

Anticoagulants: Pharmacology, and Reversal

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Disclosures

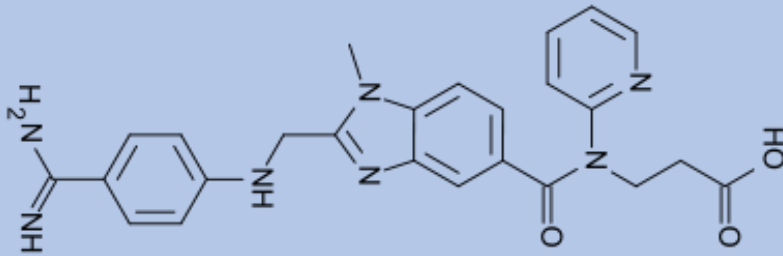
- Research funding from Takeda, Sanofi, Veralox, and CSL Behring
- Consulting for HRSA Vaccine Injury Compensation Program

Outline

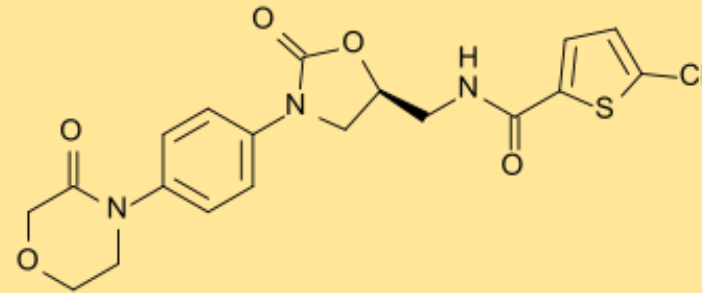
- DOACs (dabigatran, rivaroxaban, apixaban, edoxaban)
 - Clinical Trial Evidence
 - Hemorrhage Management
- Management of Hemorrhage with warfarin

Direct Oral Anticoagulants

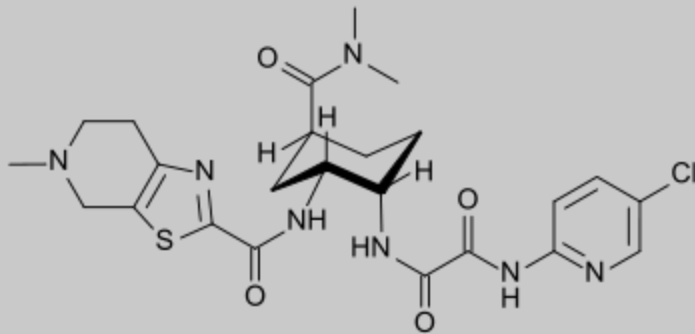
Dabigatran – *Pradaxa*
(Boehringer Ingelheim)



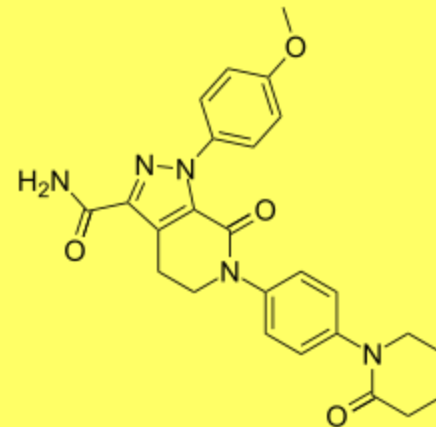
Rivaroxaban – *Xarelto*
(Janssen)



Edoxaban – *Savaysa*
(Daiichi Sankyo)



Apixaban – *Eliquis*
(Bristol-Myers Squibb / Pfizer)



Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Peak Effect(h)	2 – 3	2 – 4	1-3	1-2
Half-life (h)	12 – 14	5 – 13	9 – 14	6-11
Dosing Frequency	Twice daily	Daily	Twice daily	Daily
Clearance	80% Renal 20% Biliary	66% Renal 33% Biliary	25% Renal 75% Biliary	34% Renal 66% Biliary

DOAC FDA Approved Indications

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
VTE prophylaxis (THA, TKA)	✓ 110 mg x 1 → 220 mg Daily	✓ 10 mg Daily	✓ 2.5 mg BID	X
Atrial fibrillation	✓ 150 mg BID	✓ 20 mg Daily	✓ 5 mg BID	✓ 60 mg Daily
VTE treatment	✓ 150 mg BID	✓ 15 BID → 20 mg Daily	✓ 10 BID → 5 mg BID	✓ 60 mg Daily

Rivaroxaban (Xarelto®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf

Apixaban (Eliquis®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf

Edoxaban (Savaysa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf

Dabigatran (Pradaxa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202512s007lbl.pdf

Efficacy of DOAC to comparators

+: Superior; **NI**: Non-inferior
-: Inferior to comparator

	VTE prophylaxis	VTE treatment	Atrial fibrillation
Dabigatran	NI, —	NI	+
Rivaroxaban	+	NI	NI
Apixaban	+, —	NI	NI, +
Edoxaban	+	NI	NI

Bleeding DOAC to comparators

↑: more bleeding; = similar Bleeding; ↓: less bleeding

	VTE prophylaxis	VTE treatment	Atrial fibrillation
Dabigatran	=	=	=
Rivaroxaban	=	=	=
Apixaban	=, ↓	↓	=, ↓
Edoxaban	=	↓	↓

Intracranial Hemorrhage

Therapeutic Anticoagulation Trials

Trial	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
A Fib	0.74-0.85%/y	0.3%/y*	0.49%/y*	0.33%/y*	0.39%/y*
VTE	0.2- 0.4%	2 (0.1%)	3 (0.2%)^	3 (0.1%)	5 (0.1%)

* Statistically significant ^ All critical site bleeding

Rivaroxaban (Xarelto®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf

Apixaban (Eliquis®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf

Edoxaban (Savaysa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf

Dabigatran (Pradaxa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s001lbl.pdf

Major bleeding case fatality rates

	DOAC	Warfarin
ROCKET AF (rivaroxaban)	7%	14%
Dabigatran systematic review	9%	13%
ARISTOTLE (apixaban)	10%	12%
ENGAGE AF-TIMI 48 (edoxaban)	8%	11%

Major bleeding with warfarin has a high risk of death unchanged over the last 20 years



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Comparison of Bleeding Risk between Rivaroxaban and Apixaban in Acute VTE: The COBRRA Trial

Lana A. Castellucci, MD MSc FRCPC, on behalf of the COBRRA Trial Investigators
June 22, 2025



The Ottawa Hospital
L'Hôpital d'Ottawa
RESEARCH INSTITUTE
INSTITUT DE RECHERCHE



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Flow Chart

2760 Patients Randomized

1370 patients assigned to Apixaban

1362 received Apixaban
8 did not receive Apixaban
2 withdrew consent
5 met an exclusion criterion
1 physician decision

1345 Completed the study

17 Did not complete
4 withdrew consent
3 withdrawn by physician
9 lost to follow up
1 death

1345 analyzed for primary outcome,
intention-to-treat population

Allocation

1390 patients assigned to Rivaroxaban

1380 received Rivaroxaban
10 did not receive Rivaroxaban
6 withdrew consent
2 met an exclusion criterion
1 physician decision
1 patient decision

Follow-up

1355 completed the study

25 did not complete
10 withdrew consent
13 lost to follow up
2 deaths

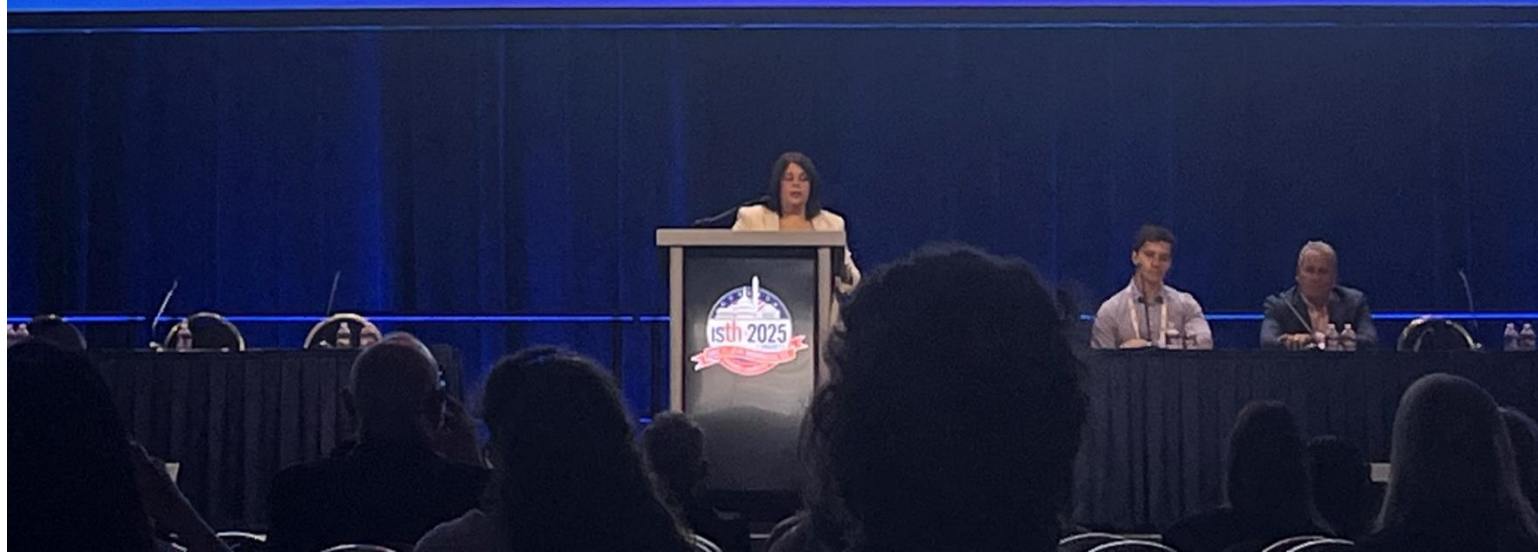
Analysis

1355 analyzed for primary outcome,
intention-to-treat population



Baseline Characteristics

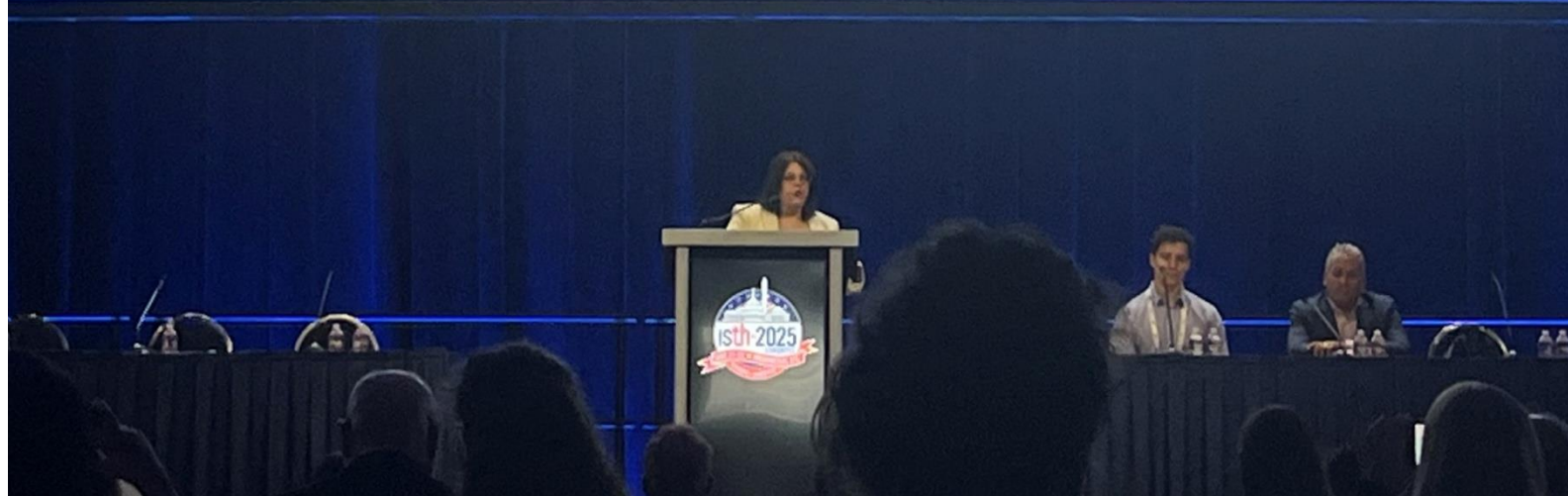
Characteristic	Apixaban (N=1345)	Rivaroxaban (N=1355)
Age, mean (SD)	58.0 years (16.3)	58.5 years (15.8)
Sex – Female	597 (44.4%)	577 (42.6%)
Race (n/n/n) – White/Black/Other	1182/51/103	1218/44/83
BMI (kg/m ²), mean (SD)	28.9 (5.1)	29.1 (5.2)
CrCl < 50 mL/minute	60 (4.5%)	63 (4.6%)
Antiplatelets (continued)	36 (2.7%)	35 (2.6%)
DVT alone	691 (51.4%)	716 (52.8%)
PE +/- DVT	654 (48.3%)	637 (47.0%)
Unprovoked/Provoked (n/n)	1022/322	1064/291



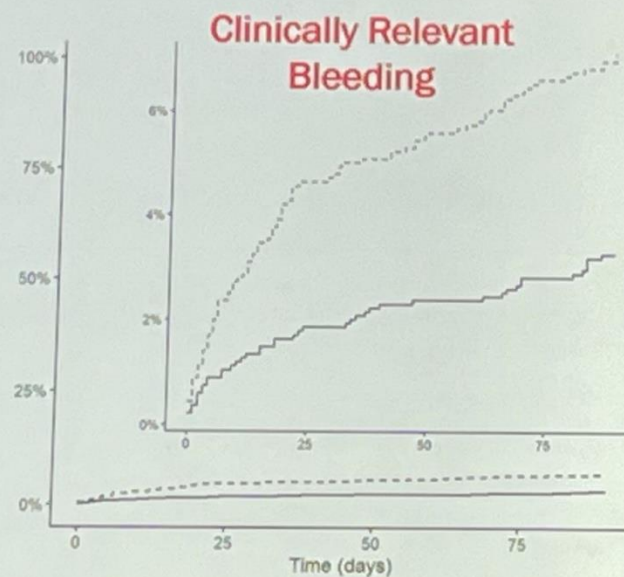
Results

Outcome	Apixaban (N=1345)	Rivaroxaban (N=1355)	OR (95% CI)	P value
Primary Outcome: Clinically Relevant Bleeding*	44 (3.3%)	97 (7.2%)	0.44 (0.31, 0.63)	<0.00001
Secondary Outcomes:				
Major Bleeding	5 (0.4%)	31 (2.3%)	0.16 (0.06, 0.41)	<0.00001
CRNMB	39 (2.9%)	68 (5.0%)	0.57 (0.38, 0.84)	<0.005
Fatal bleeding	0	0	–	–
Recurrent VTE	15 (1.1%)	14 (1.0%)	1.08 (0.52, 2.25)	0.84
Fatal recurrent VTE	0	0	–	–
Death (any cause)	1 (0.1%)	4 (0.3%)	0.25 (0.03, 2.25)	0.37

* Clinically relevant bleeding = major bleeding or clinically relevant nonmajor bleeding



Kaplan-Meier Time-to-Event

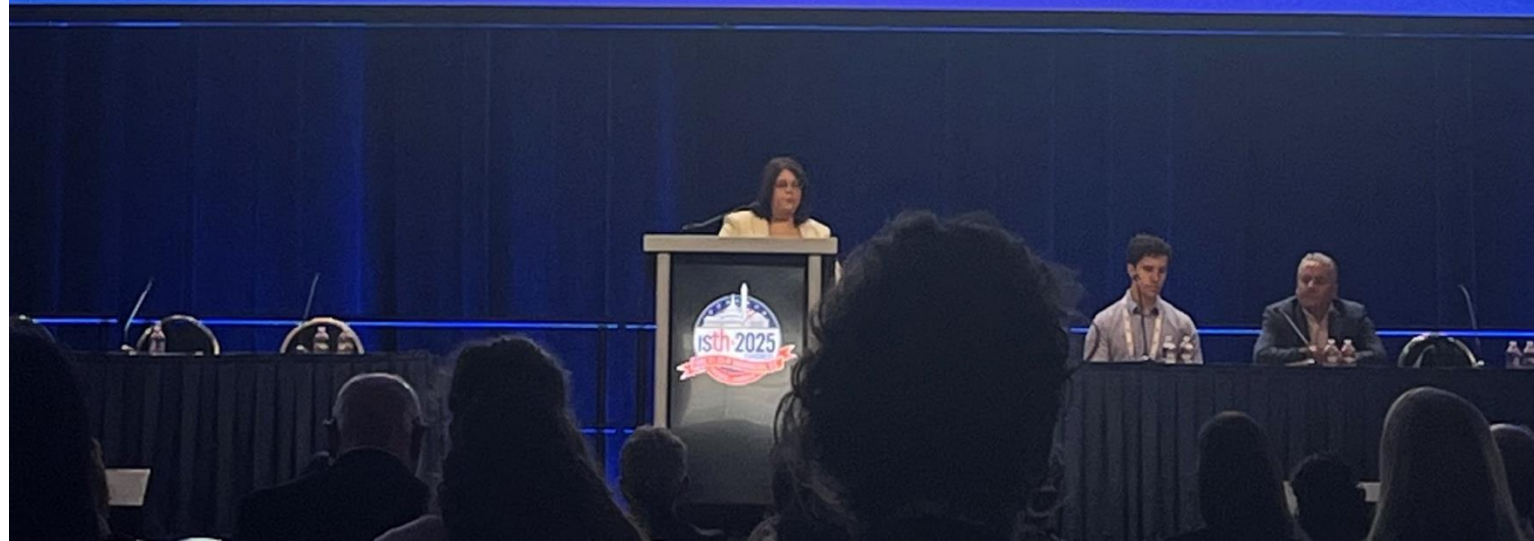


At Risk — Apixaban -- Rivaroxaban

Apixaban	1345	1320	1313	1307
Rivaroxaban	1355	1292	1280	1265

At Risk — Apixaban -- Rivaroxaban

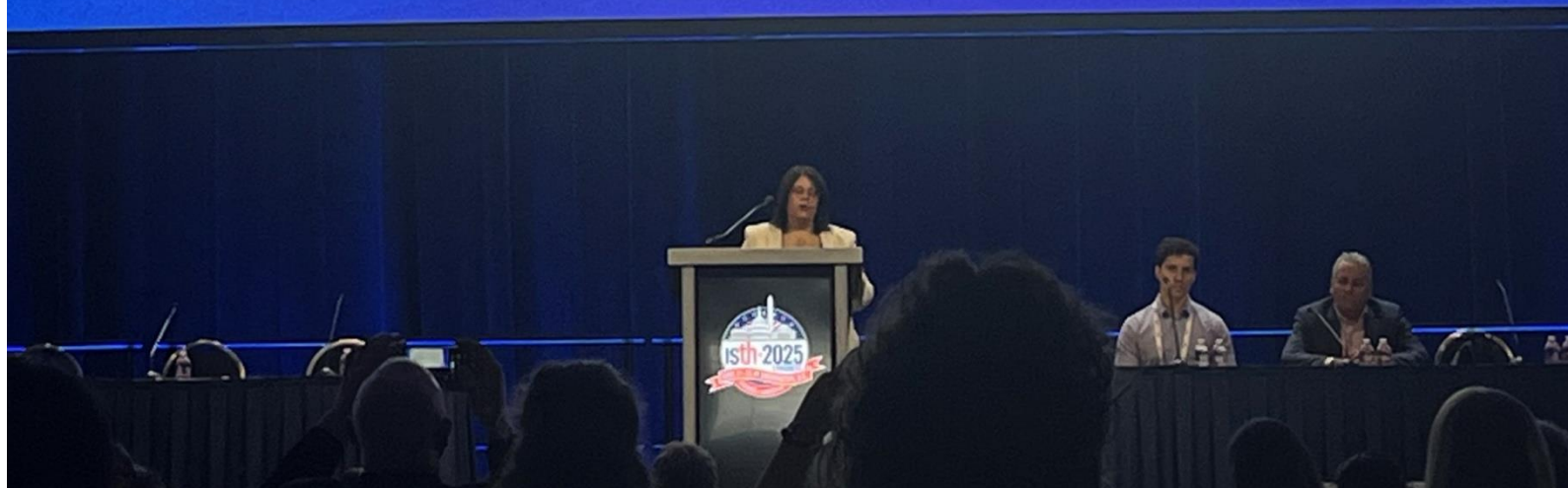
Apixaban	1345	1336	1333	1331
Rivaroxaban	1355	1345	1343	1341



Discussion

Acute VTE: Apixaban is safer than Rivaroxaban

- In patients with acute VTE, 3 months of Apixaban was superior to Rivaroxaban for the primary outcome of clinically relevant bleeding events
- Recurrent VTE and death rates were comparable



Extended treatment of venous thromboembolism with reduced-dose versus full-dose direct oral anticoagulants in patients at high risk of recurrence: a non-inferiority, multicentre, randomised, open-label, blinded endpoint trial

Francis Couturaud, Jeannot Schmidt, Olivier Sanchez, Alice Ballerie, Marie-Antoinette Sevestre, Nicolas Meneveau, Laurent Bertoletti, Jérôme Connault, Ygal Benhamou, Joël Constans, Thomas Quemeneur, François-Xavier Lapébie, Gilles Pernod, Gaël Picart, Antoine Elias, Caroline Doutrelon, Claire Neveux, Lina Khider, Pierre-Marie Roy, Stéphane Zuily, Nicolas Falvo, Philippe Lacroix, Joseph Emmerich, Isabelle Mahé, Julien Boileau, Azzedine Yaici, Sylvain Le Jeune, Dominique Stéphane, Pierre Plissonneau-Duquene, Valérie Ray, Marc Danguy des Déserts, Rafik Belhadj-Chaidi, Bouchra Lamia, Yves Gruel, Emilie Presles, Philippe Girard, Cécile Tromeur, Farès Moustafa, Vincent Rothstein, Karine Lacut, Solen Melac, Sophie Barillot, Patrick Mismetti, Silvy Laporte, Dominique Mottier, Guy Meyer, Christophe Leroyer, for the RENOVE Investigators*

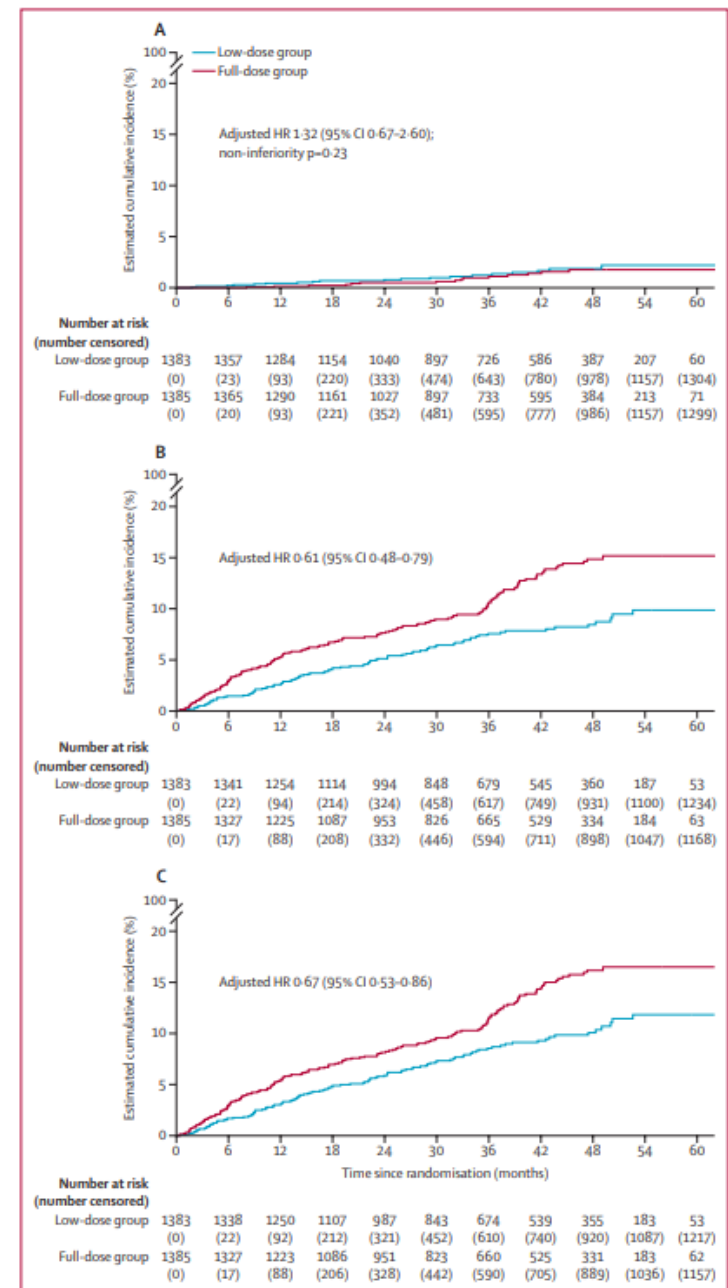


Figure 2: Cumulative incidence of outcomes during the treatment period in the intention-to-treat population (A) Cumulative incidence of symptomatic recurrent venous thromboembolism during the treatment period (primary outcome). (B) Cumulative incidence of major and clinically relevant non-major bleeding during the treatment period (first key secondary outcome). (C) Cumulative incidence of symptomatic recurrent venous thromboembolism, major bleeding, or clinically relevant non-major bleeding (net clinical benefit) during the treatment period (second key secondary outcome). Adjustment was based on randomisation strata. HR, hazard ratio.

Hemorrhage Management

Management of Hemorrhage

- Assess severity of Hemorrhage
- Laboratory testing to assess organ function
 - Understand when need to use antidotes
- Activated charcoal if <2-3 hours since ingestion
- Local Control
- Transfusion as needed
 - Massive Transfusion protocols if available

Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Peak Effect(h)	2 – 3	2 – 4	1-3	1-2
Half-life (h)	12 – 14	5 – 13	9 – 14	6-11
Dosing Frequency	Twice daily	Daily	Twice daily	Daily
Metabolism/ Excretion	80% Renal 20% Biliary	66% Renal 33% Biliary	25% Renal 75% Biliary	34% Renal 66% Biliary

PAUSE Trial

- 3007 patients with atrial fibrillation taking DOAC undergoing elective procedure
- Last dose of anticoagulant prior to procedure
 - Apixaban and Rivaroxaban : Day -3 High Risk, Day -2 Low risk procedure
 - Dabigatran: Day -2 to -5 based on creatinine clearance & bleeding risk
- 98.8% patients had drug concentration <50 ng/ml
- 30-Day major bleed 0.9-1.9%

Within 36-48 hours, no clinically relevant levels of apixaban or rivaroxaban if normal organ function

Antidotes to Anticoagulation Therapy

When and How to Use?

When → Hemorrhage or emergent procedure +

Clinically relevant drug concentrations

1. Last dose known & Pharmacokinetics of drug
2. Laboratory testing

DOACs Coagulation Testing Effect

- Dabigatran

- Peak: aPTT ~2x baseline, Trough: aPTT 1.5x Baseline
- PT/INR relatively insensitive
- TT very sensitive
 - If TT normal → No dabigatran is present

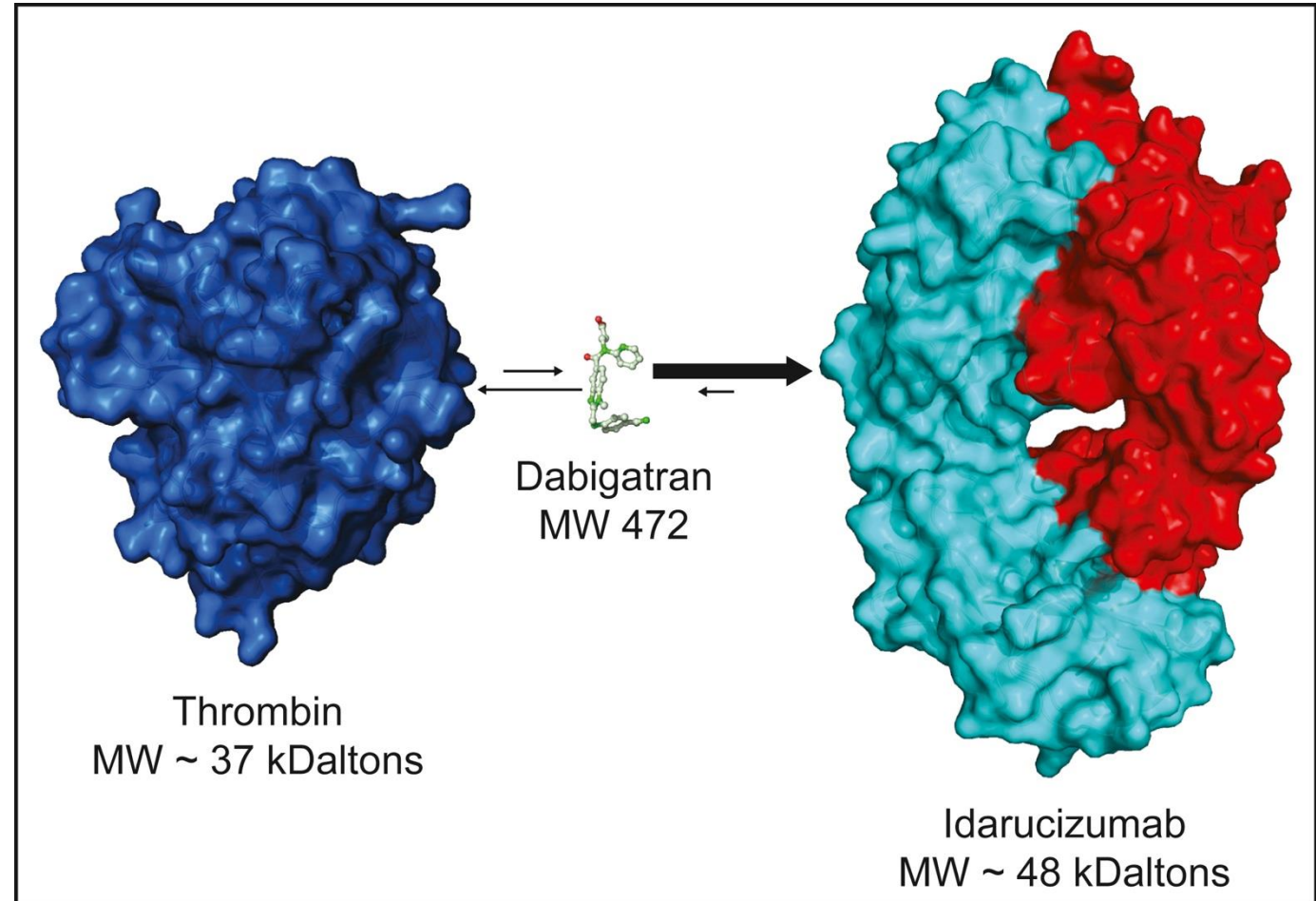
- Xa Inhibitors

- PT/INR sensitivity varies between labs
- PTT relatively insensitive
- Anti-Xa assay can be calibrated

DOAC Antidotes

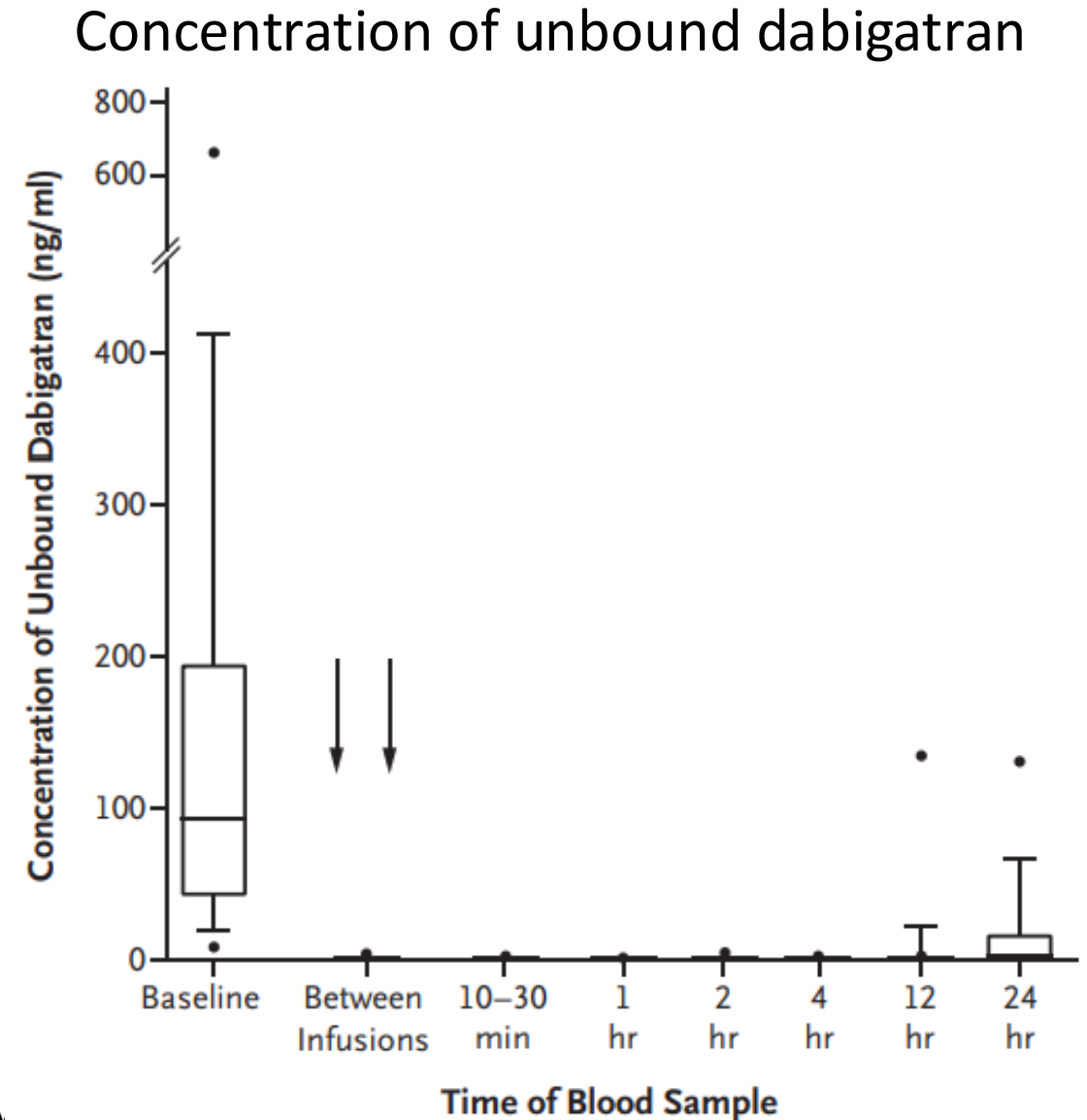
Idarucizumab

- Humanized monoclonal antibody fragment against dabigatran
- Dabigatran binds idarucizumab with affinity ~350-fold greater than to thrombin



Idarucizumab RE-VERSE AD Phase III Study

- N=301 Bleeding
 - 45% GI Bleed
 - 33% Intracranial Hemorrhage
- N=202 procedure
 - 24% Abdominal
 - 20% Orthopedic
 - 18% Cardiovascular
- 100% Reversal of dabigatran



Idarucizumab RE-VERSE AD Phase III Study

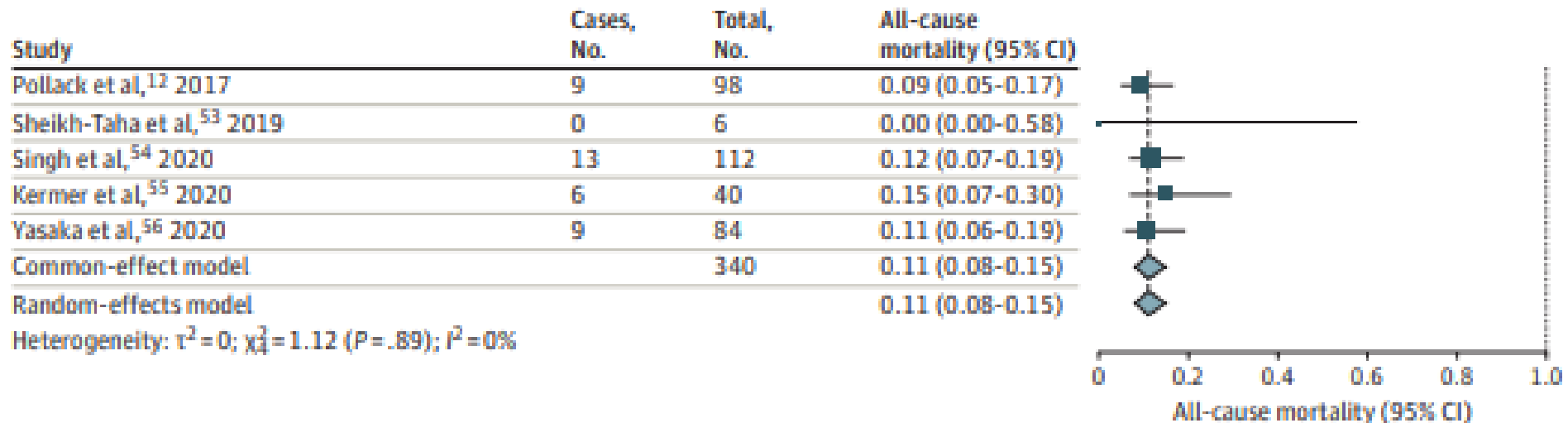
	Bleeding (n=301)	Procedure (n=202)
Efficacy	2.5 hours median stop hemorrhage (98 ICH excluded; 67 unknown)	Normal Hemostasis (93%) Mild Abnormal (5%) Moderate Abnormal (2%)

- FDA Approved Oct 2015

Meta-analysis of Intracranial Hemorrhage

- 5 Cohort studies, 340 patients
- Reversal of anticoagulation: 82% (95% CI, 55%-95%)
- Thromboembolic events 5% (95% CI, 3%-8%)
- Mortality 11% (95% CI, 8%-15%)

Idarucizumab

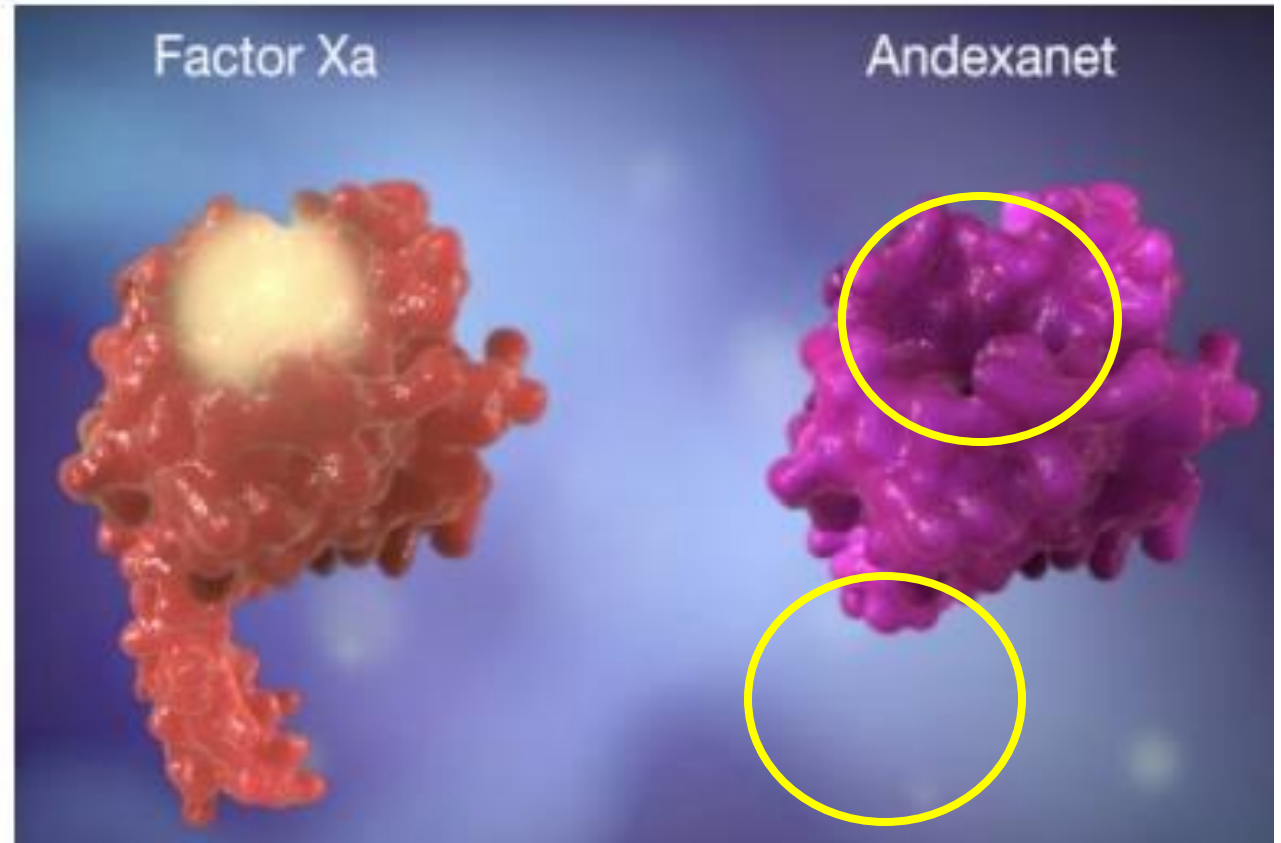


Idarucizumab Pharmacy Considerations

- Time to Mix: <5 minutes
- Stable exposed to light for 6 hours
- Administer: 2 -2.5 g bolus (infusion or syringe), 15 min apart
- Cost: ~\$3500
- Dabigatran can be restarted in 24 hours

Andexanet Alfa

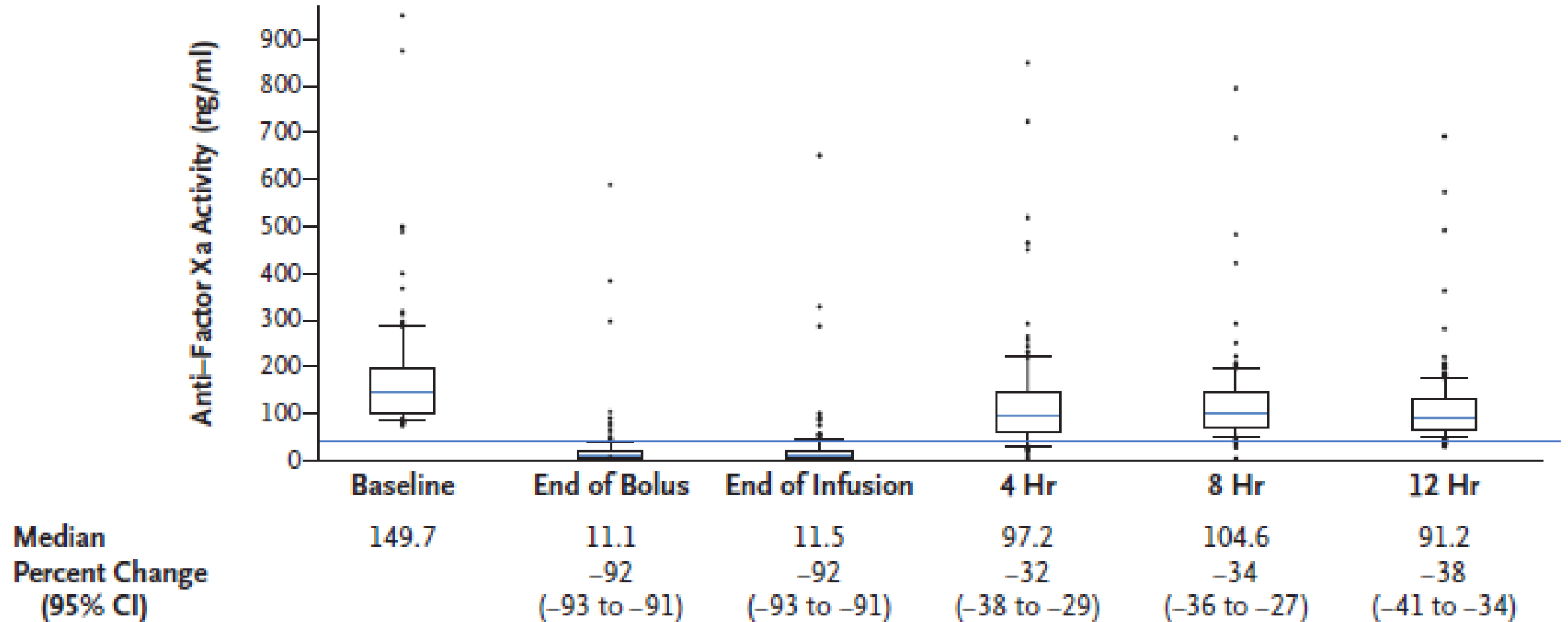
- A recombinant form of factor Xa
- Lacks catalytic and membrane-binding activity
- Retains the ability to bind factor Xa inhibitors & TFPI



Andexanet Alfa ANNEXA-4 Study

- N=352 Major Hemorrhage
 - 64% Intracranial
 - 26% GI
- Medication
 - Apixaban (n=194, 55%)
 - Rivaroxaban (n=128, 36%)
- Efficacy analysis n=254

Reduction in anti-Xa activity apixaban



Anti-Xa low during andexanet alfa administration & returns by 4 hours

Andexanet Alfa ANNEXA-4 Study

	Bleeding (n=352)
Efficacy	Excellent or Good Hemostasis: 82% (n=249)

- FDA Approved May 2018

Andexanet Alfa

- Trial exclusions:
 - Emergent surgery NOT planned within 12 hours
 - Pregnancy, sepsis, or acute thrombosis within previous 2 weeks
 - Administration of prothrombin complex concentrate or recombinant VIIa
- Andexanet alfa will bind heparin or low-molecular weight heparin/AT complex
- No indication for repeat dosing

Andexanet Alfa Pharmacy Considerations

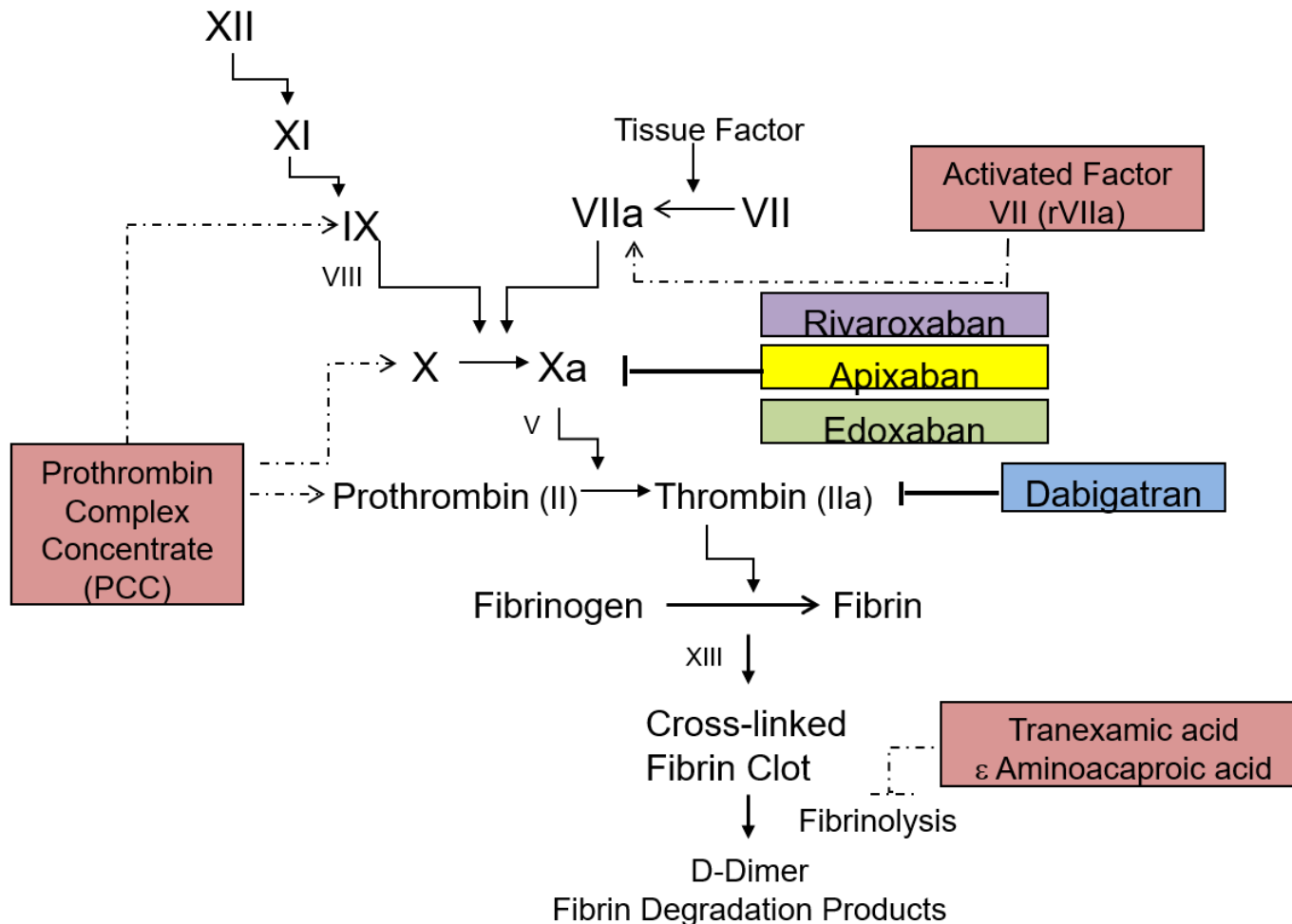
- Bolus + 2-hour infusion

Time from DOAC	Bolus Dose	Infusion Dose
> 7 Hours rivaroxaban; apixaban	400 mg	480 mg (4 mg/min x 2 hours)
<7 hours or unknown timing rivaroxaban	800 mg	960 mg (8 mg/min x 2 hours)

- Andexanet alfa can take >20 minutes to reconstitute
 - 200 mg vials that cannot be shaken
 - 5-9 Vials
 - Recommend single bag if possible
- T code (inpatient) and 340B pricing available (outpatient)

Prothrombin Complex Concentrates

Prohemostatic Medications $\neq$ DOAC Antidote



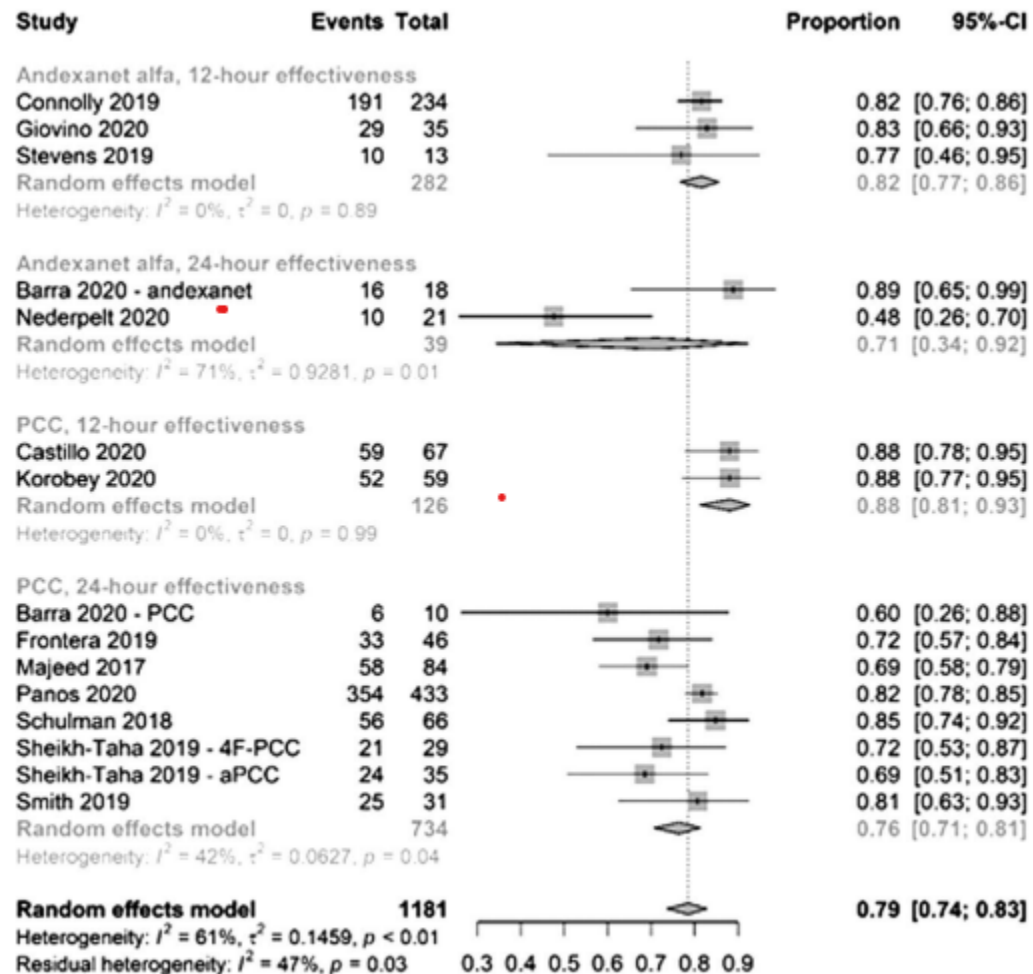
Significant amount of in-vitro and animal model data using these agents in patients treated with DOAC with inconsistent results

Prothrombin complex concentrate

Pharmacy Considerations

- Time to Mix: <5 minutes
- Administer: bolus injection
- Cost: ~\$3200 (2000 Units)
- Small amounts of heparin → contraindicated if history of HIT
- Not FDA approved for DOAC associated hemorrhage management

Meta-analysis of Effectiveness of PCC and Andexanet



Andexanet 82% effective at 12 hours & 71% effective at 24 hours

PCC 88% effective at 12 hours & 76% effective at 24 hours

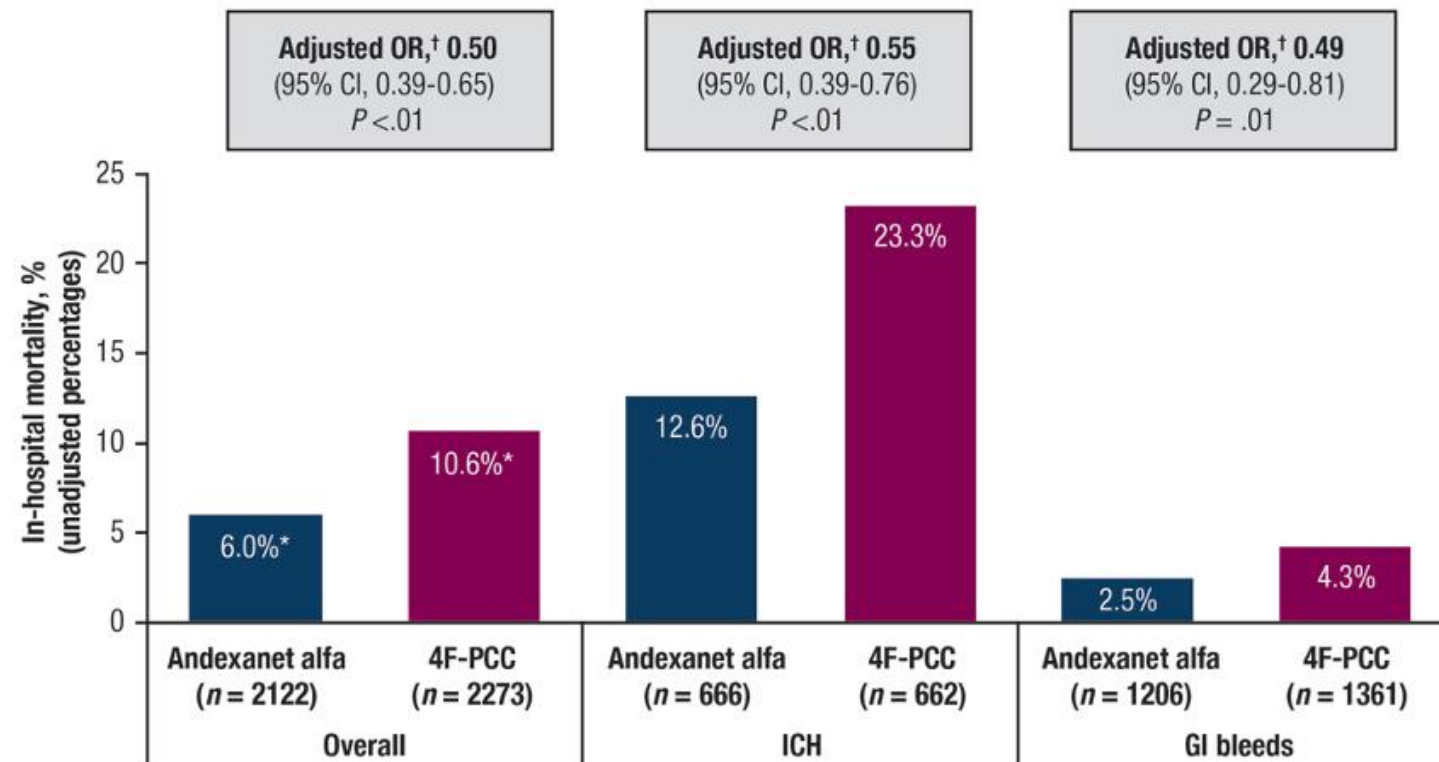
Thrombosis 5% with andexanet & 2% with PCC

Meta-analysis of Intracranial Hemorrhage

	Andexanet Alfa	4-Factor PCC
Studies, n	17 studies, 525 patients	22 studies, 967 patients
Reversal of anticoagulation	75% (67%-81%)	77% (72%-82%)
Thromboembolism	14% (10%-19%)	8% (5%-12%)
Mortality	24% (16%-34%)	26% (20%-32%)

Lower mortality with andexanet alfa vs 4-factor prothrombin complex concentrate for factor Xa inhibitor-related major bleeding in a U.S. hospital-based observational study

- Retrospective cohort from 354 hospitals of andexanet alfa (n=2122) or 4F-PCC (n=2273) use
 - 1328 ICH → 50% traumatic, 39% surgery (45% andexanet; 33% PCC)
 - GCS ≤8 30% andexanet; 35% PCC group
 - 2567 GI bleed → 40% upper, 32% lower; 51% GI procedure
 - 20% restarted anticoagulation



Annexa-I Study

- Randomized, open-label multicenter clinical trial andexanet alfa vs. usual care for ICH within 6 hours of symptom onset to baseline scan and within 15 hours of taking an oral FXa inhibitor.
- Primary outcome measure of effective hemostasis:
 - A National Institutes of Health Stroke Scale (**NIHSS**) 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
- Interim analysis planned after 450 patients study stopped after 530 patients

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Andexanet (N = 224)	Usual Care (N = 228)
Age — yr	78.9±8.5	78.9±8.5
Female sex — no. (%)	94 (42.0)	113 (49.6)
Body-mass index †	26.9±5.3	26.3±4.6
Medical history — no. (%)		
Myocardial infarction	24 (10.7)	33 (14.5) ←
Stroke	48 (21.4)	48 (21.1) ←
Deep-vein thrombosis	18 (8.0)	22 (9.6)
Pulmonary embolism	16 (7.1)	21 (9.2)
Atrial fibrillation	202 (90.2)	192 (84.2) ←
Congestive heart failure	34 (15.2)	44 (19.3)
Diabetes	82 (36.6)	59 (25.9)

Table 1. Baseline Characteristics of the Patients.*		
Characteristic	Andexanet (N = 224)	Usual Care (N = 228)
Factor Xa inhibitor used — no. (%)		
Apixaban	140 (62.5)	135 (59.2)
Rivaroxaban	64 (28.6)	65 (28.5)
Edoxaban	20 (8.9)	25 (11.0)
Hemorrhage location — no. (%)		
Intracerebral	198 (88.4)	214 (93.9)
Intraventricular	3 (1.3)	1 (0.4)
Subarachnoid	9 (4.0)	8 (3.5)
Subdural	13 (5.8)	4 (1.8)
Hemorrhage preceded by trauma — no. (%)	26 (11.6)	33 (14.5)
Systolic blood pressure in patients with intracerebral hemorrhage — mm Hg	161.2±27.0	159.8±27.7
Median hematoma volume (IQR) — ml	10.5 (4.1–24.9)	9.0 (3.1–22.8)
Median Glasgow Coma Scale score (IQR)‡	15.0 (13.0–15.0)	15.0 (13.0–15.0)
Median NIHSS score (IQR)§	9.0 (5.0–16.0)	9.0 (4.0–14.0)

Andexanet had less hematoma expansion

Table 2. Efficacy End Points.				
End Point	Andexanet (N = 224)	Usual Care (N = 228)	Adjusted Difference per 100 Patients (95% CI)*	P Value*
	<i>no./total no. (%)</i>		<i>percentage points</i>	
Hemostatic efficacy	150/224 (67.0)	121/228 (53.1)	13.4 (4.6 to 22.2)	0.003
Hematoma volume change $\leq 35\%$ †	165/215 (76.7)	137/212 (64.6)	12.1 (3.6 to 20.5)	←
NIHSS score change < 7 points	188/214 (87.9)	181/218 (83.0)	4.6 (−2.0 to 11.2)	
No receipt of rescue therapy between 3 hr and 12 hr	218/224 (97.3)	213/228 (93.4)	3.8 (−7.6 to 0.0)	
Hematoma volume increase ≥ 12.5 mL‡	24/216 (11.1)	36/214 (16.8)	−5.6 (−12.0 to 0.8)	←
Hemostatic efficacy, excluding patients nonevaluable for administrative reasons	150/218 (68.8)	121/225 (53.8)	14.5 (5.7 to 23.4)	

Andexanet had more ischemic strokes

Table 3. Thrombotic Events and Deaths at 30 Days.*				
Event	Andexanet (N = 263)	Usual Care (N = 267)	Increase per 100 Patients (95% CI)†	P Value‡
	<i>no. of patients (%)</i>		<i>percentage points</i>	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	←
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (−0.2 to 6.1)	←
Deep-vein thrombosis	1 (0.4)	2 (0.7)	−0.4 (−2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	−1.9 (−4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (−1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (−5.0 to 10.0)	← 0.51

Functional Outcomes (FDA Advisory Panel)

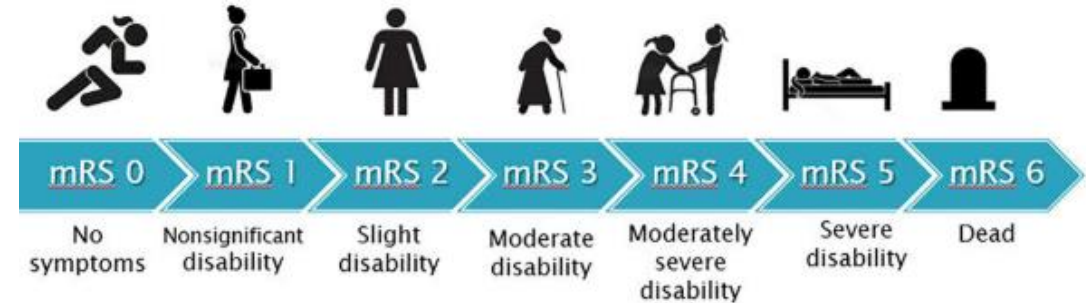


Table 9. Modified Rankin Scale in Primary Efficacy Population

Parameter	Andexanet	Usual Care
mRS 0-3 (baseline)	161/198 (81%)	156/194 (80%)
mRS 0-3 (Day 30)	54/189 (29%)	64/192 (33%)
Patients with baseline mRS 0-3	-	-
mRS remained 0-3 at Day 30	48/151 (32%)	59/151 (39%)
mRS changed to 4-6 at Day 30	103/151 (68%)	92/151 (61%)
Patients with baseline mRS 4-6	-	-
mRS remained 4-6 at Day 30	29/33 (88%)	33/36 (92%)
mRS changed to 0-3 at Day 30	4/33 (12%)	3/36 (8%)

Source: FDA reviewer calculations from ADSL, ADQS datasets, and adapted from - BLA 125586/546; Clinical Study Report 18-513

Edition # 1 CSR Addendum Tables 14.2.3.3.1a.

Abbreviations: mRS, modified Rankin Scale; PEP, primary efficacy population.

- Day 30 independence status (mRS 0-3): odds ratio 1.30 (0.81, 2.09)
- Worsening of functional status occurred in both arms similarly
- Most with severe disability at baseline continued to have severe disability

Table 18. Thrombotic Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Andexanet (N=239) n (%)	Usual Care (N=232) n (%)
Any thrombotic event	35 (14.6)	16 (6.9)
Cardiac disorders	12 (5)	2 (0.9)
Atrial thrombosis	1 (0.4)	0
Myocardial infarction*	11 (4.6)	2 (0.9)
General disorders	0	1 (0.4)
Sudden cardiac death	0	1 (0.4)
Investigations	0	1 (0.4)
Troponin increased	0	1 (0.4)
Nervous system disorders	21 (8.8)	4 (1.7)
Cerebellar stroke	1 (0.4)	0
Cerebral ischemia	1 (0.4)	0
Cerebral infarction	1 (0.4)	2 (0.9)
Cerebral venous thrombosis	0	1 (0.4)
Cerebrovascular accident	4 (1.7)	0
Ischemic stroke***	14 (5.9)	1 (0.4)
Renal and urinary disorders	1 (0.4)	0
Renal infarct	1 (0.4)	0
Respiratory, thoracic, and mediastinal disorders	4 (1.7)	7 (3)
Pulmonary embolism	4* (1.7)	7 (3)
Vascular disorders	4 (1.7)	3 (1.3)
Arterial occlusive disease	0	1 (0.4)
Deep vein thrombosis	1 (0.4)	2 (0.9)
Embolism arterial	1** (0.4)	0
Femoral artery embolism	1 (0.4)	0
Peripheral ischemia	1 (0.4)	0

Andexanet had more ischemic strokes

- Thrombotic events occurred earlier with andexanet: median 3.5 days (range 1- 24) vs. median of 16 days (range 2 to 25) in the UC arm.
- Of the 35 andexanet-treated patients who experienced a thrombotic event, 18 (53%) had the TE during the first 3 days, compared with 1 of 16 patients (6.3%) in the UC group.

AstraZeneca Says Andexxa Will Not Convert To Full Approval, Quietly Reveals Complete Response

13 Dec 2024 • By [Sarah Karlin-Smith](#)

Whether the FDA will seek withdrawal of the anticoagulant-reversal agent or request additional confirmatory data is unclear.

Cost Comparison between PCC and Andexanet

- Retrospective review of 2 NYC hospitals over 4 years
- 126 received PCC due to DOAC (most 50 units/kg)
 - 46 would have met ANNEXA-4 criteria
- 70% with ICH

	PCC (actual)	Andexanet (projected)
Total reimbursement	\$11,492 (4270-136,567)	
Cost	\$5670	\$22,120
Projected amount exceeding reimbursement	0 (0-3643)	\$7,604 (0-36,539)

Warfarin Reversal

Warfarin Hemorrhage Management

- 4-Factor PCC (Kcentra) approved 4/2013
- Randomized trial 216 acute major hemorrhage

	4-Factor PCC	Plasma	Significance
Effective hemostasis	72%	65%	NI
INR $\leq$ 1.3 at 30 min	62%	10%	Superior
Thromboembolism	7.8%	6.4%	
Fluid Overload	4.9%	12.8%	

Network Meta-analysis of Warfarin Reversal 7 Randomized Controlled Trials

	4-Factor PCC vs Plasma
INR Correction	OR 13.54 (7.59–24.15)
Reversal of anticoagulation	OR 1.89 (0.83–4.30)
Circulatory Overload	OR 0.3 (0.13–0.69)
Thromboembolism	OR 1.03 (0.48–2.23)
Mortality	OR 0.7 (0.22–2.24)

No difference in RBC transfused, length of stay in ED or hospital

4-Factor PCC- Warfarin Reversal

Pre-Treatment INR	2- <4	4-6	>6
Dose (Units of Factor IX)/ kg	25 U/kg	35 U/kg	50 U/kg
Max Dose	2500 U	3500 U	5000 U

- Administered at ~3 Units/kg/min
- Not approved for repeat dosing
 - Give with Vitamin K

Fixed Dose of PCC for Warfarin reversal

- Meta-analysis of 10 studies, 988 patients
- Fixed dose 500 units-2000 units

	Fixed dose	Variable dose	RR (95% CI)
Mortality	12.6%	19.6%	0.65 (0.47-0.9)
Thrombosis	2%	1.5%	1.1 (0.44-2.8)
Goal INR reached	70%	81%	0.87 (0.78-0.96)
Baseline INR<4			0.72 (0.48-1.08)
Order to needle time	68 min	88 min	-22.5 min (-31to -13)

Antidotes to Anticoagulation Therapy

When and How to Use

When → Hemorrhage or emergent procedure +
Clinically relevant drug concentrations

1. Last dose known & PK of drug
2. Laboratory testing

How

Dabigatran → idarucizumab bolus

Apixaban & Rivaroxaban → andexanet alfa (bolus, infusion)

Prothrombin complex concentrate (bolus)

Warfarin → prothrombin complex concentrate

Summary

- Mechanism of action of anticoagulants differ
- The last dose of DOAC and metabolism will influence management of hemorrhage.
 - Half life ~12 hours
- Identify which laboratory tests can be used to determine if clinically relevant amount of DOACs are present
 - Dabigatran (elevated aPTT or TT); Rivaroxaban or apixaban (anti-Xa)
- Understand available antidotes and prohemostatic medications for management of anticoagulation associated hemorrhage
 - Specific antidotes: idarucizumab (dabigatran) or andexanet alfa (rivaroxaban or apixaban), PCC (warfarin)
 - Prohemostatic medications: prothrombin complex concentrates