Optimizing Outcomes for Patients With DOAC-Related Bleeding:

A Multidisciplinary Appraisal of Data-Driven Management Strategies Using Specific Reversal Agents

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  - **Deborah Siegal, MD, MSc, FRCPC** – has disclosed receipt of honoraria from BMS, Pfizer, Servier, AstraZeneca, and Roche, all of which were paid directly to her institution.
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- Planning Committee
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Learning Objectives

- Discuss the widespread clinical utility of DOACs, alongside the incidence and patient burden of DOAC-related bleeding, including life-threatening and uncontrolled bleeding events
- Recognize patient-specific factors that increase the risk of bleeding while taking DOACs
- Using an innovative whiteboard animation, describe and differentiate the mechanisms of action of andexanet alfa, idarucizumab, and ciraparantag in reversing DOAC-related bleeding
- Evaluate the established and evolving evidentiary base for specific DOAC-reversal agents, highlighting recent readouts, ongoing studies, and pending regulatory updates
- Apply the latest trial evidence, guideline statements, and expert consensus pathways to develop safe, effective DOAC-reversal treatment plans for individual patients across diverse clinical scenarios

Characterizing the Need for DOAC Reversal

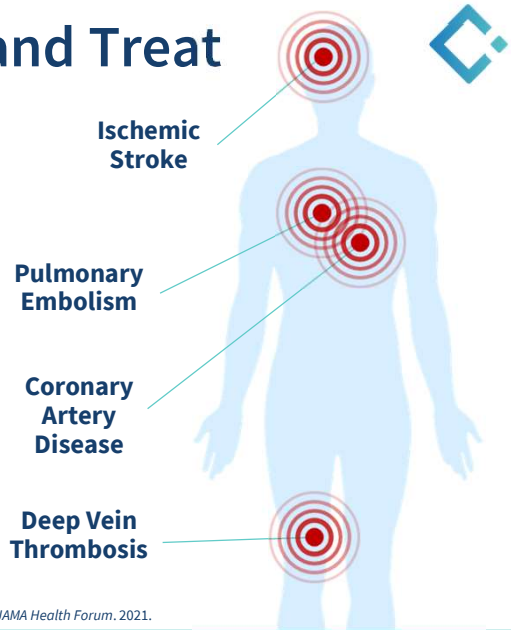
Risk Stratification, Clinical Gravity, and Ongoing Chasms in Care

Anticoagulants Prevent and Treat Cardiovascular Disease

Cardiovascular disease (CVD) is the **leading cause of death and disability** worldwide

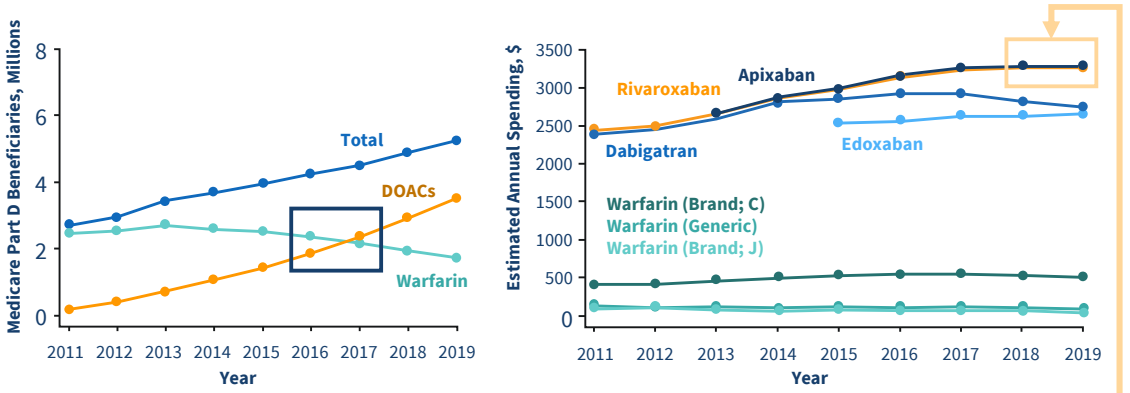
CVD is responsible for an estimated **~18 million deaths annually**

~40 million prescriptions for oral anticoagulants (OACs) annually in North America



WHO CVD Fact Sheet. 2021; WHO CVD Risk Chart Writing Group. *Lancet Glob Health*. 2019; Troy A, et al. *JAMA Health Forum*. 2021.

The Rise of the Direct-Acting Oral Anticoagulants (DOACs)



Recent and ongoing **increases in DOAC clinical utilization** driven principally by **rivaroxaban** and **apixaban** usage.

Troy A, et al. *JAMA Health Forum*. 2021.

Bleeding Complications Limit DOAC Use (*even in 2024*)

Bleeding Rates

Major Bleeding
2% to 4% per year

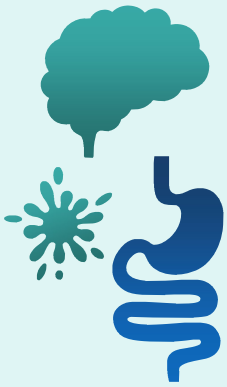
Clinically Relevant Non-Major Bleeding
10% to 12% per year

DOACs* vs. VKA

50% Intracranial

14-40% Major Bleeding

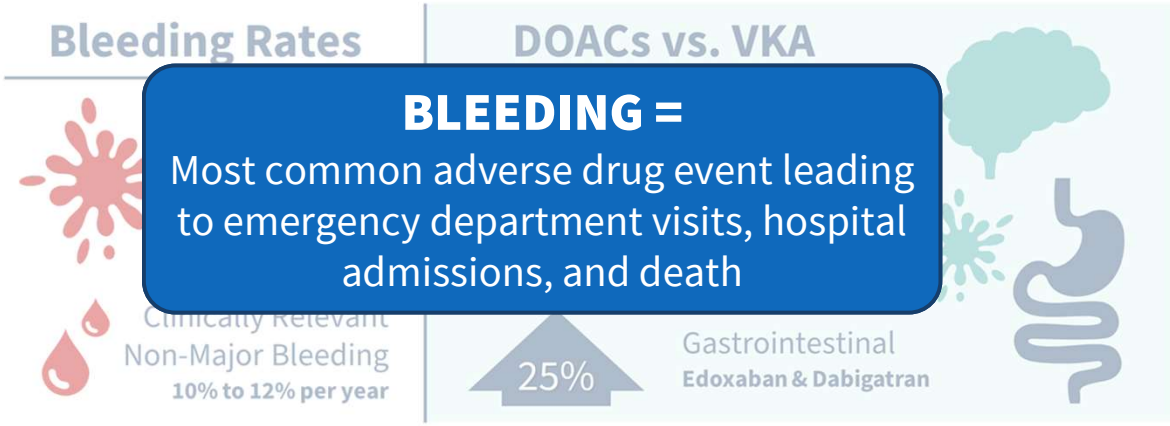
25% Gastrointestinal



*With notable variations by specific DOAC agent

Ruff CT, et al. *Lancet*. 2014; Kirchhof P, et al. *Eur Heart J*. 2016; van Es N, et al. *Blood*. 2014; van Es N, et al. *Eur Heart J*. 2023.

Bleeding Complications Limit DOAC Use (*even in 2024*)



Ruff CT, et al. *Lancet*. 2014; Kirchhof P, et al. *Eur Heart J*. 2016; Van Es N, et al. *Blood*. 2014; Van Es N, et al. *Eur Heart J*. 2023.

DOAC-Related Bleeding Increases the Risk of Death

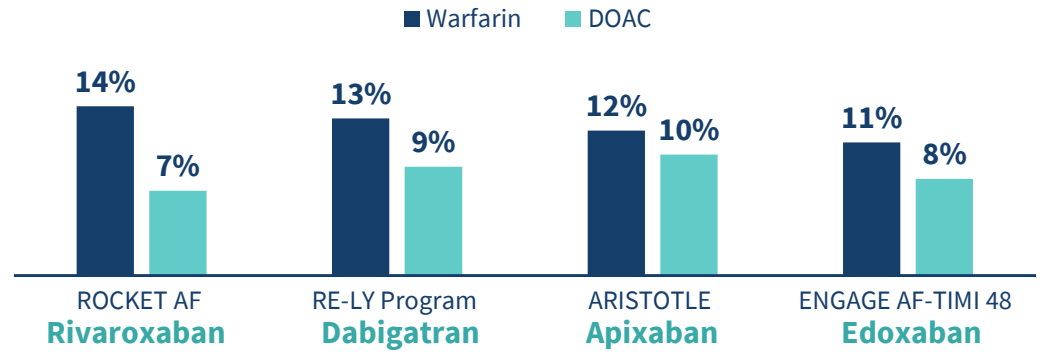
Oral Anticoagulant Therapy (RE-LY and ACTIVE-Warfarin Trials)

	Events/Deaths	HR (95% CI)	Weight
Ischemic Stroke	516/170	8.33 (7.09-9.79)	1.00
Systemic Embolism	65/17	5.10 (3.16-8.24)	0.61
Hemorrhagic Stroke	105/70	**26.92 (21.08-34.39)**	3.23
Subdural Bleeding	90/27	**6.89 (4.70-10.09)**	0.83
Extracranial Bleeding	1164/291	**5.23 (4.60-5.95)**	0.63
Myocardial Infarction	301/107	7.40 (6.06-9.04)	0.89

Eikelboom J, et al. *J Am Coll Cardiol*. 2013.

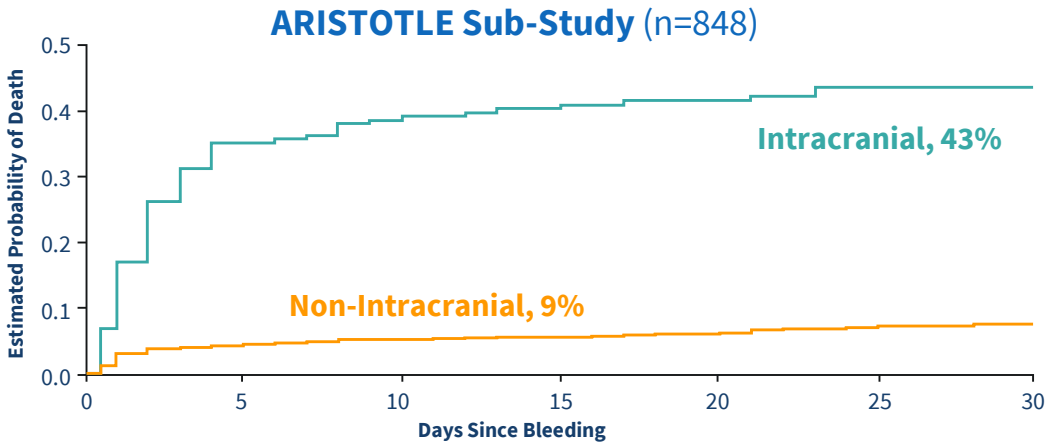
High Mortality After DOAC-Related Major Bleeding

Phase III Clinical Trials in Atrial Fibrillation – **Fatality Rates for Major Bleeding Events**



Patel et al. *NEJM*. 2011; Majeed et al. *Circulation*. 2013; Granger et al. *N Engl J Med*. 2011; Giugliano et al. *N Engl J Med*. 2013; Connolly et al. *N Engl J Med*. 2019.

High Mortality After DOAC-Related Major Bleeding



Held et al. *Eur Heart J*. 2015.

Other Consequences of DOAC-Related Bleeding

- Impaired quality of life
- Functional impairment
- DOACs withheld due to concerns about bleeding risk
- DOACs permanently discontinued after bleeding
- Off-label use of low doses of DOACs with limited data

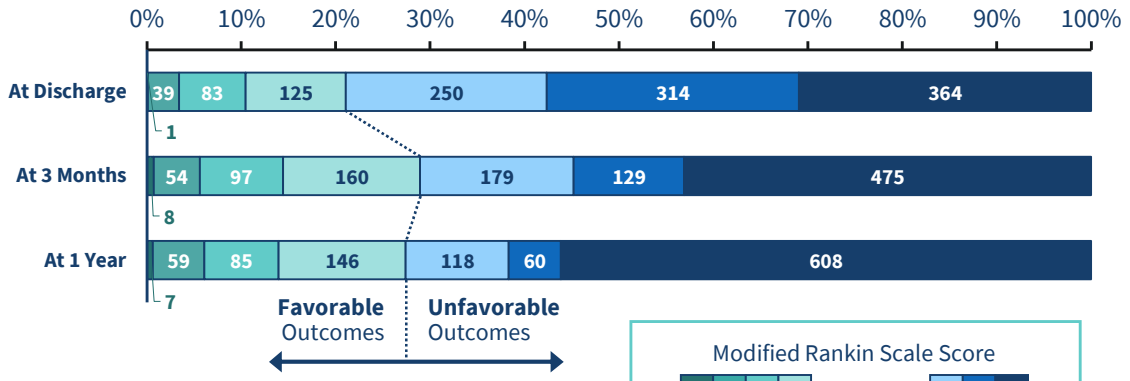
Over the next **50 Years**

Patients eligible for DOACs **↑ 2.5x**

Bleeding is a growing **Health Problem!**

Little D, Siegal DM, et al. *Thromb Res*. 2019; Arbel et al. *Am J Med*. 2019; Steinberg et al. *J Am Coll Cardiol*. 2016; Camm et al. *Heart*. 2017; Wang et al. *J Am Heart Assoc*. 2017.

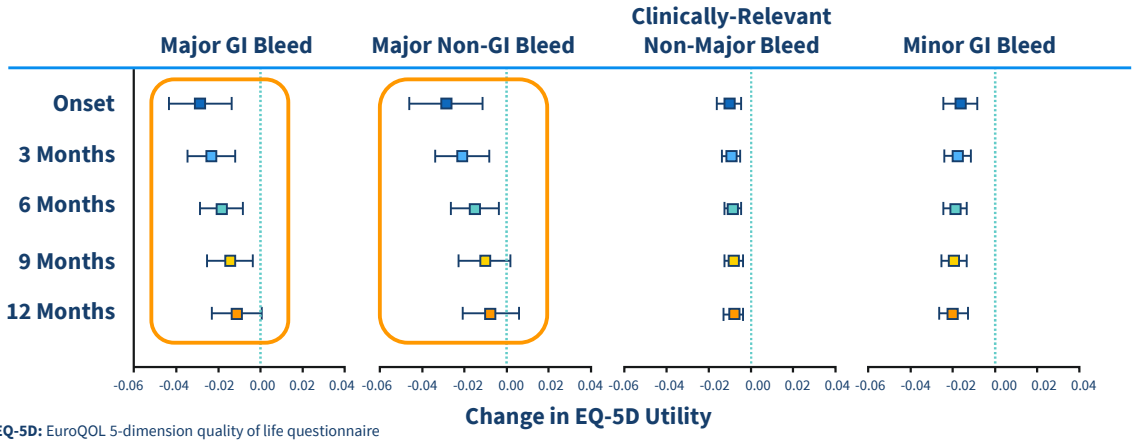
Unfavorable Functional Outcomes After VKA-Related ICH



ICH: intracranial hemorrhage
VKA: vitamin K antagonist

Kuramatsu et al. *JAMA*. 2015.

Quality-of-Life is Impaired After Edoxaban-Related Major Bleeding Events



EQ-5D: EuroQOL 5-dimension quality of life questionnaire

Wang et al. *J Am Heart Assoc*. 2017.

In other words,

this is why we need an antidote!

Why Reverse Factor Xa Inhibitors for Bleeding?

Rapidly Remove Anticoagulant Effect to Restore Hemostasis

Reduce the Severity and Duration of Bleeding

Facilitate Definitive Interventions
(e.g. surgery, GI endoscopy)

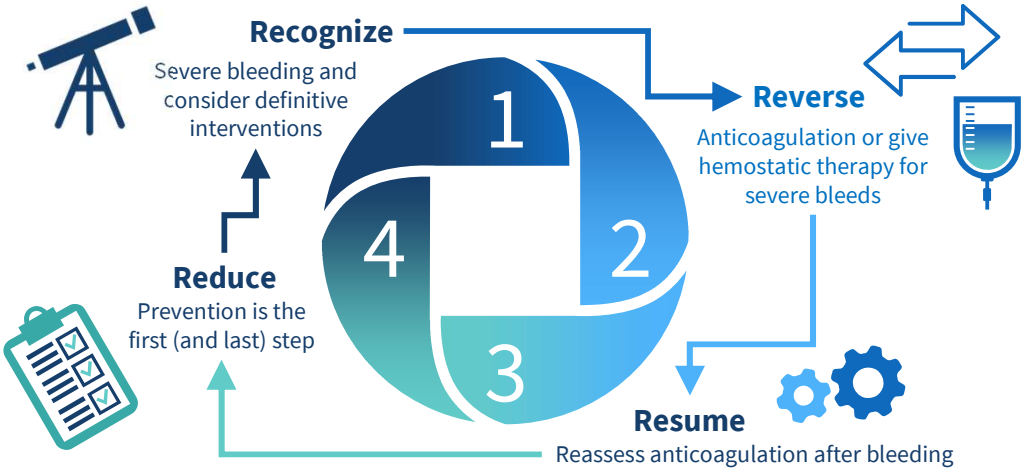
Reduce Complications of Bleeding
(e.g. transfusion, anemia)

Improve Outcomes
(e.g. clinical and health resources)

van Es et al. *Eur Heart J*. 2023; Ruff et al. *Circulation*. 2016; Pollack et al. *N Engl J Med*. 2017; Siegal et al. *N Engl J Med*. 2015; Connolly et al. *N Engl J Med*. 2019; Milling et al. *Circulation*. 2023.

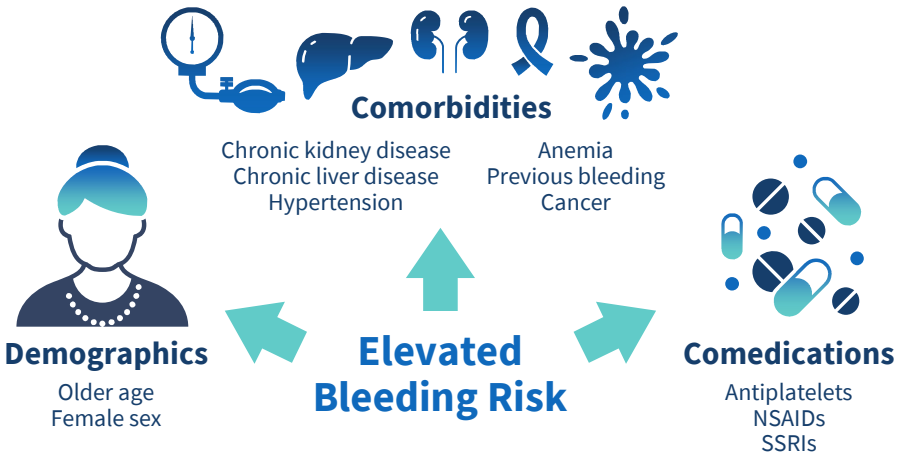
Endoscopy in a patient with active GI bleeding

Bleed Management Framework



van Es et al. *Eur Heart J*. 2023; Cuker et al. *Am J Hematol*. 2019; Tomaselli et al. *J Am Coll Cardiol*. 2020; Baugh et al. *Ann Emerg Med*. 2020.

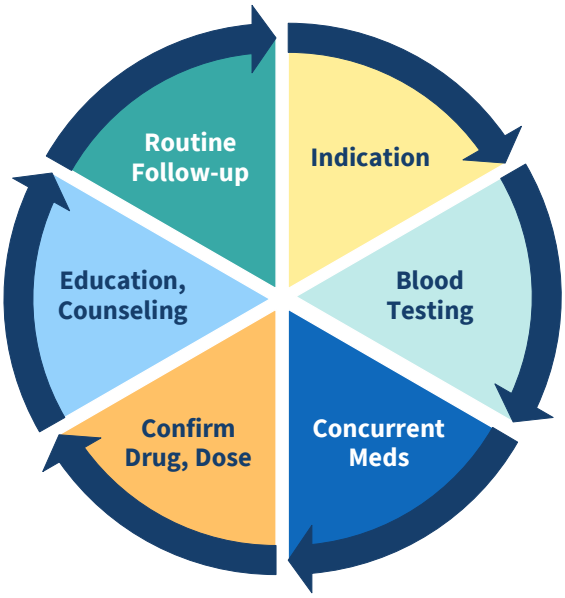
Patient-Specific Risk Factors for Bleeding



van Es et al. *Eur Heart J*. 2023; van Rein et al. *Circulation*. 2019; den Exter et al. *J Thromb Haemost*. 2022; Chang et al. *JAMA*. 2017.

Longitudinal Bleeding Prevention

Evaluate and Address *Modifiable* Bleeding Risk Factors



van Es et al. *Eur Heart J*. 2023; Cuker et al. *Am J Hematol*. 2019; Tomaselli et al. *J Am Coll Cardiol*. 2020; Baugh et al. *Ann Emerg Med*. 2020.

Current and Evolving Approaches to *DOAC-Specific* Reversal

Reverse

Anticoagulation or give hemostatic therapy for severe bleeds

- **Idarucizumab**
- **Andexanet Alfa**
- **Ciraparantag**

van Es et al. *Eur Heart J*. 2023; Ruff et al. *Circulation*. 2016; Pollack et al. *N Engl J Med*. 2017; Siegal et al. *N Engl J Med*. 2015; Connolly et al.. *N Engl J Med* 2019; Milling et al. *Circulation*. 2023; Ansell et al. *Blood*. 2021; Ansell et al. *Eur Heart J*. 2022; ClinicalTrials.gov; FDA Prescribing Information.

Leveraging Novel Pharmacology to Advance the Calculus

An Animated Whiteboard Mechanistic Review of Specific Reversal Agents

Animated Whiteboard Video

van Es et al. *Eur Heart J*. 2023; Troy et al. *JAMA Health Forum*. 2021; Ruff et al. *Lancet*. 2014; van Es et al. *Blood*. 2014; van Rein et al. *Circulation*. 2019; Fralick et al. *Ann Intern Med*. 2020; Selak et al. *JAMA.* 2018; Chai-Adisaksopha et al. *J Thromb Haemost*. 2015; Gomez-Outes et al. *J Am Coll Cardiol*. 2021; Tomaselli et al. *J Am Coll Cardiol*. 2020; Eerenberg et al. *Circulation*. 2011; Schiele et al. *Blood*. 2013; Sarich et al. *Am Heart J.* 2015; Ruff et al. *Circulation*. 2016; Pollack et al. *N Engl J Med*. 2017; Fanikos et al. *Thromb Haemost.* 2020; Siegal et al. *N Engl J Med*. 2015; Heo et al. *Drugs.* 2018; Connolly et al.. *N Engl J Med* 2019; Milling et al. *Circulation.* 2023; Ansell et al. *J Thromb Thrombolysis.* 2016; Ansell et al. *Blood*. 2021; Ansell et al. *Eur Heart J*. 2022; ClinicalTrials.gov; FDA Prescribing Information.

New Horizons in DOAC Reversal

The Evolving Evidentiary Base and Regulatory Landscape

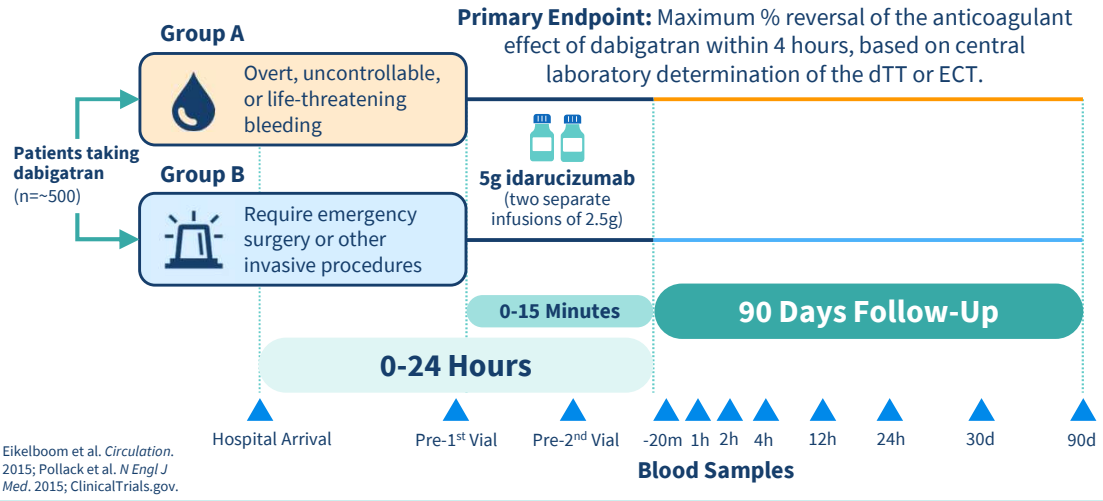
Three Specific DOAC "Reversal" Agents

	Idarucizumab	Andexanet Alfa	Ciraparantag
Non-Randomized Trials	RE-VERSE AD	ANNEXA-4	Ansell et al 2016
RCTs		ANNEXA-A & -R, ANNEXA-I	Ansell et al 2022

Ruff et al. *Circulation*. 2016; Pollack et al. *N Engl J Med*. 2017; Siegal et al. *N Engl J Med*. 2015; Connolly et al. *N Engl J Med*. 2019; Milling et al. *Circulation*. 2023; ClinicalTrials.gov; Connolly S. *World Stroke Congress*. Plenary Presentation. October 10-12, 2023; Ansell et al. *J Thromb Thrombolysis*. 2016; Ansell et al. *Eur Heart J*. 2022.

Idarucizumab

RE-VERSE AD: Study Design



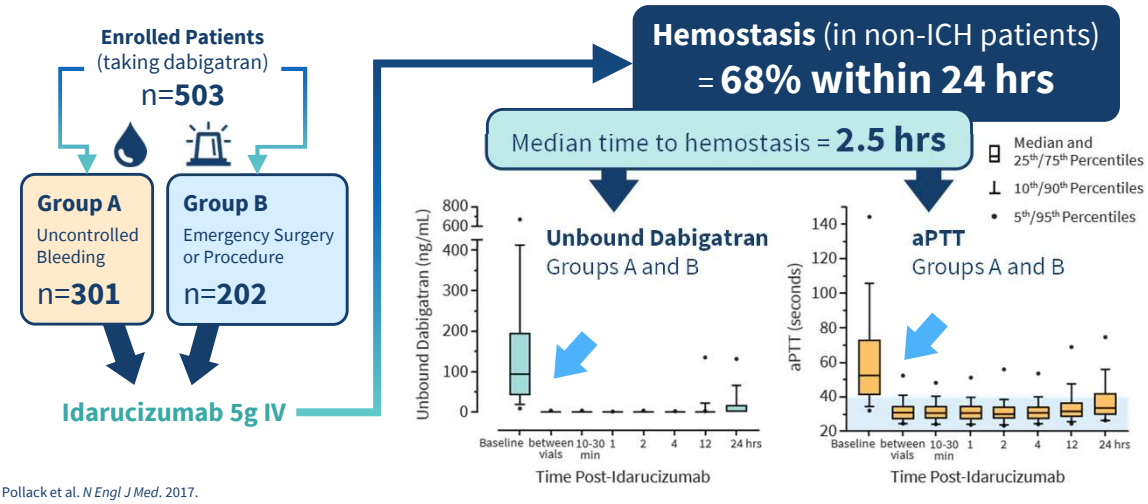
Eikelboom et al. *Circulation*. 2015; Pollack et al. *N Engl J Med*. 2015; ClinicalTrials.gov.

RE-VERSE AD: Baseline Characteristics

	Group A (Bleeding) N=301	Group B (Surgery) N=202	Total N=503
Age (y), median (range)	79 (24-96)	77 (21-96)	78 (21-96)
Male Sex	57%	51%	55%
Weight (kg), median (range)	74 (35-231)	77 (39-169)	75 (35-231)
CrCl (ml/min), median (range)	51 (6-217)	56 (8-199)	53 (6-217)
Time From Last Dose to Infusion (median)	14.6 hrs	18.0 hrs	15.6 hrs
Bleeding Source			
Gastrointestinal	46%		
Intracranial hemorrhage	33%		

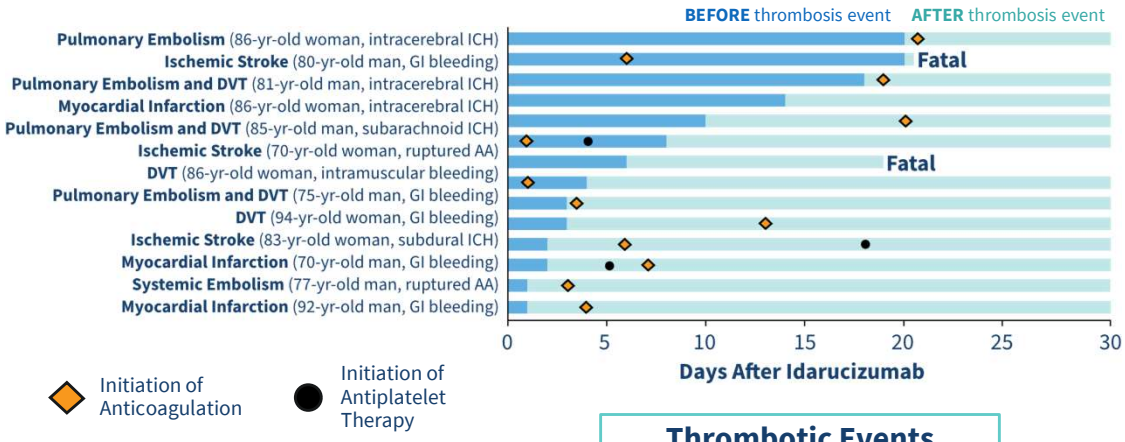
Pollack et al. *N Engl J Med*. 2017.

RE-VERSE AD Study: Key Outcomes



Pollack et al. *N Engl J Med*. 2017.

RE-VERSE AD: Thrombotic Risk Post-Idarucizumab?



Thrombotic Events
30-day: **4.8%** 90-day: **6.8%**

Pollack et al. *N Engl J Med*. 2017.

FDA U.S. FOOD & DRUG ADMINISTRATION

October 16, 2015

- Idarucizumab granted FDA **accelerated approval** for "***patients treated with dabigatran when reversal of the anticoagulant effects of dabigatran is needed, including emergent surgery/urgent procedures and life-threatening or uncontrolled bleeding***"

April 17, 2018

- Idarucizumab accelerated approval **converted to full approval** by the FDA

FDA Prescribing Information.

Andexanet Alfa

ANNEXA-A and ANNEXA-R: Study Design

- **Design:** Two-part, randomized trials evaluating andexanet alfa as a bolus dose or bolus + 2-hour infusion
  - **ANNEXA–A**: patients taking 5 mg **apixaban** BID
  - **ANNEXA–R**: patients taking 20 mg **rivaroxaban** QD
- **Patient Population:** healthy older volunteers, not bleeding
- **Primary endpoint:** mean % change in anti-factor Xa activity, stratified by specific DOAC

Siegal et al. *N Engl J Med*. 2015.

ANNEXA-A and ANNEXA-R: Key Outcomes

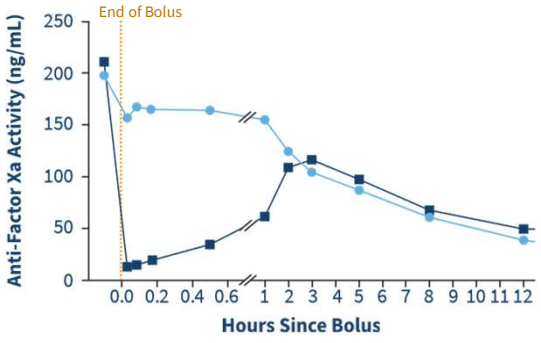
	ANNEXA-A (Apixaban)	ANNEXA-R (Rivaroxaban)
Reduction in Anti-Factor Xa Activity	94%	92%
Thrombin Generation Restored (within 2-5 minutes)	100%	96%
Serious Adverse Events?	No	No
Thrombotic Events?	No	No
Efficacy sustained when given as bolus + infusion	Yes	Yes

Siegal et al. *N Engl J Med*. 2015.

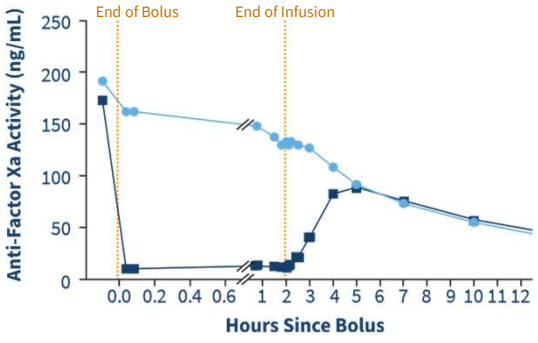
ANNEXA-A: Key Outcomes

Placebo
Andexanet

Bolus Only



Bolus + Infusion

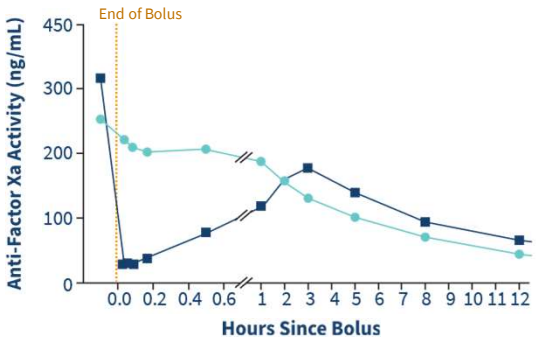


Siegal et al. *N Engl J Med*. 2015.

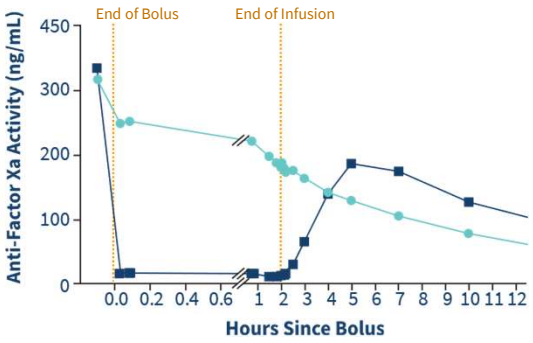
ANNEXA-R: Key Outcomes

Placebo
Andexanet

Bolus Only



Bolus + Infusion



Siegal et al. *N Engl J Med*. 2015.

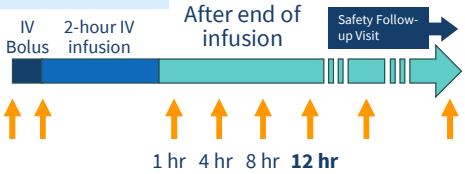
ANNEXA-4: Study Design

Patient Screening

Patient with acute major bleeding → Within 18 hours of last dose of FXa inhibitor

Bleeding and Laboratory Assessment

Andexanet



Assessments: Day 1 | Day 3 | Day 30

Acute major bleeding: defined as one or more of the following:
- Potentially life-threatening
- Signs/symptoms of hemodynamic compromise
- Decrement in Hb ≥2 g/dL
- Symptomatic bleeding in a critical area or organ
- Note – in efficacy population, 53% had GI bleeding and 43% had intracranial

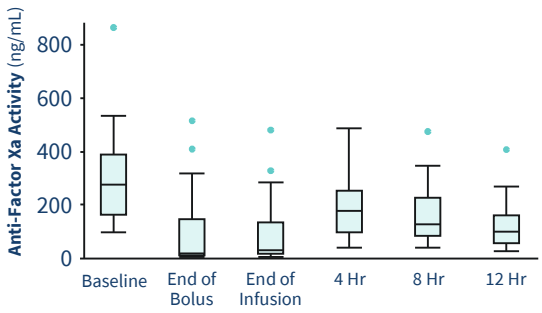
Efficacy Outcomes:
- Change in anti-FXa activity
- Clinical hemostatic efficacy through 12 hours

Safety Measures:
- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day mortality

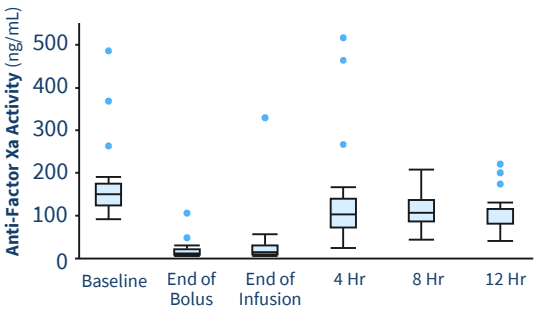
Connolly et al. *N Engl J Med*. 2016.

ANNEXA-4: Preliminary Analysis

Rivaroxaban Median Anti-Factor Xa ↓ **89%**



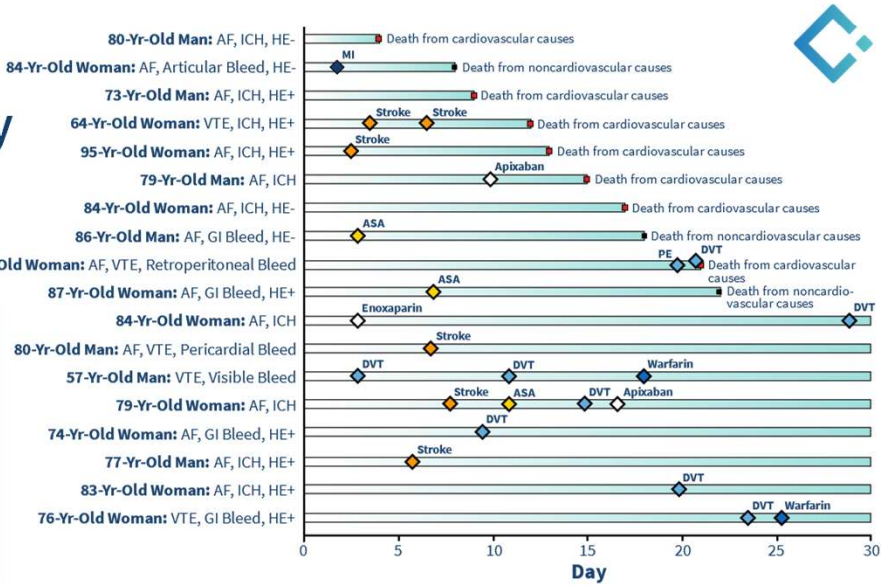
Apixaban Median Anti-Factor Xa ↓ **93%**



12-hour Efficacy Analysis (n=47): **79%** with Excellent or Good Hemostasis

Connolly et al. *N Engl J Med*. 2016.

ANNEXA-4: Preliminary Analysis



18% with thrombotic events (safety analysis n=67) during 30-day follow-up

Only 1 patient with anticoagulation resumed *BEFORE* thrombosis occurred

Connolly et al. *N Engl J Med*. 2016.

ANNEXA-4: Interim Analysis

Efficacy (n=254):

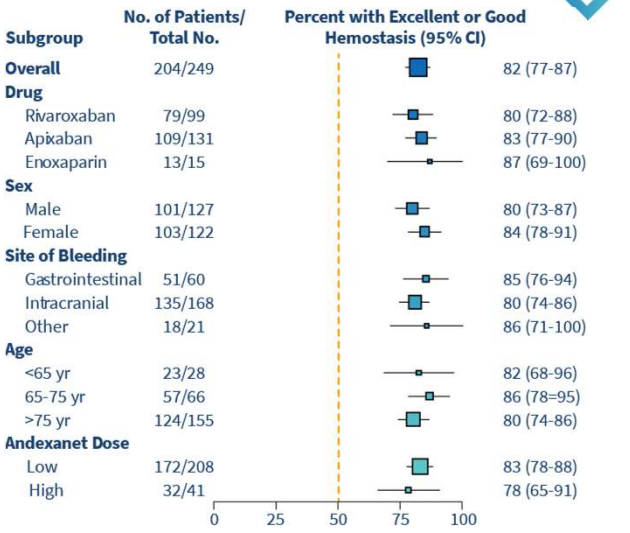
- Excellent or good hemostasis at 12-hours = 82%

Safety (n=352):

- 30-day mortality rate = 14%
- 30-day thrombotic event rate = 10%

Rivaroxaban Median Anti-Factor Xa ↓ 92%

Apixaban Median Anti-Factor Xa ↓ 92%



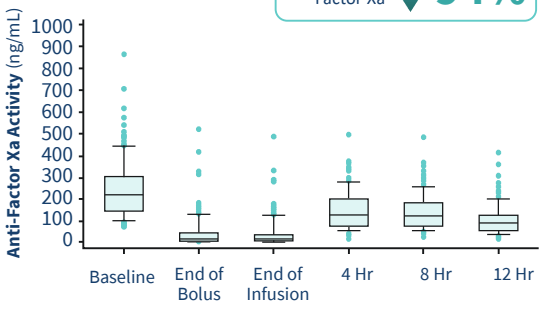
Connolly et al. *N Engl J Med*. 2019.

ANNEXA-4: Final Analysis

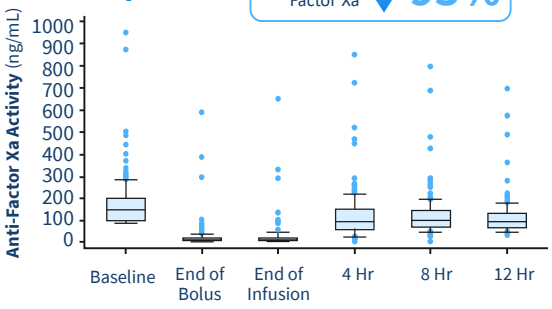
Efficacy (n=349)
- Excellent or good hemostasis = 80%

Safety (n=479)
- 30-day mortality rate = 15.7%
- 30-day thrombotic event rate = 10.4%

Rivaroxaban Median Anti-Factor Xa ↓ 94%



Apixaban Median Anti-Factor Xa ↓ 93%



Milling et al. *Circulation*. 2023.

ANNEXA-4: Key Takeaways

- Robust efficacy, particularly for patients taking apixaban or rivaroxaban
- Anti-factor Xa activity reduction:
  - Predicted hemostatic efficacy in ICH
  - Associated with improved mortality in patients <75 years old
- Restoration of normal thrombin potential was achieved within 24h of andexanet alfa bolus for *all patients taking a factor Xa inhibitor*

Milling et al. *Circulation*. 2023.

FDA U.S. FOOD & DRUG ADMINISTRATION

May 3, 2018

- Andexanet alfa granted FDA accelerated approval for ***"patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding."***

Forthcoming

- Conversion to full FDA approval will be **predicated on recently-reported results from the post-marketing phase IV trial, ANNEXA-I.**

FDA Prescribing Information; FDA Approval Letter. May 3, 2018; ClinicalTrials.gov.

ANNEXA-I: Study Design

Phase 4, Multicenter, Prospective, Randomized, Open-Label, Blinded-Endpoint Trial

Primary Efficacy Population (N=452)
Extended Population (N=530)

Patients ≥18 years old with acute ICH within **6 hours of symptom onset** and **within 15 hours following the last dose** of apixaban, rivaroxaban, or edoxaban.

R
1:1

- **Andexanet Alfa**
- **Usual Care**

Primary Efficacy Endpoint:
Effective Hemostasis at 12 Hours
Defined as ***meeting all 3*** of the following criteria:

1. <35% hematoma volume expansion at 12 hours
2. NIHSS score increase of <7 at 12 hours
3. No rescue therapy administered between 3 and 12 hours after randomization

Secondary Efficacy Endpoint
Percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomization

Select Safety Endpoints
- Thrombotic events at 30 days
- 30-day mortality

ClinicalTrials.gov; Connolly S. *World Stroke Congress*. Plenary Presentation. October 10-12, 2023.

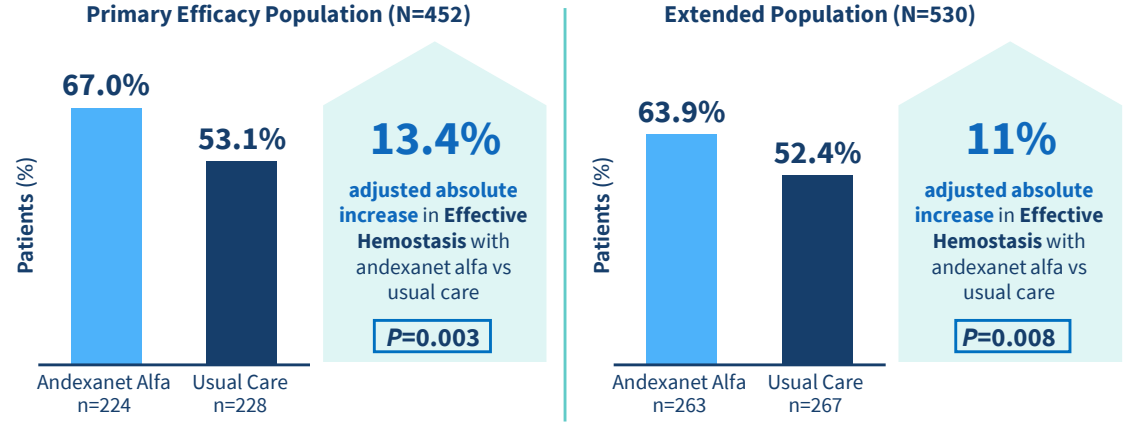
ANNEXA-I: Baseline Characteristics

	Andexanet Alfa N=263	Usual Care N=267
Age, mean (SD)	79.4 (8.5)	78.7 (8.6)
Female Sex	44.5%	47.9%
A-Fib	90.5%	84.3%
Door to Needle Time (h), median (IQR)	2.1 (1.6-2.8)	2.3 (1.7-3.1)
	75.7% received low-dose andexanet alfa	87% received PCC as a component of usual care

Connolly S. *World Stroke Congress*. Plenary Presentation. October 10-12, 2023.

ANNEXA-I – Key Efficacy Outcomes

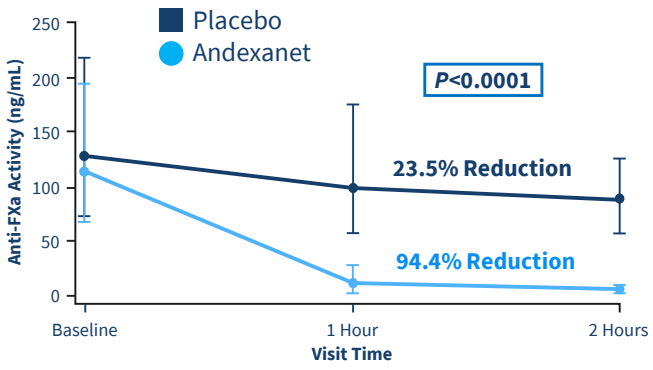
Primary Endpoint: Effective Hemostasis at 12 Hours

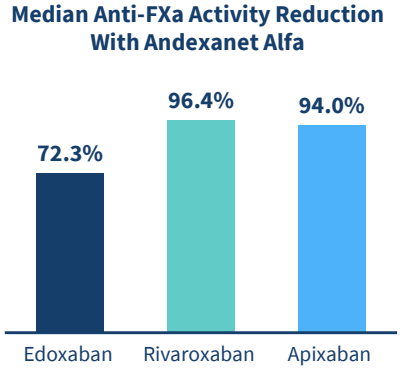


Connolly S. *World Stroke Congress.* Plenary Presentation. October 10-12, 2023.

ANNEXA-I – Key Efficacy Outcomes

Secondary Endpoint: Change in Anti-FXa Activity From Baseline to Nadir at 2 Hours



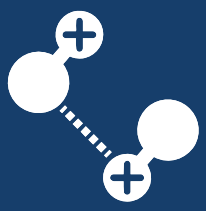


Connolly S. *World Stroke Congress.* Plenary Presentation. October 10-12, 2023.

ANNEXA-I – Key Safety Outcomes

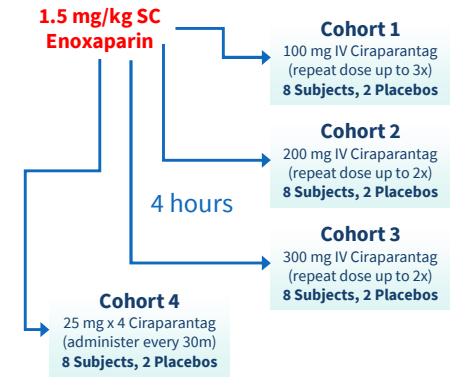
Extended Population (N=530)	**Andexanet Alfa** (n=263)	**Usual Care** (n=267)	Adjusted Absolute Difference with Andexanet Alfa (95% CI)
Patients with ≥1 Thrombotic Event, n (%)	**27 (10.3)**	**15 (5.6)**	**4.6 (0.1, 9.2)**
Transient ischemic attack, n (%)	0 (0)	0 (0)	-
Ischemic stroke, n (%)	17 (6.5)	4 (1.5)	5.0 (1.5, 8.8)
Myocardial infarction, n (%)	11 (4.2)	4 (1.5)	2.7 (-0.2, 6.1)
Deep vein thrombosis, n (%)	1 (0.4)	2 (0.7)	-0.4 (-2.4, 1.5)
Pulmonary embolism, n (%)	1 (0.4)	6 (2.2)	-1.9 (-4.5, 0.2)
Arterial systemic embolism, n (%)	3 (1.1)	2 (0.7)	0.4 (-1.7, 2.7)
All-Cause Mortality, n (%)	**73 (27.8)**	**68 (25.5)**	**2.3 (-5.2, 9.8)**

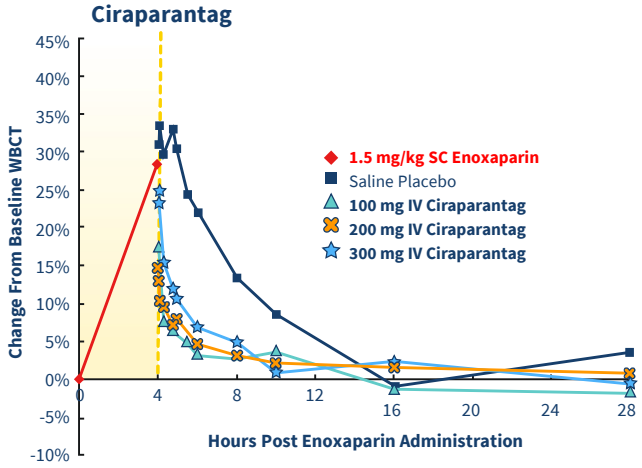
Connolly S. *World Stroke Congress.* Plenary Presentation. October 10-12, 2023.



Ciraparantag

Ciraparantag and LMWH Reversal: Study Design and Key Outcomes

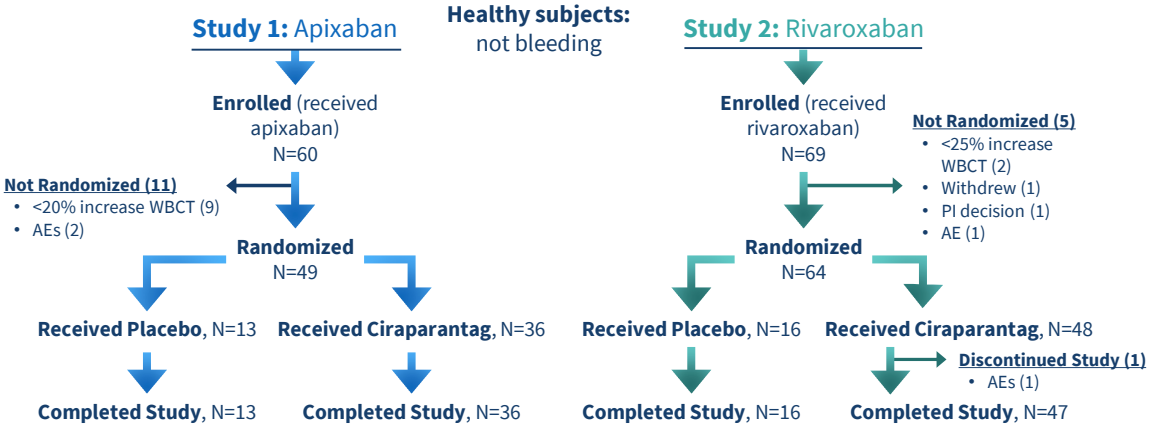




LMWH: low-molecular-weight heparin
WBCT: whole blood clotting time
40 subjects: healthy volunteers, not bleeding

Ansell et al. *Thromb Res.* 2016.

Ciraparantag for DOAC "Reversal": Study Design

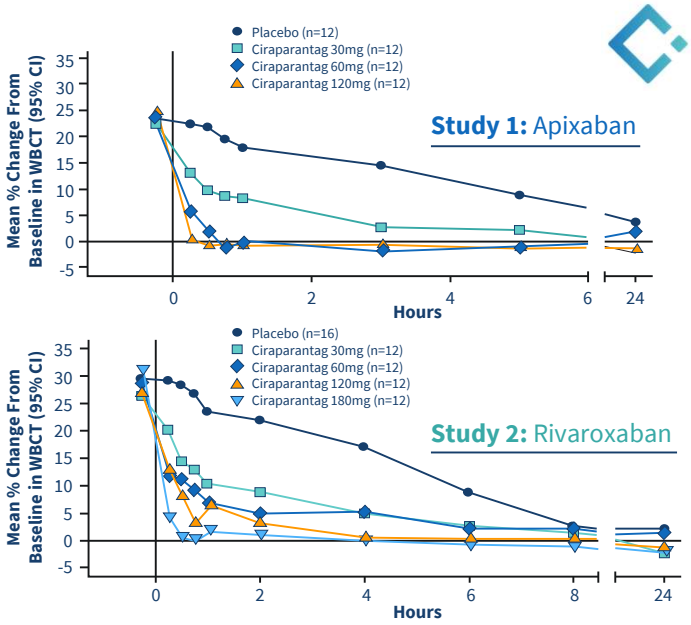


Ansell et al. *Eur Heart J.* 2022.

Ciraparantag for DOAC "Reversal": Key Outcomes

Key Takeaways:

- 60 mg and 120 mg doses of ciraparantag both achieved rapid and sustained reversal of apixaban
- 180 mg dose of ciraparantag achieved rapid and sustained reversal of rivaroxaban
- Ciraparantag was well-tolerated, with the most common event being vascular flushing; no prothrombotic signals or trends were observed



Ansell et al. *Eur Heart J*. 2022.

DOAC-Specific Reversal Agents: Summary of Current Regulatory Landscape

	Idarucizumab	Andexanet Alfa	Ciraparantag
Dabigatran – Life-Threatening Bleeding	☑		
Dabigatran – Emergent Surgery	☑		
Apixaban/Rivaroxaban – Life-Threatening/ Uncontrolled Bleeding		☑	
Apixaban/Rivaroxaban – Emergent Surgery			

FDA Prescribing Information.

Noteworthy Ongoing Clinical Trials

- **Andexanet alfa**
  - **ANNEXA-RS** (NCT05926349) – **phase III study** investigating andexanet alfa in *patients taking factor Xa inhibitors who require an urgent surgery or procedure vs. usual care*
- **Ciraparantag**
  - NCT04593784 – **phase II, randomized, double-blind** study evaluating ciraparantag for the *reversal of edoxaban, rivaroxaban, or apixaban in healthy adult patients*

ClinicalTrials.gov.

The Collaborative Imperative in Managing DOAC-Related Bleeds

Practical Pearls and Multidisciplinary Insights

Expert Consensus (for FXa Inhibitor Reversal)

Generally, three camps (prior to ANNEXA-I readout in October 2023):

1. Andexanet alfa first line, PCC second line (majority)
2. Andexanet alfa and PCC are equal (minority)
3. There is no good, sufficient evidence that either works, so andexanet alfa, PCC, and just stopping the anticoagulant are all equal (ASH)

van Es et al. *Eur Heart J*. 2023; Cuker et al. *Am J Hematol*. 2019; Tomaselli et al. *J Am Coll Cardiol*. 2020; Baugh et al. *Ann Emerg Med*. 2020; Witt et al. *Blood Adv*. 2018; Milling et al. *Am J Emerg Med*. 2020.

Evidence Summary: FXa Inhibitor Reversal

- **Andexanet alfa**
  1. Prospective healthy normal RCTs, ANNEXA-R and ANNEXA-A
  2. Prospective single cohort, ANNEXA-4
  3. Prospective ICH RCT, ANNEXA-I
- **PCC**
  - Retrospective analyses (Panos et al *Circulation* is largest and best, but many others)
- **Investigational Agents**
  - Ciraparantag
- **Plasma**
  - Historical use

Siegal et al. *N Engl J Med*. 2015; Connolly et al. *N Engl J Med*. 2019; Milling et al. *Circulation*. 2023; Connolly S. *World Stroke Congress*. Plenary Presentation. October 10-12, 2023; Panos et al. *Circulation*. 2020; Ansell et al. *Eur Heart J*. 2022.

Pathways – ACEP

Anticoagulated Patient enters Emergency Department

Is the patient bleeding?
OR
Non-bleeding and needs emergent surgery/urgent procedure?

NO → **Routine Care & Reassessment** (NEXT)

YES

Provide emergent treatment/supportive care
Clinical | Labs | Imaging

AND

Is the bleed life-threatening or at a critical site?
OR
Does the non-bleeding patient need emergent surgery/urgent procedure?

NO → **Routine Care & Reassessment** (NEXT)

YES (NEXT)

Baugh et al. *Ann Emerg Med*. 2020.

Routine Care & Reassessment

Class	Direct Thrombin Inhibitor	Direct FXa Inhibitor			AT-Mediated Inhibition of FXa	Inhibition of Thrombin; Indirectly Inactivates Xa		Vitamin K Antagonist
Agent	Dabigatran	Rivaroxaban/ Apixaban	Edoxaban	Betrixaban	Fondaparinux	Unfractionated Heparin	Enoxaparin/ Daltaparin	Warfarin
Last Dose	(<8-12 hrs)	(<18 hrs)	(10-14 hrs)	(19-24 hrs)	(17-21 hrs)	**PTT Based** (1-2 hours)	3-5 hours	**INR Based** (20-60 hrs)
Tier 1	**Idarucizumab**	**Andexanet alfa**	**Andexanet alfa**		**4F-PCC**	**Protamine**		**Vit K & 4F-PCC**
Tier 2	PCC | Dialysis	PCC	PCC		PCC			PCC | FFP

Reassess: **Clinical | Labs | Imaging**

Is the patient improving?

NO → **Consider Redosing & Admit to Hospital**

YES →  **Admit to Hospital**

Is the patient improving?

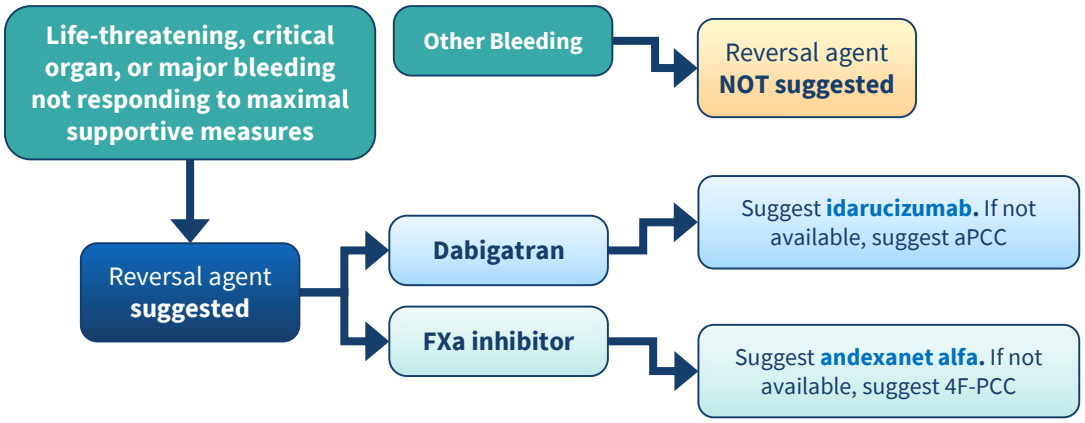
NO → **Admit to Hospital**

YES → **Consider Discharge**

Baugh et al. *Ann Emerg Med*. 2020.

Pathways – Anticoagulation Forum

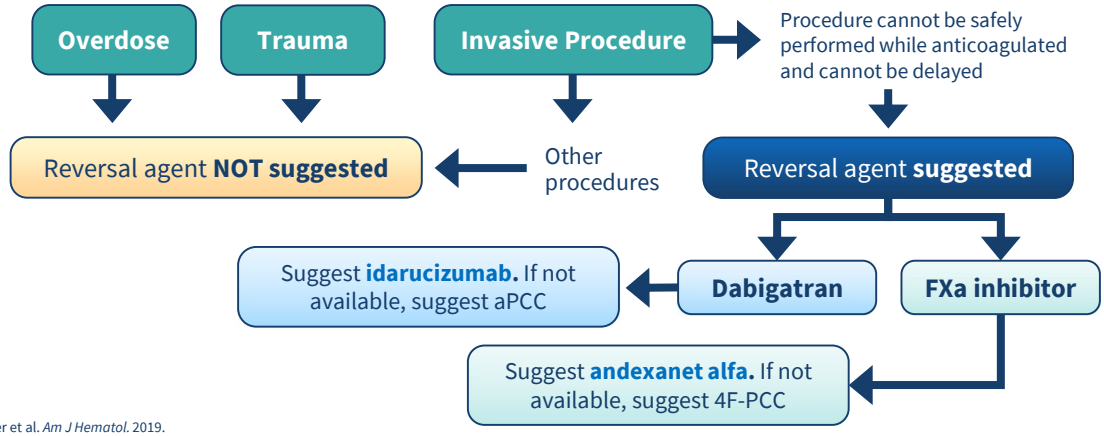
Patient on DOAC: **Bleeding**



Cuker et al. *Am J Hematol*. 2019.

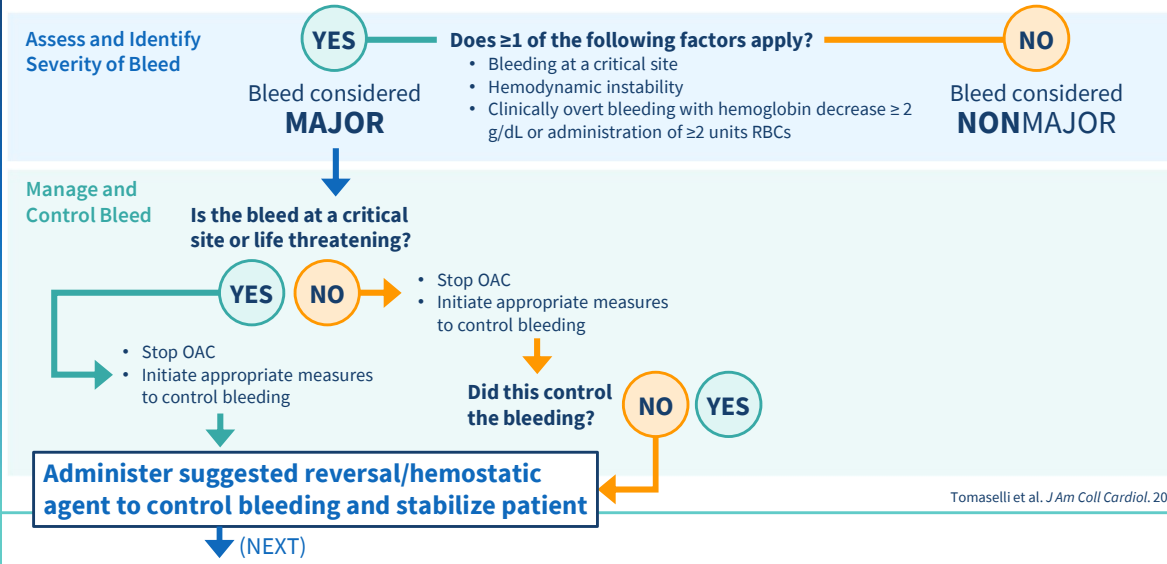
Pathways – Anticoagulation Forum

Patient on DOAC: **Not Bleeding**



Cuker et al. *Am J Hematol*. 2019.

Pathways – ACC



Tomaselli et al. *J Am Coll Cardiol*. 2020.

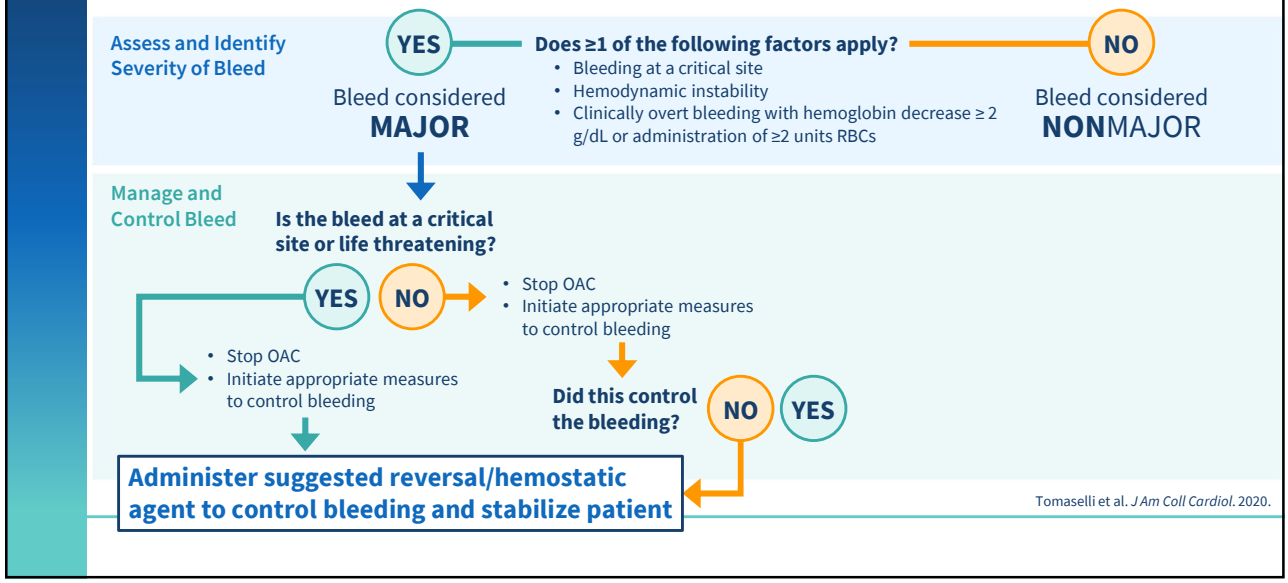
Pathways – ACC

Which OAC is patient currently taking?

VKA (warfarin and other coumarins)	DTI (dabigatran)	FXa Inhibitor (apixaban and rivaroxaban)	FXa Inhibitor (betrixaban and edoxaban)
Administer 4F-PCC: • INR 2 to <4, 25 units/kg • INR 4-6, 35 units/kg • INR >6, 50 units/kg **Or low fixed-dose option** • 1000 units for any non-intracranial major bleed • 1500 units for ICH **If 4F-PCC is not available, use plasma 10-15 mL/kg**	• Administer **5g idarucizumab IV** • If idarucizumab is not available, **administer PCC or aPCC** • **Consider activated charcoal** for known recent ingestions (**within 2-4 hrs**)	• Administer **andexanet alfa** • If andexanet alfa is not available, **administer PCC or aPCC** • **Consider activated charcoal** for known recent ingestions (**within 2-4 hrs**)	• Administer **off-label treatment with high-dose andexanet alfa** • If andexanet alfa is not available, **administer PCC or aPCC** • **Consider activated charcoal** for known recent ingestions (**within 2-4 hrs**)

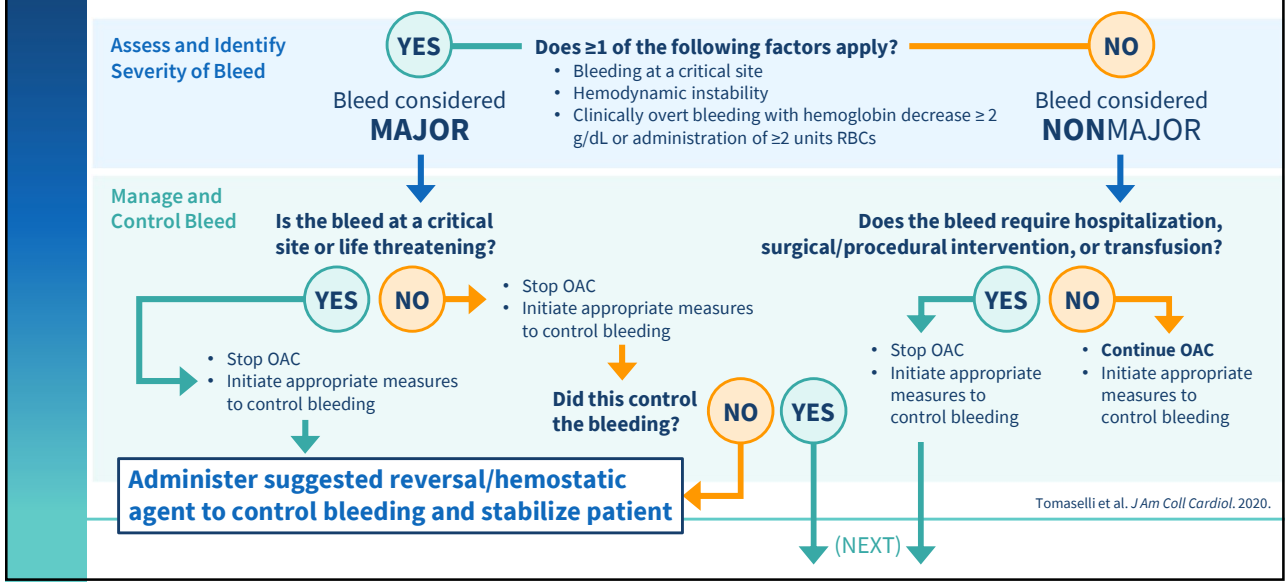
Tomaselli et al. *J Am Coll Cardiol*. 2020.

Pathways – ACC



Tomaselli et al. *J Am Coll Cardiol.* 2020.

Pathways – ACC



Tomaselli et al. *J Am Coll Cardiol.* 2020.

Pathways – ACC

Determine Whether and When to Restart Anticoagulation

Once patient is stable, is there a clinical indication for continued OAC?

NO → Suggest **discontinuing** anticoagulation.

YES → **Does ≥1 of the following factors apply?**

- Bleed occurred at a critical site
- Patient is at high risk of rebleeding or of death/disability with rebleeding
- Source of bleed has not yet been identified
- Surgical or invasive procedures are planned
- Patient does not wish to restart OAC at this time

YES → Suggest **delaying restart** of anticoagulation.

NO → Suggest **restarting** anticoagulation.

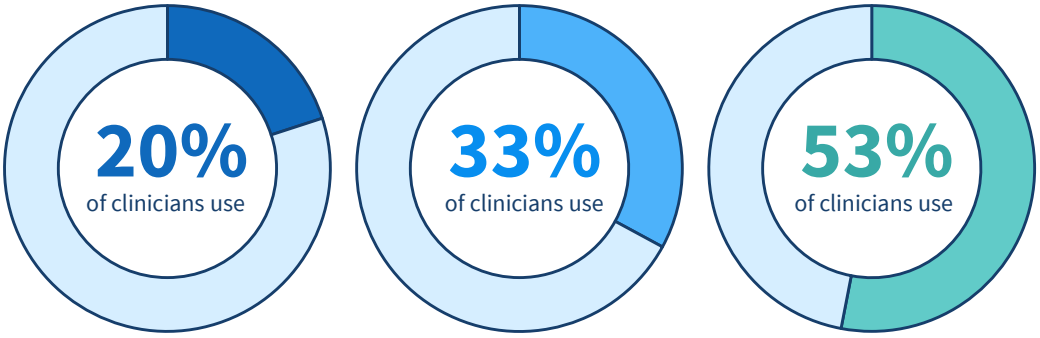
Tomaselli et al. *J Am Coll Cardiol*. 2020.

Factor Equivalency

Plasma	PCC	Andexanet
(0.8-0.9 units per cc)	(40 units per cc)	(10-100-Fold x PCC)
(2.25 liters)	(50 cc) = (2000-unit doses)	

FDA Prescribing Information.

Interesting Findings From Clinician Survey



Plasma for **DOAC-Related Bleeding**

Fixed or Low-Dose PCC for **DOAC-Related Bleeding**

Plasma for **Warfarin-Related Bleeding**

Refaai et al. *Clin Appl Thromb Hemost*. 2023.

Andexanet vs. 4F-PCC: Real-World Data

- Observational study of 4,395 hospitalized patients with apixaban- or rivaroxaban-associated major bleeding
  - 2,211 managed with andexanet alfa
  - 2,273 managed with 4F-PCC
- The mortality benefit with andexanet vs. 4F-PCC was demonstrable and comparable for both ICH and gastrointestinal bleeds

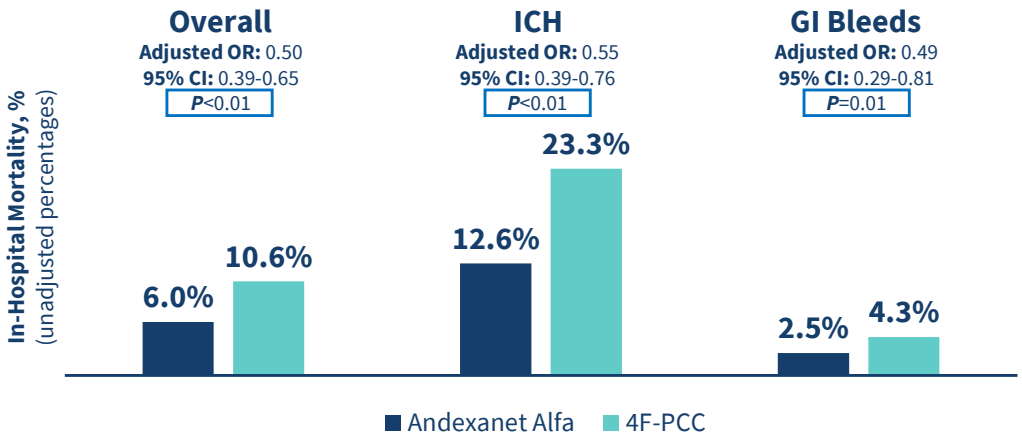
In-Hospital Mortality

50%

with andexanet vs 4F-PCC

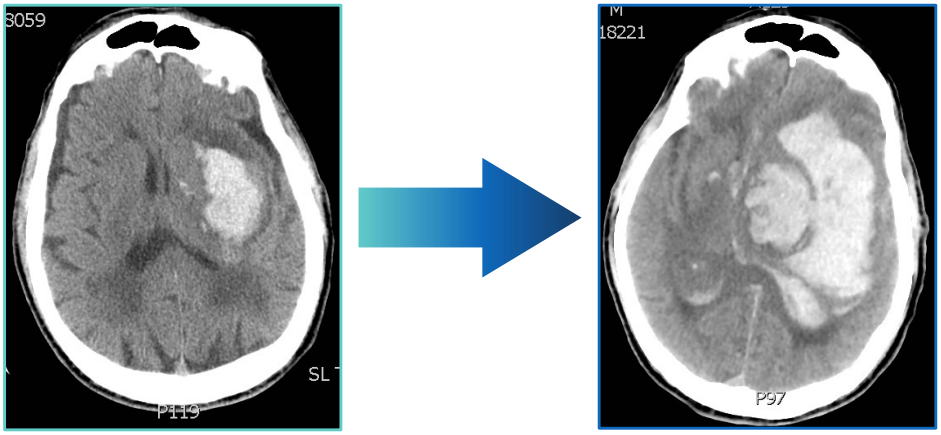
Dobesh et al. *Res Pract Thromb Haemost*. 2023.

Andexanet vs. 4F-PCC: Real-World Data



Dobesh et al. *Res Pract Thromb Haemost.* 2023.

Hematoma Expansion



Images provided courtesy of Dr. Truman Milling, Jr.

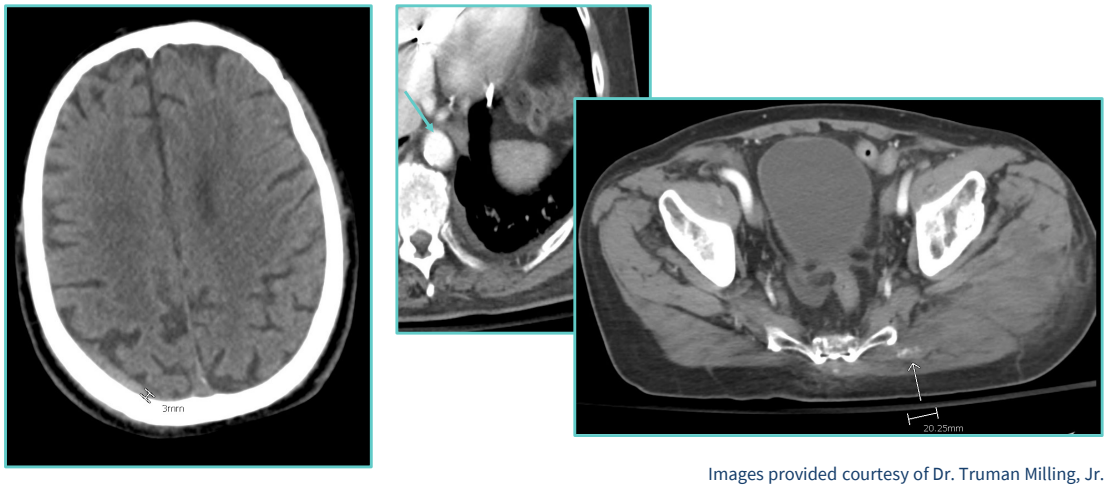
Patient Case: An Elderly Fall Victim

- Presents to the ED
- **CC:** Fall/Head Injury
- **HPI:** 84-yo male with PMH of coronary artery disease and atrial fibrillation fell down a flight of 8 stairs just prior to arrival. Brought in by EMS, backboard and collar. Doesn't know why he fell, but reports 4 prior falls in the past week
- **PMH:** CAD, HTN, hyperlipidemia, Afib

Patient Case: Exam

- **Patient:** Awake and protecting his airway
  - Alert, moving all extremities and following commands
- **Breathing:** Spontaneous, slightly labored with some splinting and tenderness on the left, SaO2 95% on RA
- **Circulation:** Tachycardia to 150 BPM with irregularly irregular rhythm, BP 150/90, strong peripheral pulses, cap refill <2 secs, no overt bleeding
- **Pupils:** Equal and reactive
- There is scalp swelling to the right occiput, no cervical/thoracic/lumbar spine tenderness or deformity, tenderness in the left posterior chest without crepitus or subQ air, tenderness swelling and ecchymosis to bilateral gluteal muscles left > right

Patient Case: Imaging



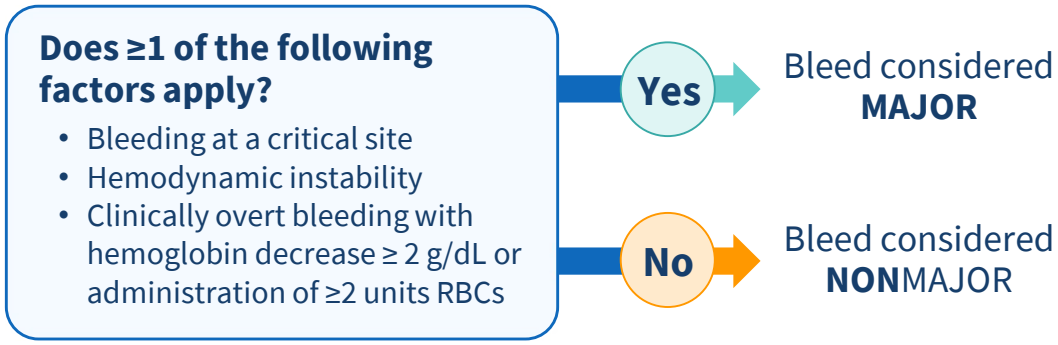
Images provided courtesy of Dr. Truman Milling, Jr.

Patient Case: Management

- A-fib RVR treated with diltiazem push and drip? (Pgp inhibitor)
  - Could use esmolol or metoprolol
- CTs
  - Head: 3 mm SDH right posterior convexity without mass effect.
  - C, T and L spine: degen change no acute fracture or dislocation.
  - Chest: Left 8-11 nondisplaced posterior rib fractures, small bilateral pleural effusions.
  - AP: No solid organ injury, small free fluid in the pelvis, left gluteal hematoma with active extravasation

Patient Case: Bleed Assessment

- What severity would you classify the bleed as?



Tomaselli et al. *J Am Coll Cardiol*. 2020.

Patient Case: Discussion

The patient's daughter is on the way to the hospital and tells you via phone that *he is on rivaroxaban. He took his dose about 9 hours ago with dinner.*

- Would you wait for coagulation tests to come back before initiating reversal therapy?
- What reversal agent would you use and at what dose?

Patient Case: Coagulation Tests

- CBC 10>10.6/31.6<253
- BMP 139/3.9; 107/24; 19/1.0
- PT 27.1
- Anti-FXa level 1.4

Next Steps?

Optimizing Outcomes for Patients With DOAC-Related Bleeding:

A Multidisciplinary Appraisal of Data-Driven Management Strategies Using Specific Reversal Agents

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