J Am Coll Cardiol 2021;77:2987–3001

Author's Conclusions

McLeod Health

A high rate of effective hemostasis, around 80%

TEs occurred with a high frequency with andexanet

It remains unknown whether specific reversal agents are more effective and/or safer than nonspecific reversal with 4PCC

Source: Gomez, A, et al. J Am Coll Cardiol 2021;77:2987–3001

McLeod Health

Chaudhary, R, et al. 2022.

Original Investigation | Neurology

Evaluation of Direct Oral Anticoagulant Reversal Agents in Intracranial Hemorrhage

A Systematic Review and Meta-analysis

Rahul Chaudhary, MD, MBA; Amteshwar Singh, MD, MEHP; Rohit Chaudhary, MS; Michael Bashline, MD; Damon E. Houghton, MD, MS; Alejandro Rabinstein, MD; Jill Adamski, MD, PhD; Richard Arndt, PharmD; Narith N. Ou, PharmD; Maria I. Rudis, PharmD; Caitlin S. Brown, PharmD; Erin D. Wieruszewski, PharmD; Matthew Wanek, Pharm D, MBA; Nathan J. Brinkman, PharmD; Jane A. Linderbaum, APRN, CNP; Melissa A. Sorenson, CNP; John L. Atkinson, MD; Kristine M. Thompson, MD; Aryan N. Aiyer, MD; Robert D. McBane II, MD

Methods

McLeod Health

Study Design

- Meta-analysis
- 39 studies
  - 22 4F-PCC
    - 967 patients
  - 17 Andexanet
    - 525 patients

Inclusion Criteria

- 18+
- ICH and receiving a DOAC
- Reversal of DOAC
- Reported safety and AC reversal outcomes

Outcomes

- AC reversal
- All-cause mortality
- TEs

Source: Chaudhary, R, et al. JAMA Network Open. 2022;5(11)

Results

McLeod Health

4F-PCC

- Successful AC reversal: 77%
- All-cause mortality: 26%
- TEs: 8%

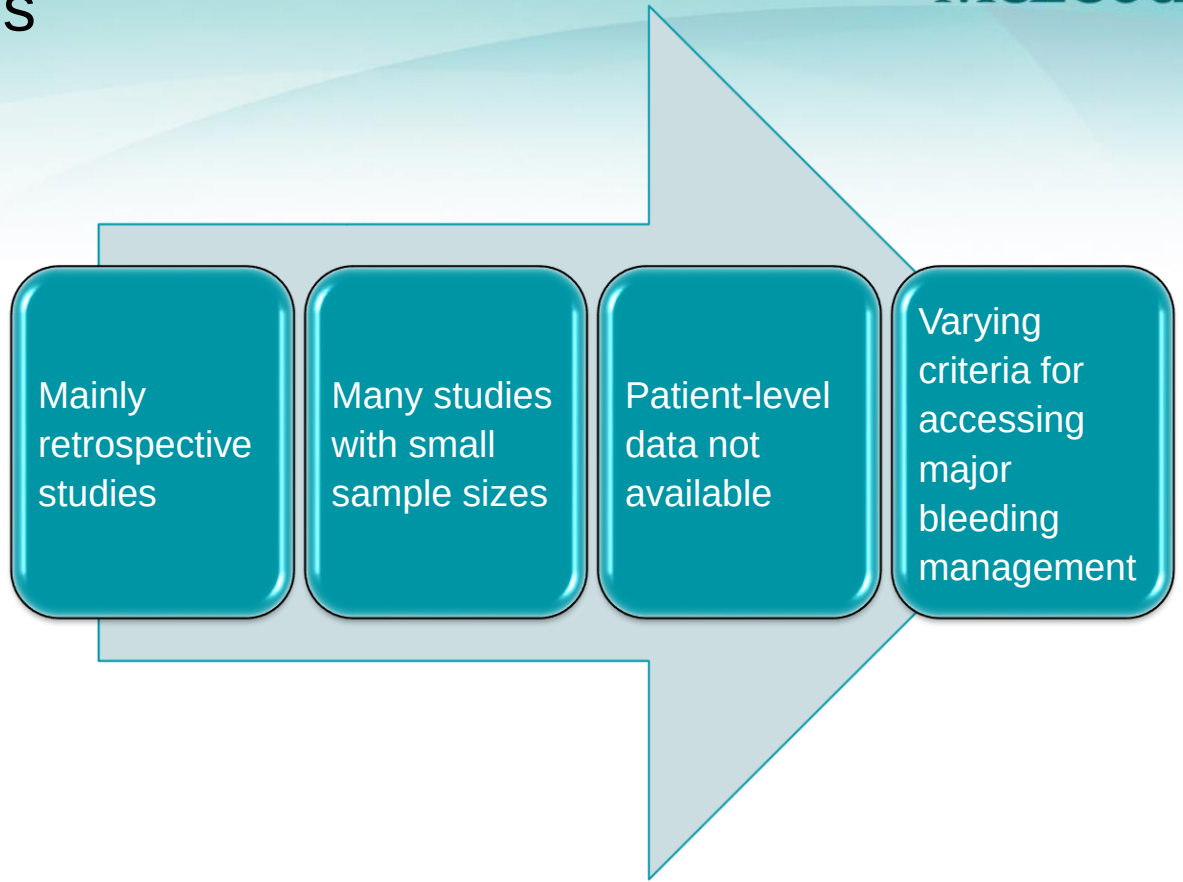
Andexanet

- Successful AC reversal: 75%
- All-cause mortality: 24%
- TEs: 14%

Source: Chaudhary, R, et al. JAMA Network Open. 2022;5(11)

Limitations

McLeod Health



Source: Chaudhary, R, et al. JAMA Network Open. 2022;5(11)

Author's Conclusions

McLeod Health

The decision to reverse DOAC-associated AC and choice of agent should be individualized

The proportion of AC reversed, mortality, and TE event rates appear similar between 4F-PCC and andexanet

Source: Chaudhary, R, et al. JAMA Network Open. 2022;5(11)

McLeod Health

Guideline recommendations?

2016 Neurocritical Care Guidelines

McLeod Health

Suggest administering a 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 or in the context of liver failure. (Conditional recommendation, low-quality evidence)

Source: Frontera, J, et al. Neurocrit Care. 2016.

American Society of Hematology 2018 Guidelines

McLeod Health

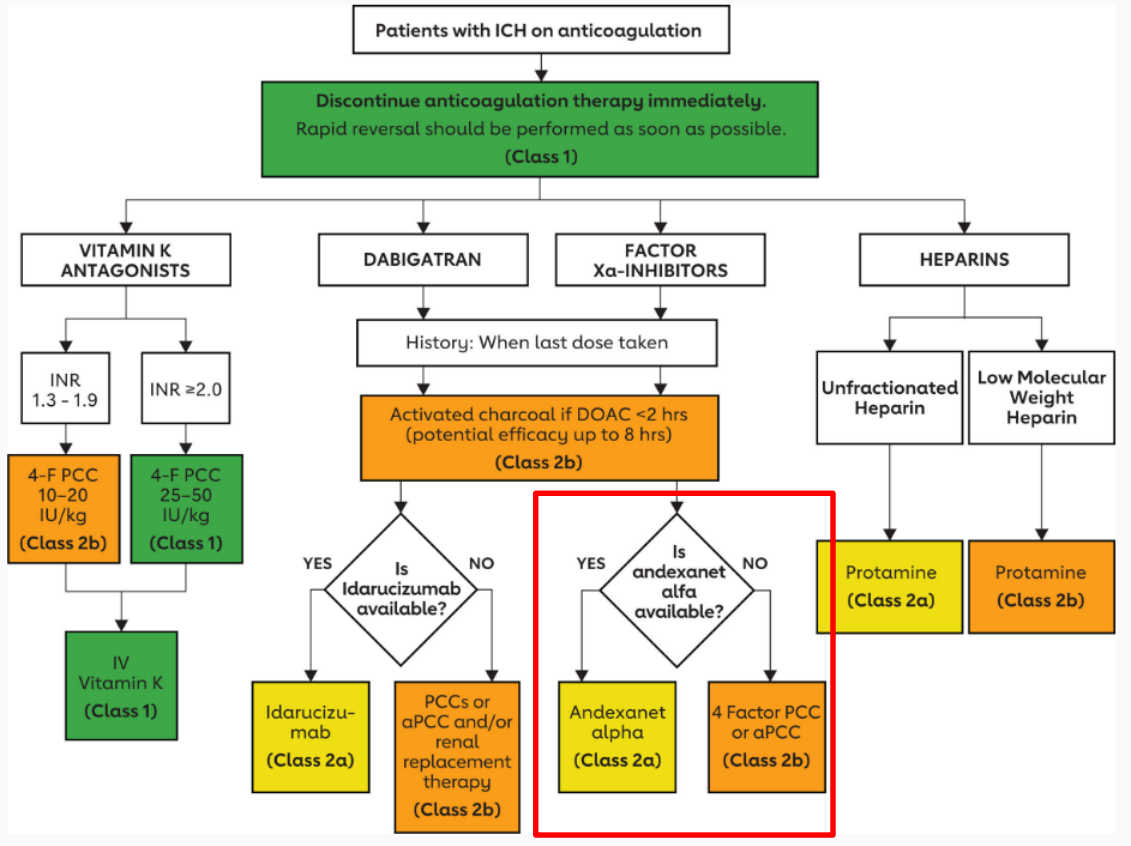
Suggest either 4-factor PCC in combo with temporary cessation of oral direct Xa inhibitor or cessation alone be used for patients with life-threatening bleeding during treatment of VTE

Conditional recommendation for administration of andexanet, primarily based on the evidence for direct Xa inhibitor reversal and biological plausibility of preventing worsening of bleeding

Source: Witt, D, et al. Blood Adv. ASH. 2018.

2022 American Heart Association Guidelines

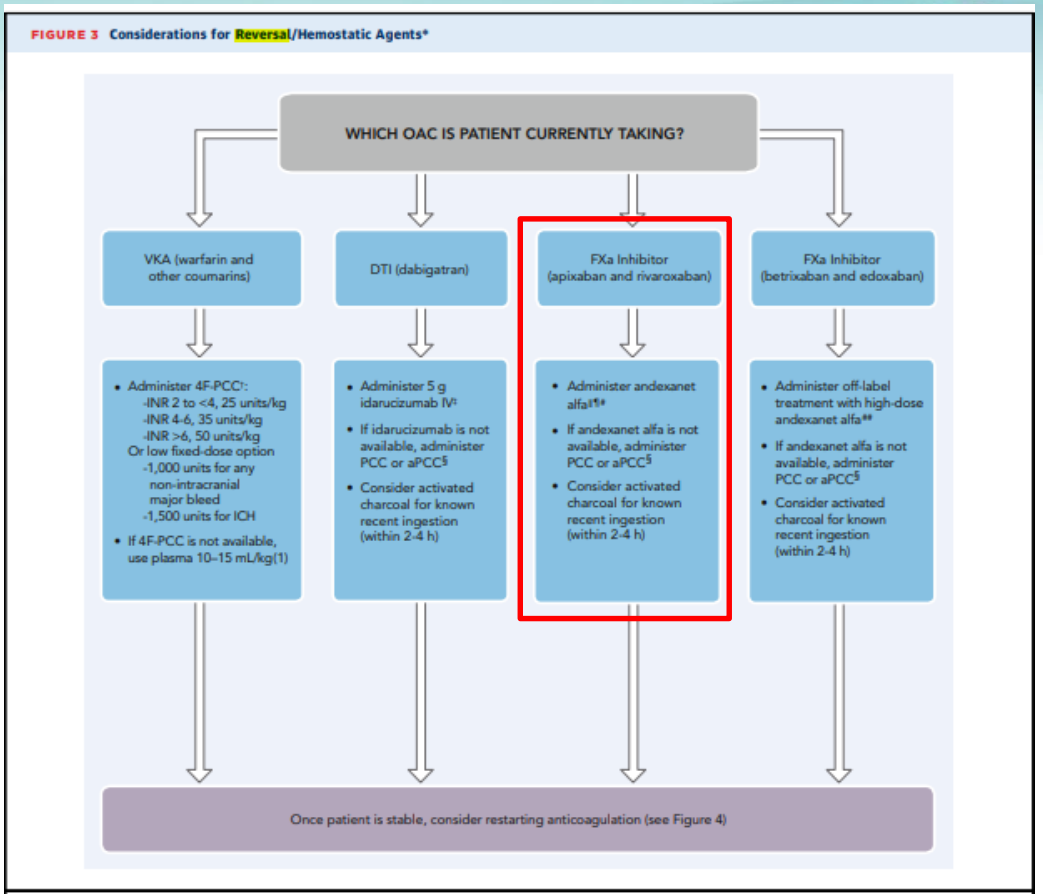
McLeod Health



Source: Greenberg, S, et al. AHA/ASA. Stroke. 2022.

2020 ACC Expert Consensus Decision Pathway

McLeod Health



Source: Tomaselli, G, et al. J Am Coll Cardiol. 2021.

Future Considerations - ANNEXA-I

McLeod Health

Methods

- Randomized, multicenter trial to determine the safety and efficacy of andexanet alfa vs usual care for the treatment of ICH

Primary Outcome

- A National Institutes of Health Stroke Scale change of +6 or less from baseline to 12 hours
- A hematoma volume increase of 35% or less at 12 hours compared with baseline on a repeat CT or MRI scan
- No rescue therapies given between 3 and 12 hours after randomization

Connolly, J, et al. N Engl J Med 2024;390:1745-1755

Future Considerations - ANNEXA-I

McLeod Health

Patient Population

- 530 patients with an average age of ~ 79 years

Results

- An excellent or good result was seen in 63.9% of patients in the andexanet alfa group versus 52.4% in the usual care group
- 10.3% of patients experienced at least 1 TE following treatment with andexanet alfa vs 5.6% in the usual care group
- There were no significant differences in deaths between groups

Connolly, J, et al. N Engl J Med 2024;390:1745-1755

McLeod Health

Which is the best option?

Key Takeaways/Considerations

McLeod Health

- Lack of head-to-head comparison
- In need of randomized control trials comparing 4F-PCC vs. andexanet
- Retrospective data with small sample sizes
- Varying trial protocols
- Inconclusive data

Key Takeaways/Considerations

McLeod Health

- Efficacy seems to be similar
- Potentially higher rates of TEs with andexanet
- Availability concerns
- 4F-PCC is a more cost-effective alternative

Conclusion

McLeod Health

- In the absence of prospective comparative trials, it cannot be determined which reversal agent is more effective and/or safer

- Randomized clinical trials directly comparing the effectiveness and safety of 4F-PCC with andexanet are needed to determine the optimal reversal strategies for patients with DOAC-related major bleeding

- Therapy selection should be based off availability, cost, and individual clinician discretion

Assessment Question #1

McLeod Health

Which of the following mechanisms of action are true? (Select all that apply)

a. Andexxa binds and sequesters the factor Xa inhibitors as well as increases tissue factor-initiated thrombin generation
b. 4F-PCC binds and sequesters the factor Xa inhibitors as well as increases tissue factor-initiated thrombin generation
c. 4F-PCC provides the coagulation factors (II, VII, IX, and X) as well as protein C and protein S
d. Andexxa provides the coagulation factors (II, VII, IX, and X) as well as protein C and protein S

Assessment Question #1

McLeod Health

Which of the following mechanisms of action are true? (Select all that apply)

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d. Andexxa provides the coagulation factors (II, VII, IX, and X) as well as protein C and protein S

Assessment Question #2

McLeod Health

There is currently insufficient evidence to recommend one reversal agent over the other for patients experiencing DOAC-related major bleeding?

a. True
b. False

Assessment Question #2

McLeod Health

There is currently insufficient evidence to recommend one reversal agent over the other for patients experiencing DOAC-related major bleeding?

a. True
b. False

Assessment Question #3

McLeod Health

Which may be a benefit in using 4F-PCC over Andexxa?

a. Decreased mortality
b. Increased rates of hemostasis
c. Decreased cost
d. Decreased adverse effects

Assessment Question #3

McLeod Health

Which may be a benefit in using 4F-PCC over Andexxa?

a. Decreased mortality
b. Increased rates of hemostasis
c. Decreased cost
d. Decreased adverse effects

References

McLeod Health

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Thank You!

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