Anticoagulants: Pharmacology, and Reversal

Lisa Baumann Kreuziger, MD, MS

Investigator, Blood Research Institute

Medical Director, Versiti

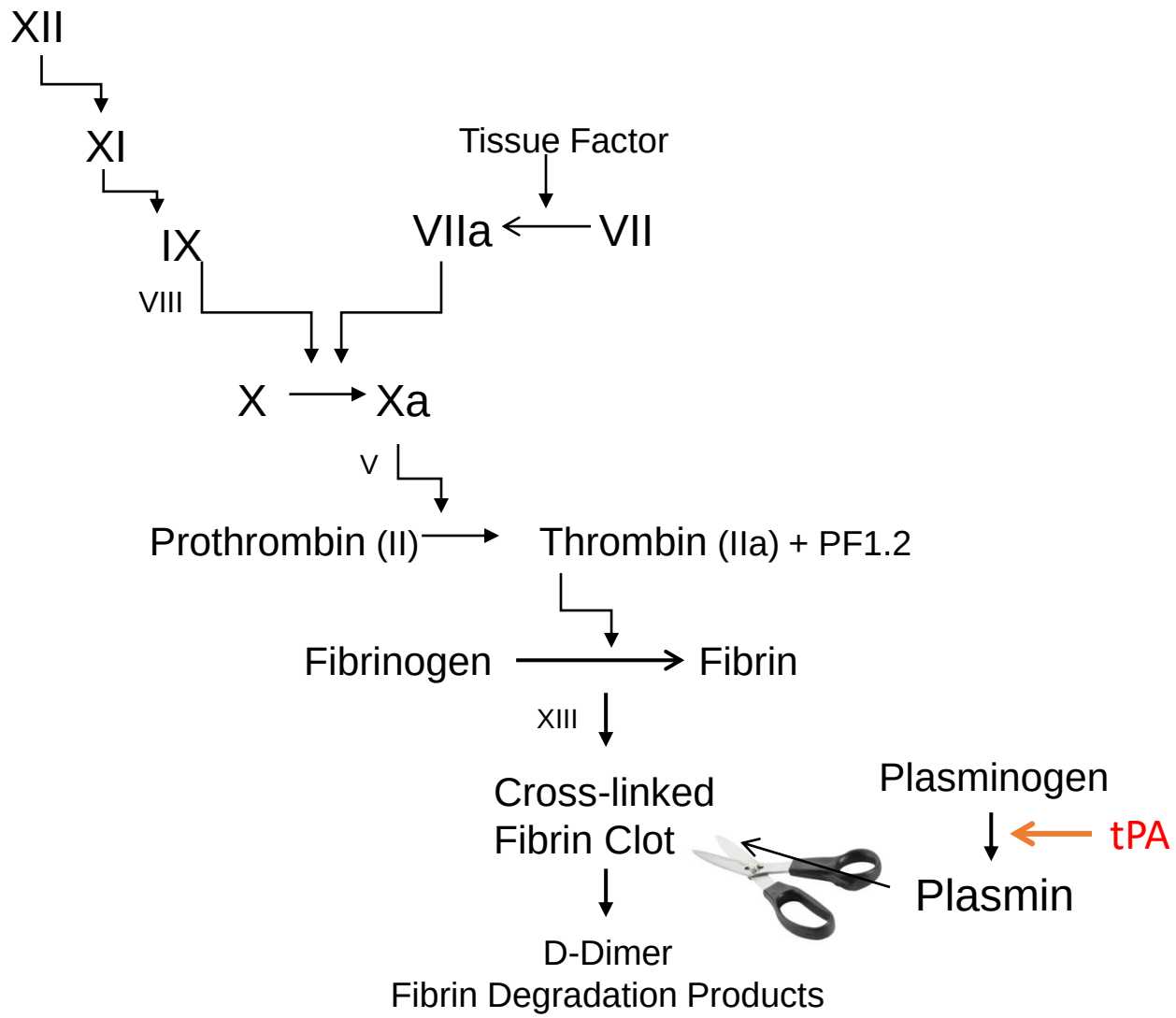
Professor, Medical College of Wisconsin

lisakreuziger@versiti.org

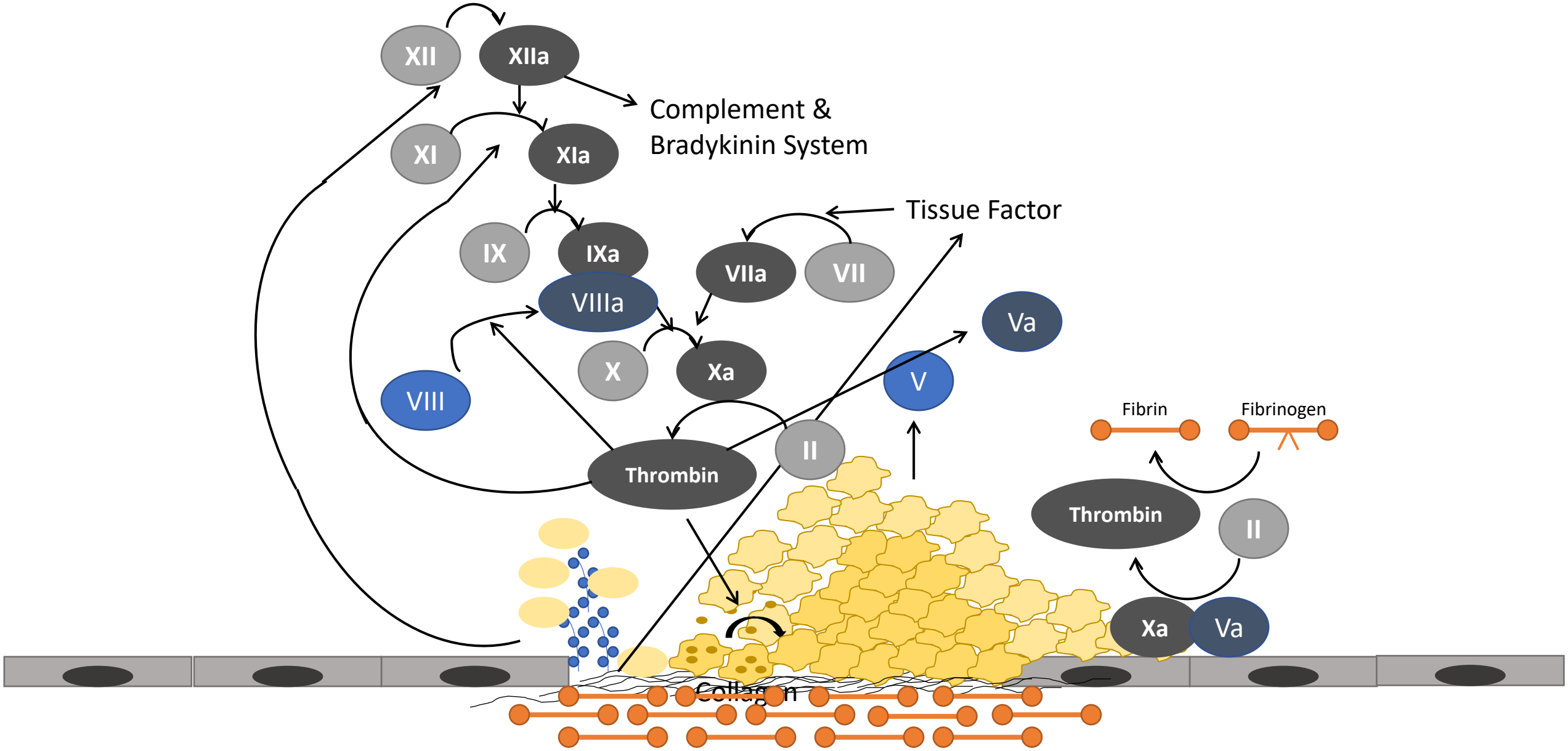
Outline

- Review of coagulation system
  - Anticoagulant mechanism of action
- DOACs (dabigatran, rivaroxaban, apixaban, edoxaban)
  - Clinical Trial Evidence
  - Hemorrhage Management
- Management of Hemorrhage with warfarin

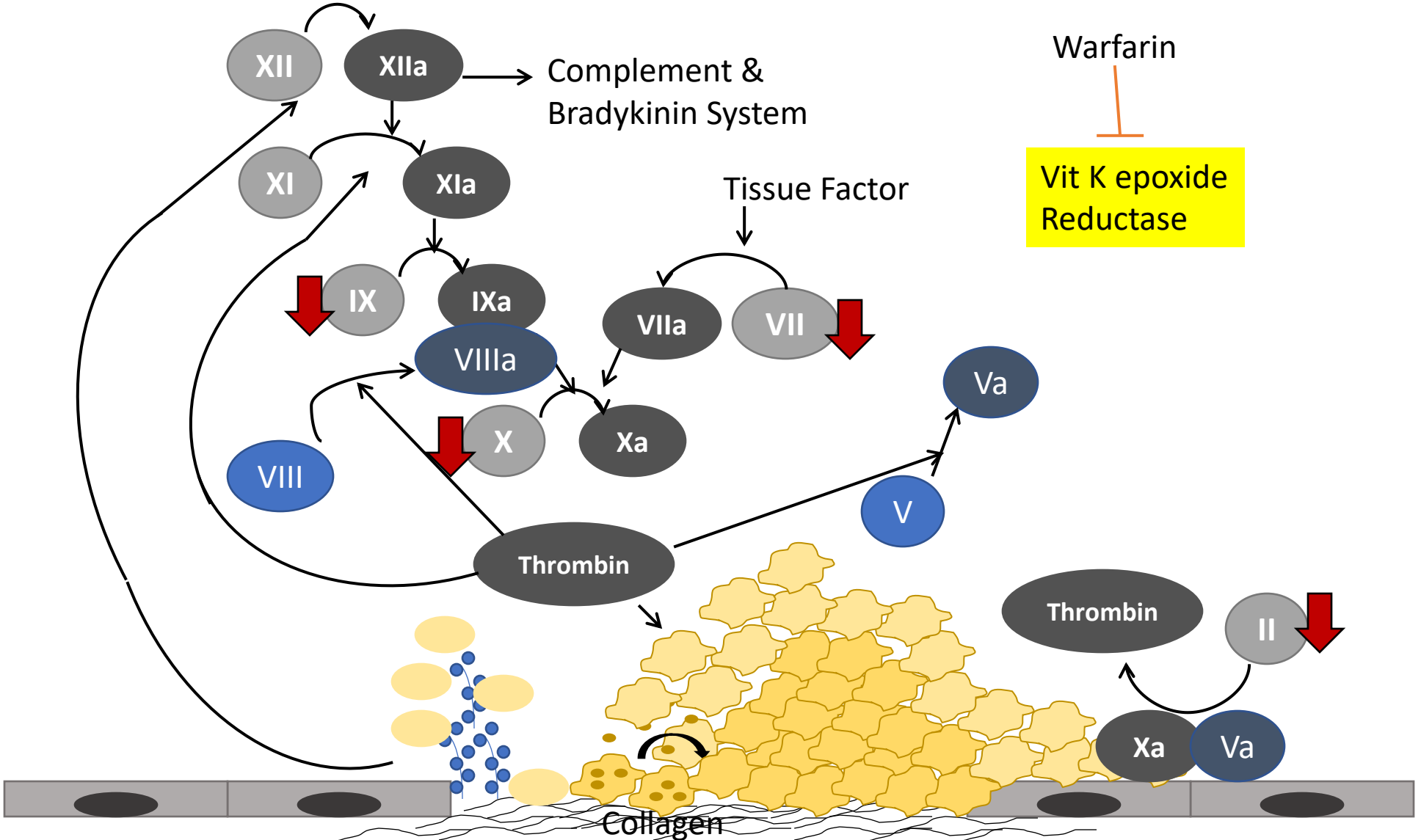
Coagulation System



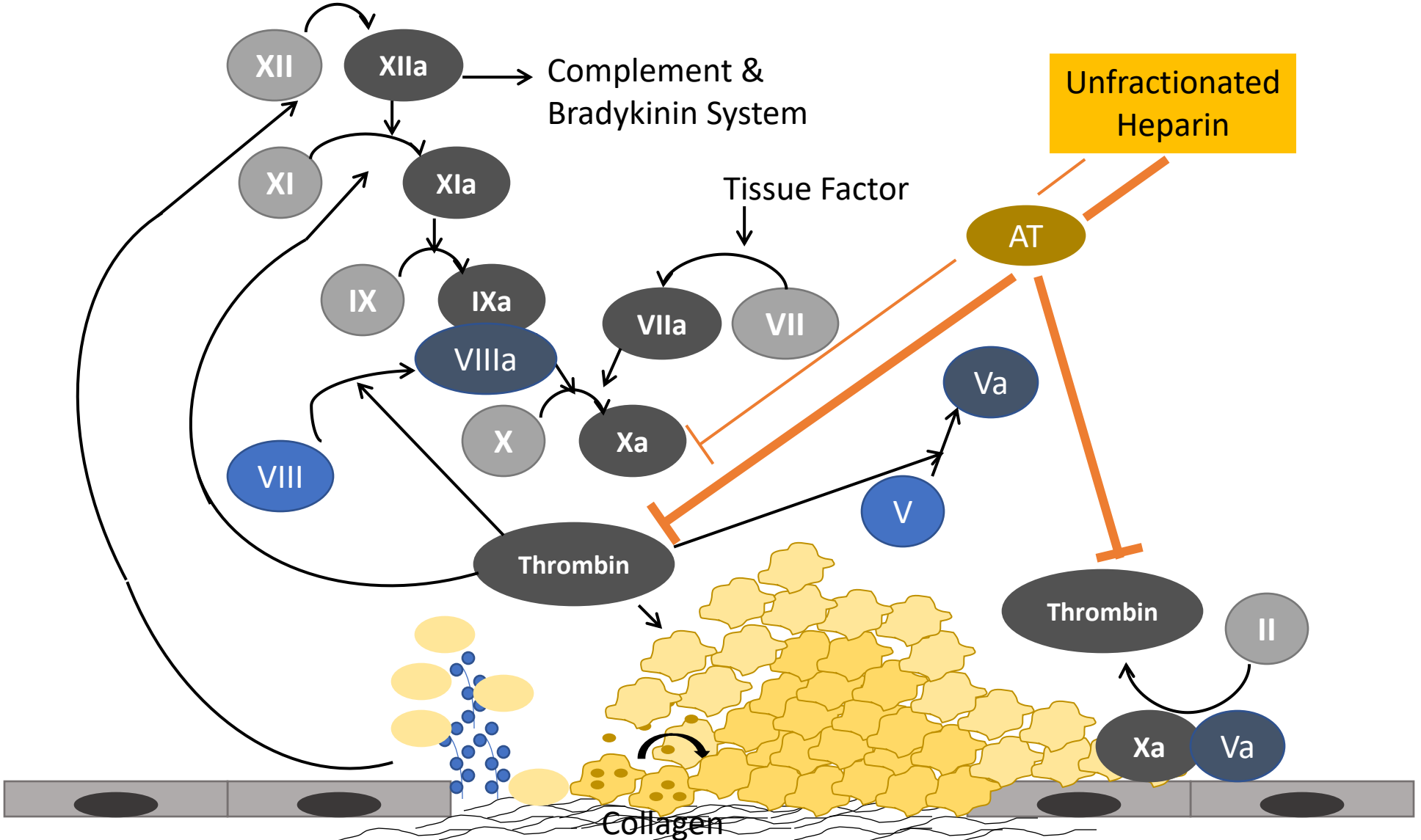
Coagulation system



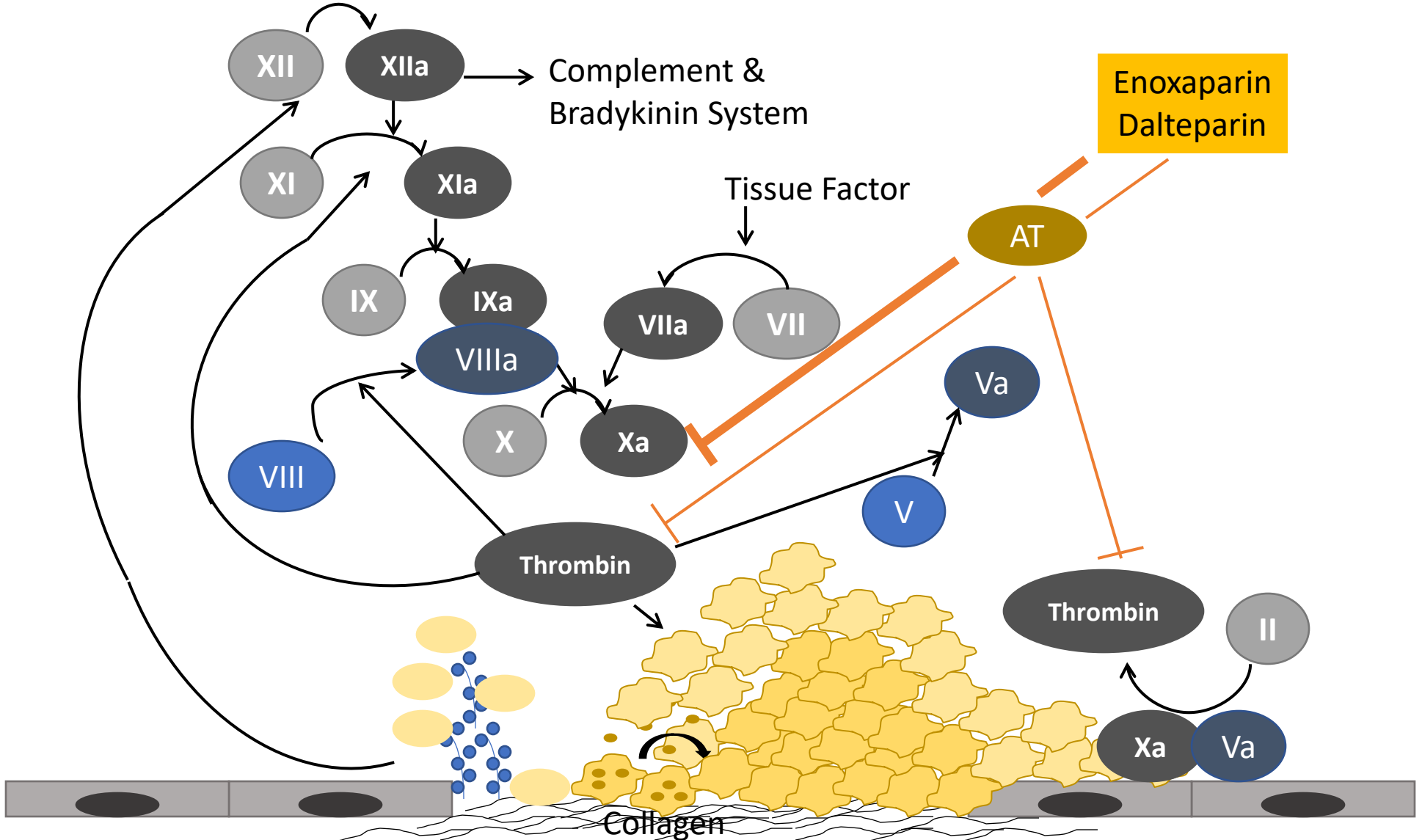
Warfarin Mechanism of Action



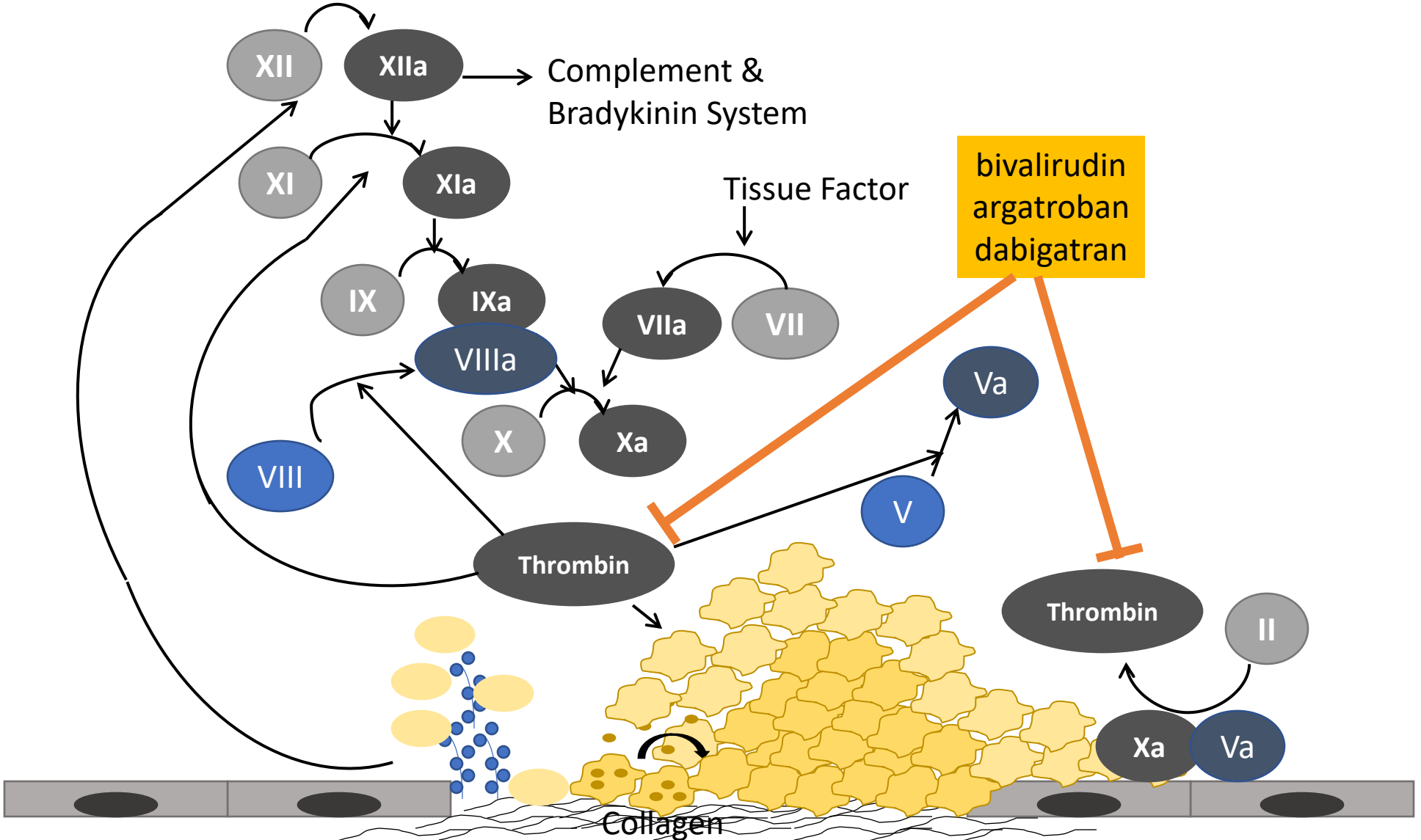
Heparin Mechanism of Action



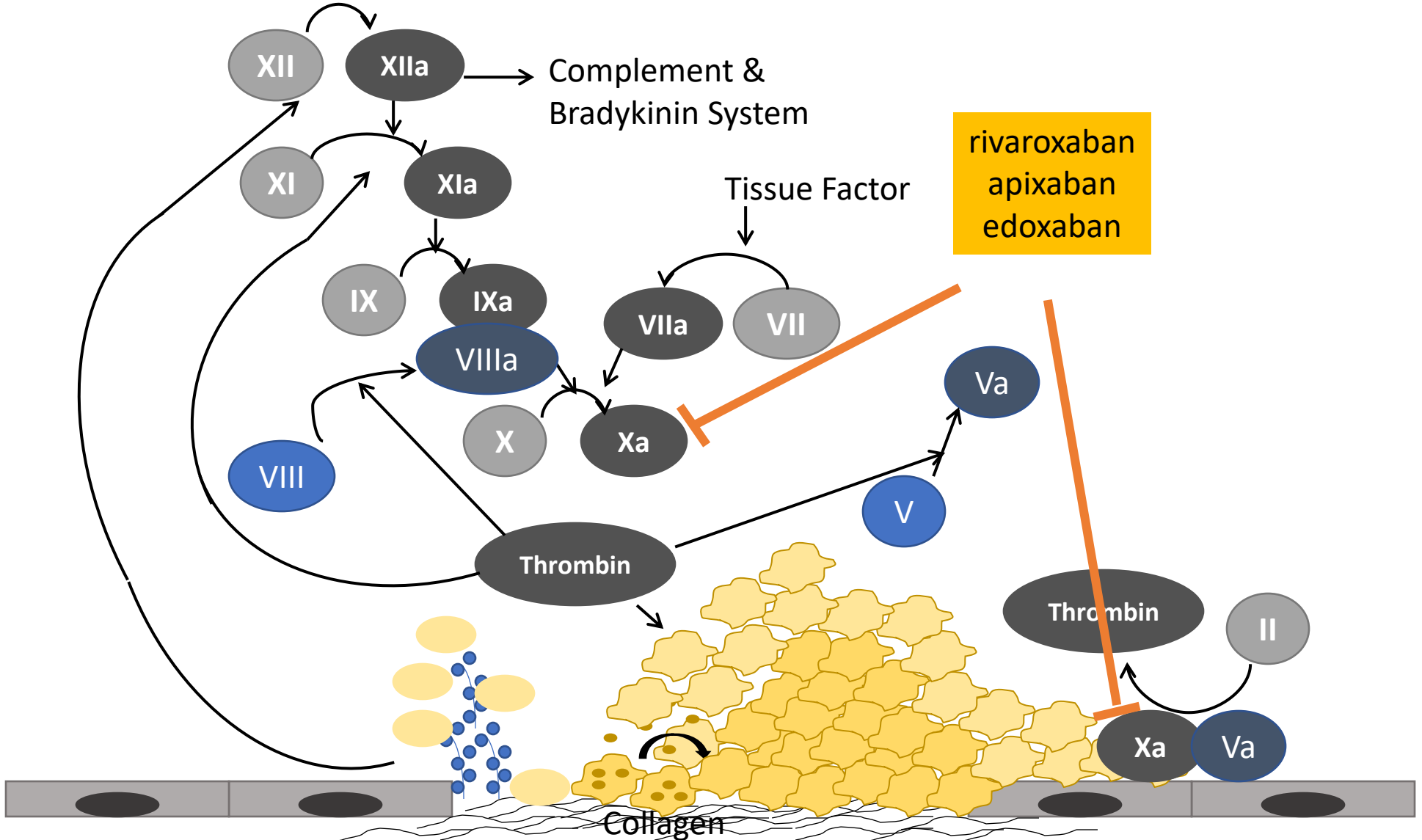
LMWH Mechanism of Action



Direct Thrombin Inhibitor Mechanism of Action



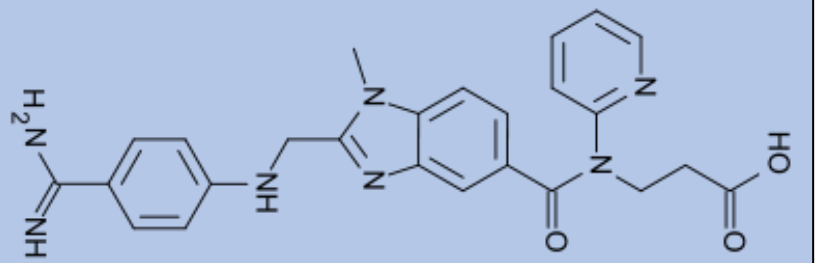
Direct Oral Anticoagulant Mechanism of Action



Direct Oral Anticoagulants

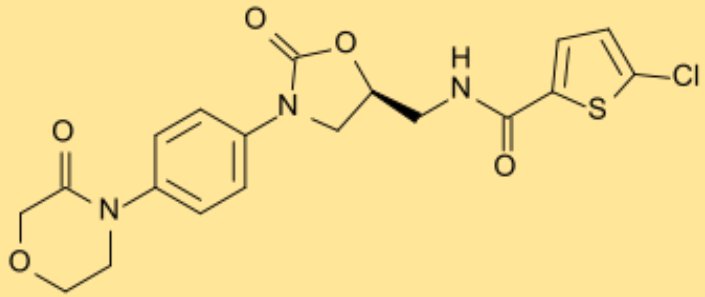
Dabigatran – *Pradaxa*

(Boehringer Ingelheim)



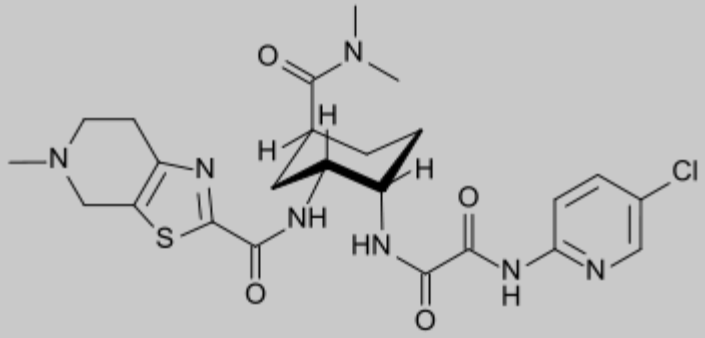
Rivaroxaban – *Xarelto*

(Janssen)



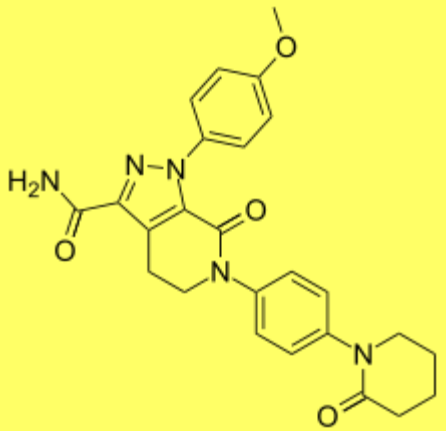
Edoxaban – *Savaysa*

(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

Harder & Graff. EJCP 2013; 69: 1617

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/2011/022512s007lbl.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/2011/022512s007lbl.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

Patel et al. NEJM 2011; Majeed et al. Circ 2013; Granger et al. NEJM 2011; Giugliano et al. NEJM 2013. Adapted from Dr. Deborah Siegal.

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

Harder & Graff. EJCP 2013; 69: 1617.

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

JAMA Intern Med. doi:10.1001/jamainternmed.2019.2431

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

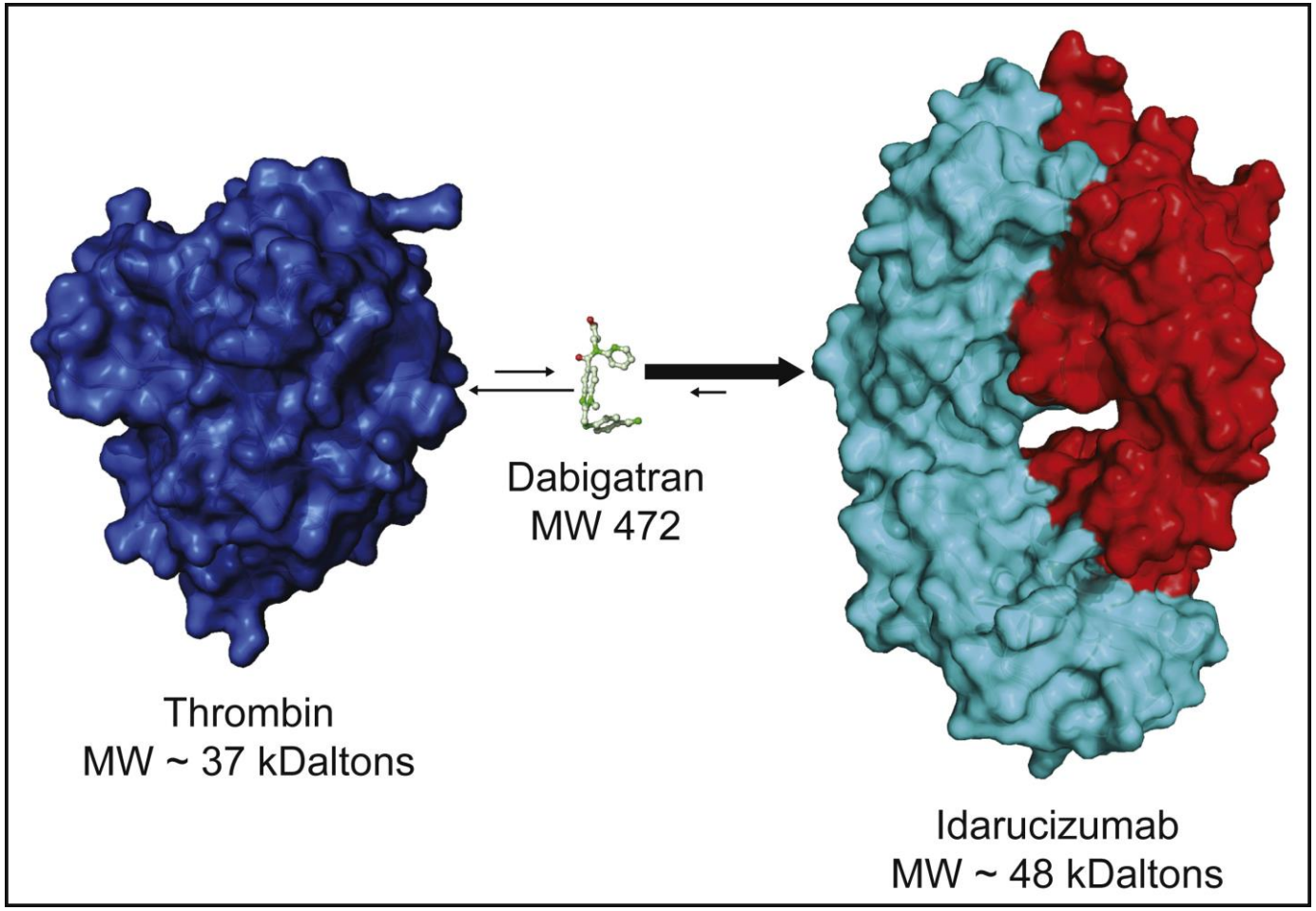
- Dabigatran
  - Peak: aPTT ~2x baseline, Trough: aPTT 1.5x Baseline
  - PT/INR relatively insensitive
  - TT very sensitive
    - If TT normal→ No dabigatran is present
- Xa Inhibitors
  - PT/INR sensitivity varies between labs
  - PTT relatively insensitive
  - Anti-Xa assay can be calibrated

Lindahl TL, et al. *Thromb Haemost* 2011; 105: 371-379; Van Rynn et al. *Thromb Haemost* 2010; 103: 116-1127.
Hillarp A, et al. *J Thromb Haemost* 2011; 9: 133-139.

DOAC Antidotes

Idarucizumab

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

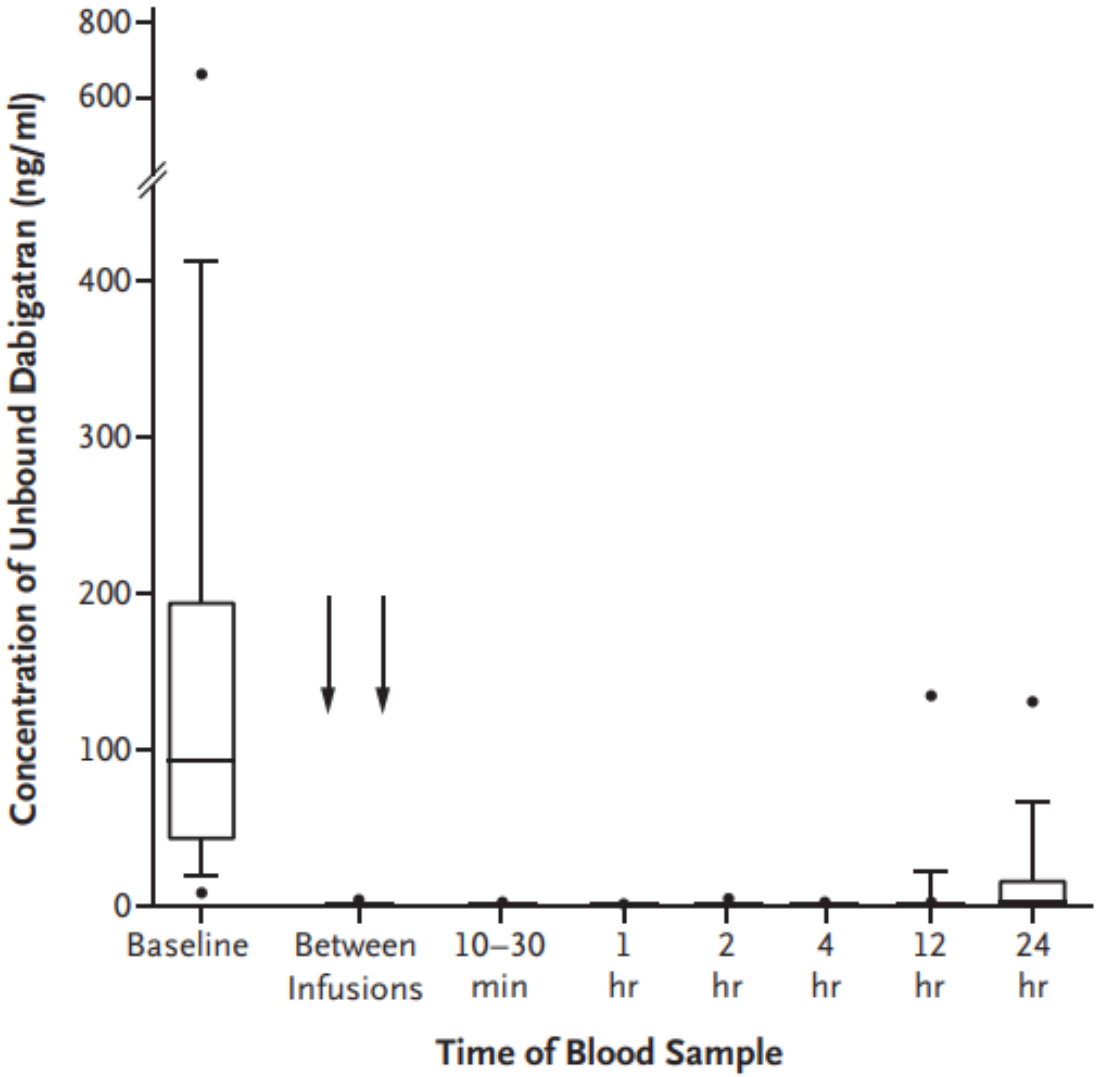


http://creativecommons.org/licenses/by-nc-nd/4.0/).The American Journal of Medicine (2016) 129, S64-S72

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

Concentration of unbound dabigatran



N Engl J Med 2015;373:511-20. N Engl J Med 2017; 377:431-441.

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

N Engl J Med 2015;373:511-20. N Engl J Med 2017; 377:431-441.

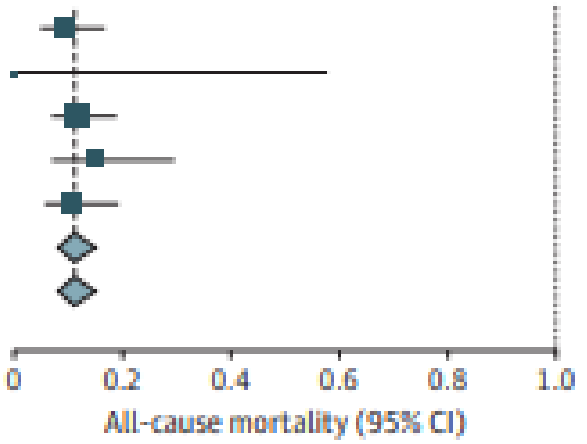
Meta-analysis of Intracranial Hemorrhage

- 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%)

C Idarucizumab

Study	Cases, No.	Total, No.	All-cause mortality (95% CI)
Pollack et al,[12] 2017	9	98	0.09 (0.05-0.17)
Sheikh-Taha et al,[53] 2019	0	6	0.00 (0.00-0.58)
Singh et al,[54] 2020	13	112	0.12 (0.07-0.19)
Kermer et al,[55] 2020	6	40	0.15 (0.07-0.30)
Yasaka et al,[56] 2020	9	84	0.11 (0.06-0.19)
Common-effect model		340	0.11 (0.08-0.15)
Random-effects model			0.11 (0.08-0.15)

Heterogeneity: $\tau^2 = 0$; $\chi^2_4 = 1.12$ ($P = .89$); $I^2 = 0\%$



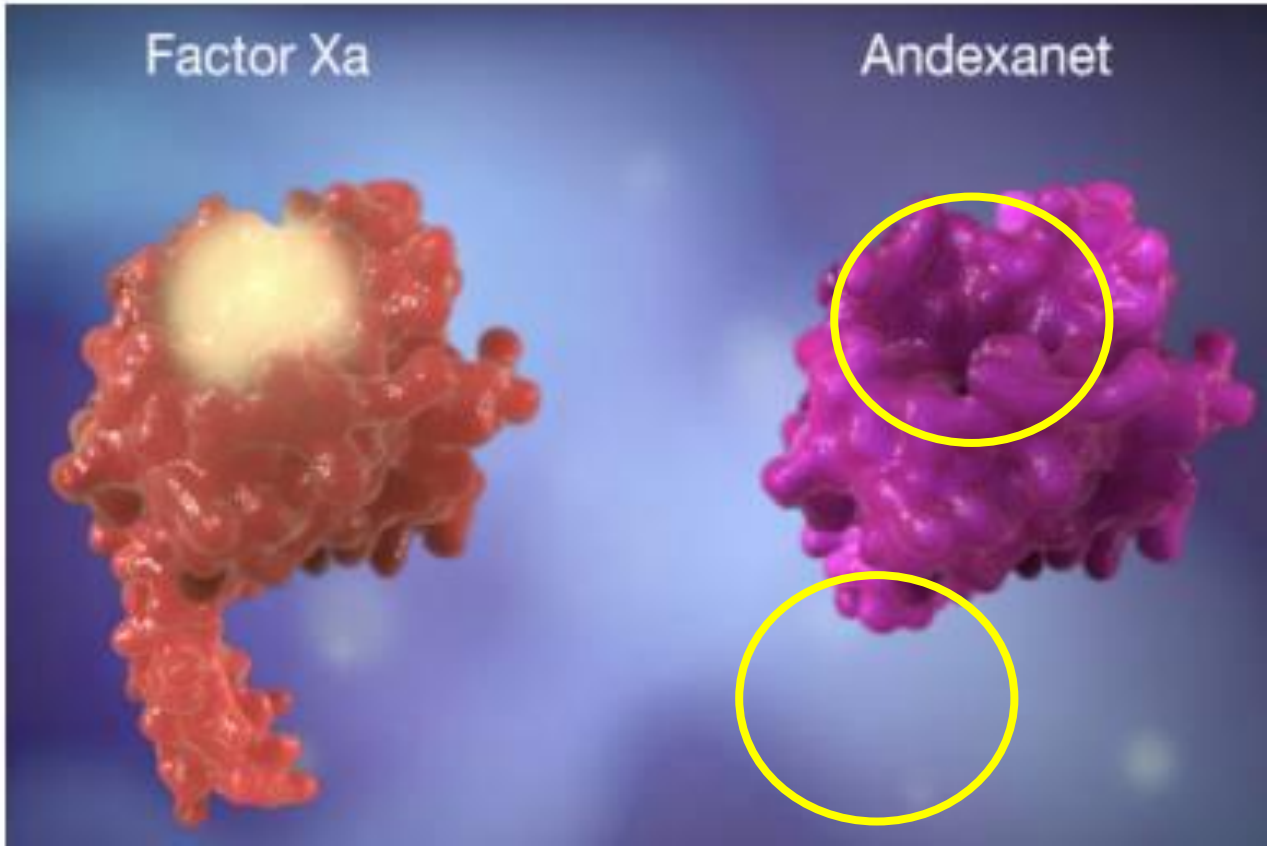
JAMA Network Open. 2022;5(11):e2240145. doi:10.1001/jamanetworkopen.2022.40145

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



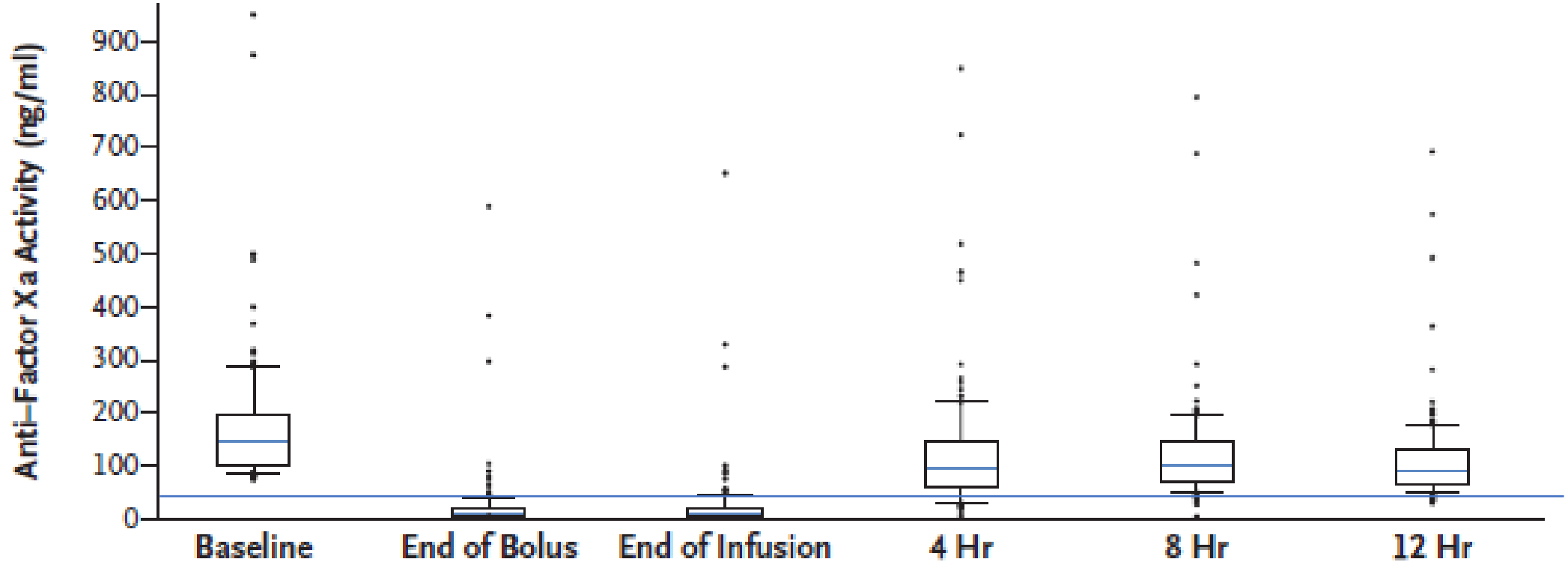
Lu et al. Nat Med 2013 Apr;19(4):446-5. West J Emerg Med. 2016;17(3):264–270. open access at http://escholarship.org/uc/uciem_westjem

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

N Engl J Med. 2019 Apr 4;380(14):1326-1335

Reduction in anti-Xa activity apixaban



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	149.7	11.1	11.5	97.2	104.6	91.2
Percent Change (95% CI)		−92 (−93 to −91)	−92 (−93 to −91)	−32 (−38 to −29)	−34 (−36 to −27)	−38 (−41 to −34)

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

N Engl J Med. 2019 Apr 4;380(14):1326-1335

Andexanet Alfa ANNEXA-4 Study

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

- FDA Approved May 2018

N Engl J Med. 2019 Apr 4;380(14):1326-1335.

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

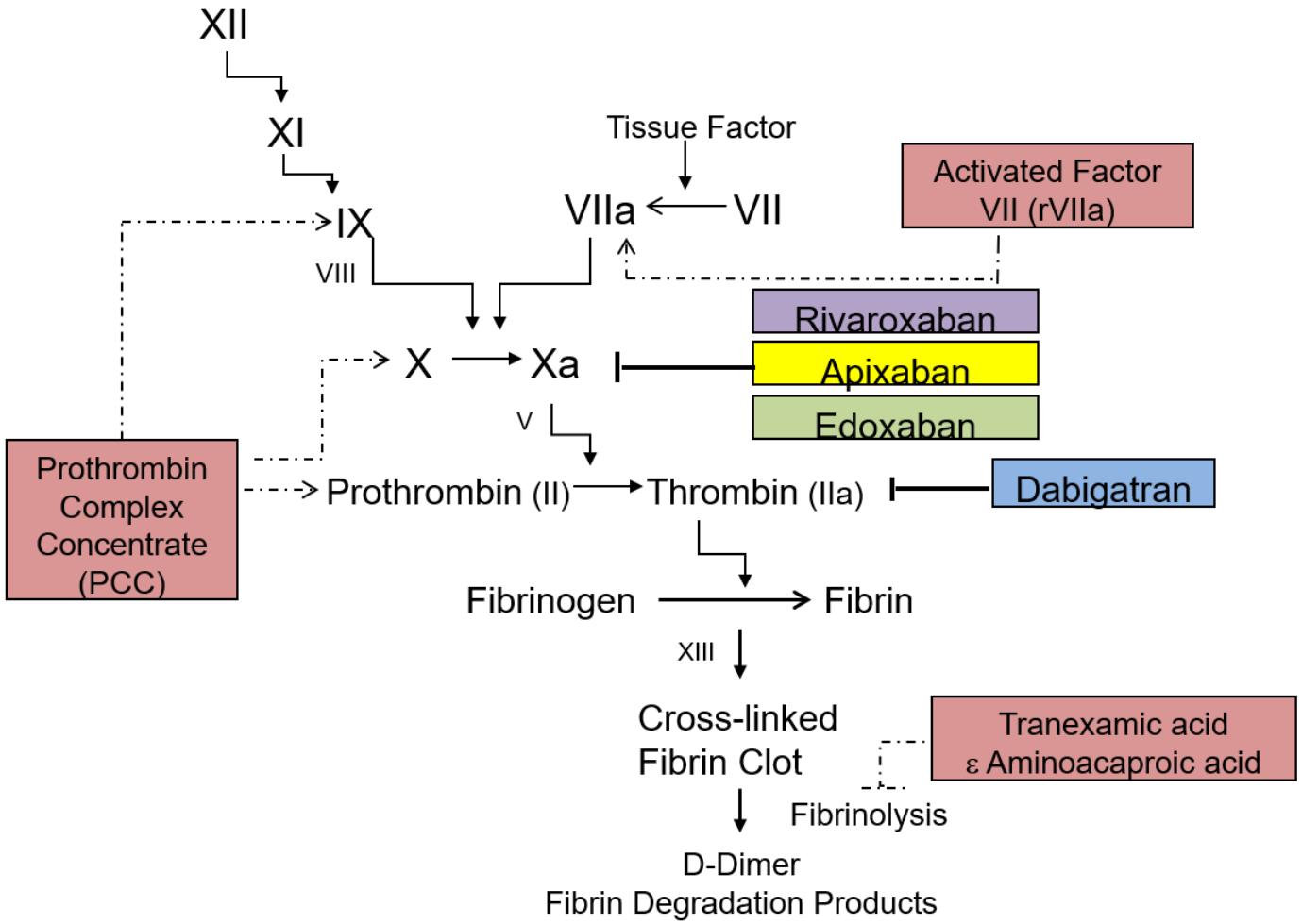
- Bolus + 2-hour infusion

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 ≠ DOAC Antidote



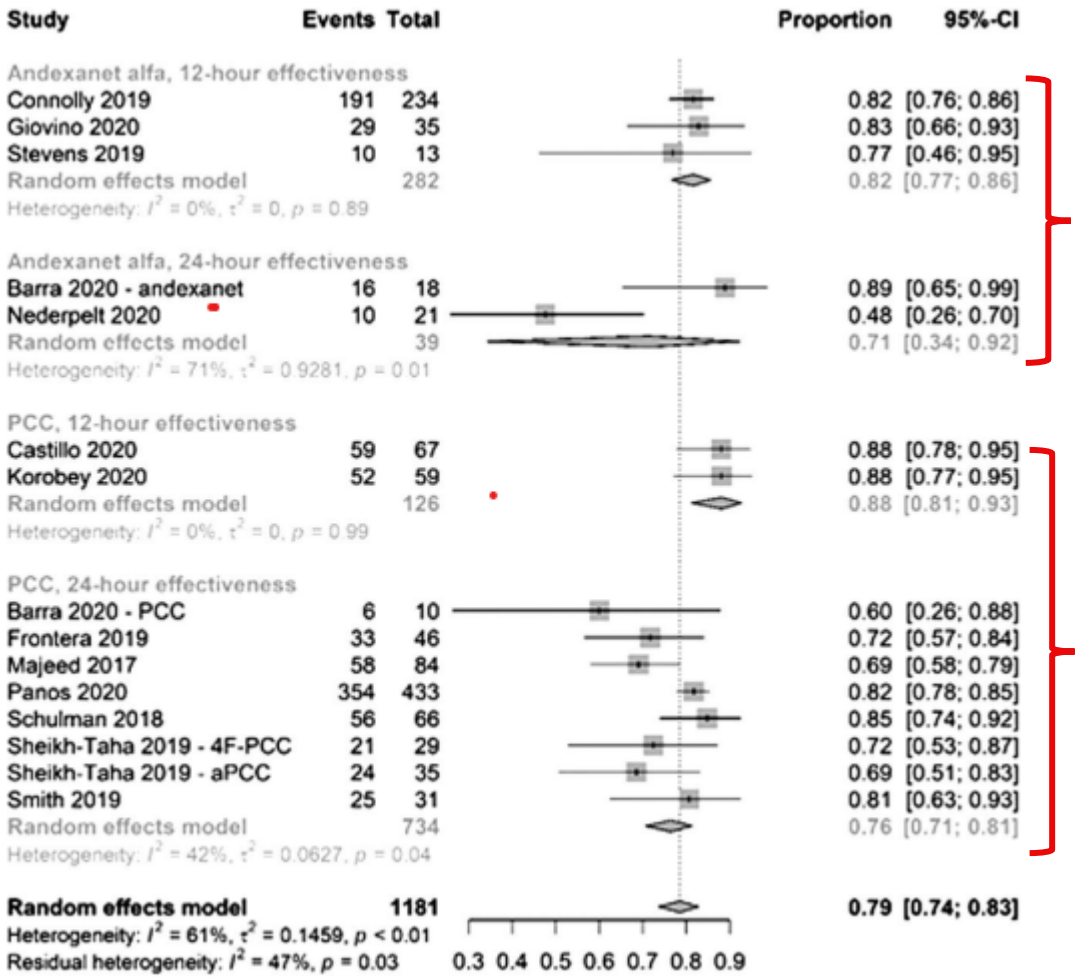
Significant amount of in-vitro and animal model data using these agents in patients treated with DOAC with inconsistent results

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

Crit Care Med. 2021 Oct 1;49(10):e1025-e1036. doi: 10.1097/CCM.0000000000005059.

Meta-analysis of Intracranial Hemorrhage

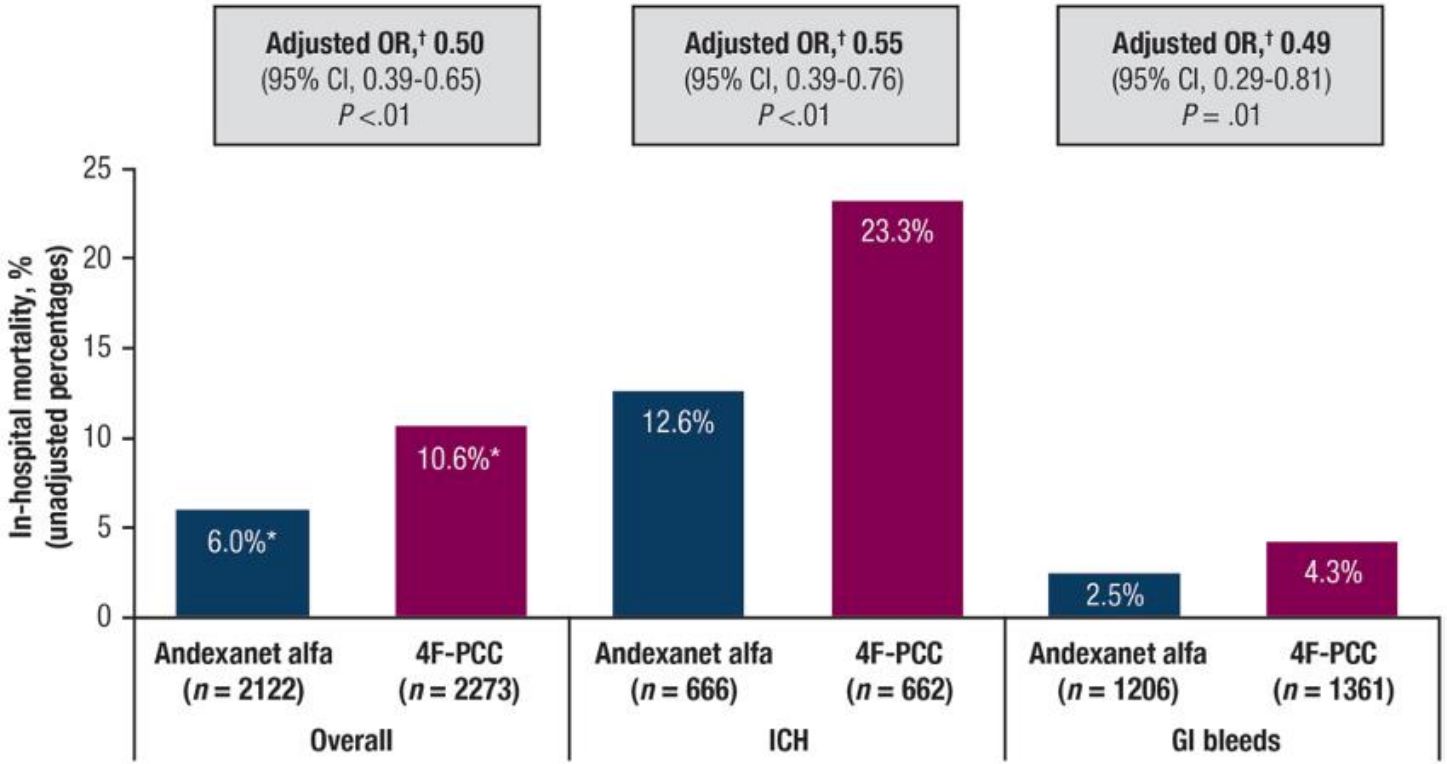
	Andexanet Alfa	4-Factor PCC
Studies, n	17 studies, 525 patients	22 studies, 967 patients
Reversal of anticoagulation	75% (67%-81%)	77% (72%-82%)
Thromboembolism	14% (10%-19%)	8% (5%-12%)
Mortality	24% (16%-34%)	26% (20%-32%)

JAMA Network Open. 2022;5(11):e2240145. doi:10.1001/jamanetworkopen.2022.40145

rpth research & practice in thrombosis & haemostasis

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



https://doi.org/10.1016/j.rpth.2023.102192

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

N Engl J Med 2024;390:1745-55.

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*
	no./total no. (%)		*percentage points*	
Hemostatic efficacy	150/224 (67.0)	121/228 (53.1)	13.4 (4.6 to 22.2)	0.003
Hematoma volume change ≤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)	

N Engl J Med 2024;390:1745-55.

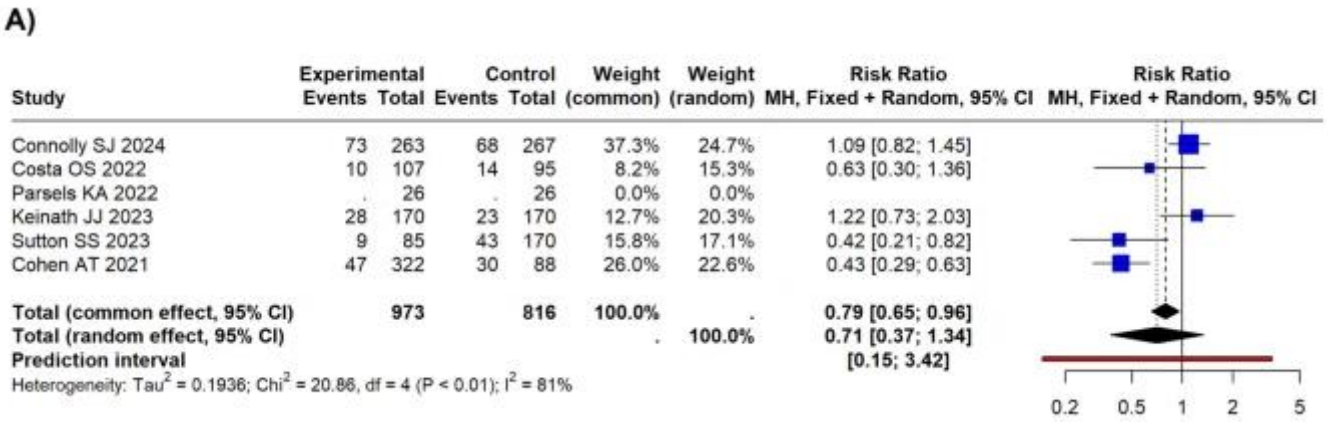
Andexanet had more ischemic strokes

Table 3. Thrombotic Events and Deaths at 30 Days.*

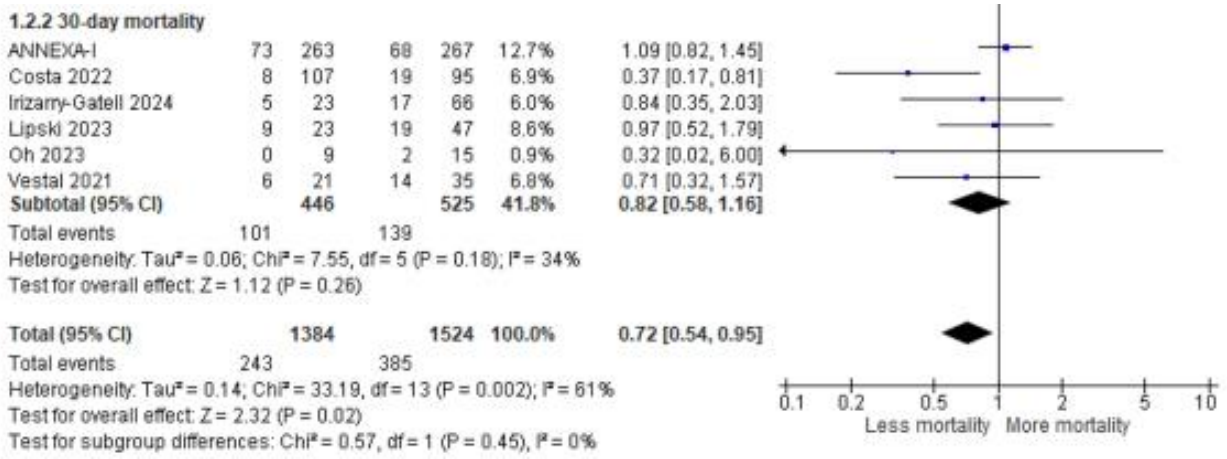
Event	Andexanet (N=263)	Usual Care (N=267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (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

First of many meta-analysis to come

Meta-analysis of mortality
RCT or propensity-matched studies



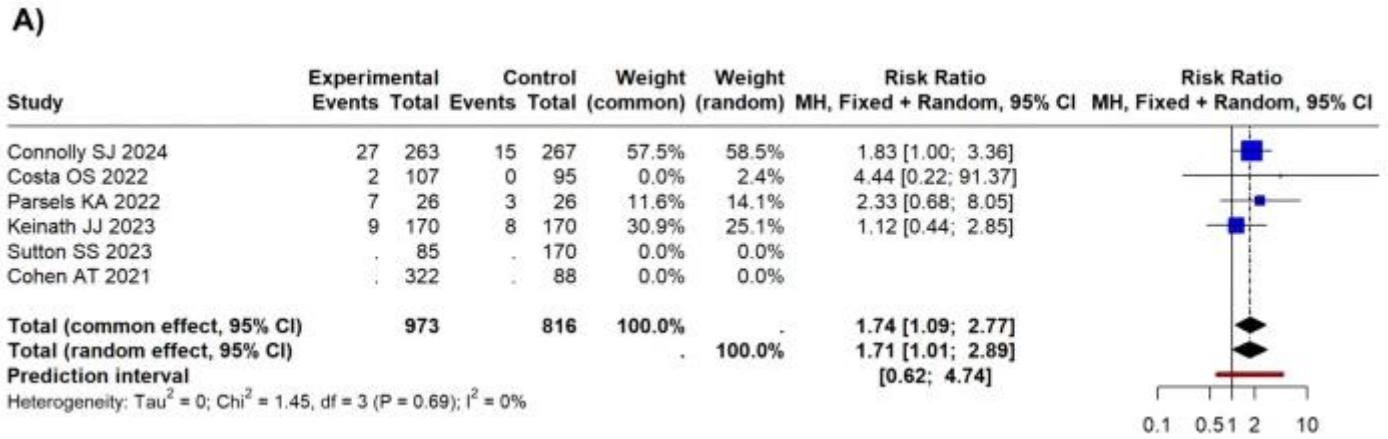
Meta-analysis of mortality in ICH



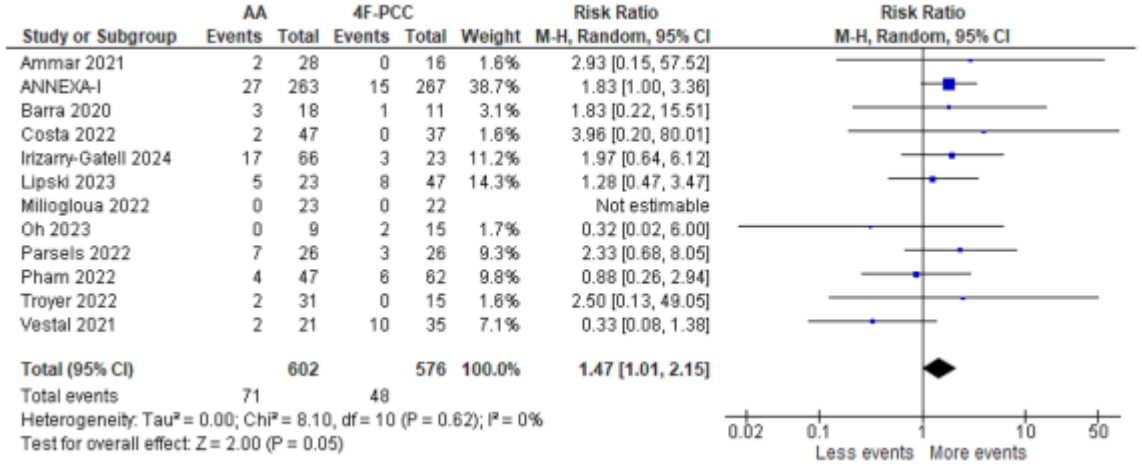
Crit Care. 2024;28:221. Neurocrit Care https://doi.org/10.1007/s12028-024-02130-y.

Meta-analysis agree about increased thrombosis

Meta-analysis of thrombosis
RCT or propensity-matched studies



Meta-analysis of thrombosis in ICH



Crit Care. 2024;28:221. Neurocrit Care https://doi.org/10.1007/s12028-024-02130-y.

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)

Journal of Thrombosis and Thrombolysis (2020) 49:121–131

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≤ 1.3 at 30 min	62%	10%	Superior
Thromboembolism	7.8%	6.4%	
Fluid Overload	4.9%	12.8%	

Sarode, et al. Circulation. 2013 Sep 10;128(11):1234-43

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

JAMA Network Open. 2022;5(11):e2240145. doi:10.1001/jamanetworkopen.2022.40145

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

Kcentra Prescribing Information. http://labeling.cslbehring.com/PI/US/Kcentra/EN/Kcentra-Prescribing-Information.pdf

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)

Cardiovasc Drugs Ther. 2021 Apr 17. doi: 10.1007/s10557-021-07192-0.

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