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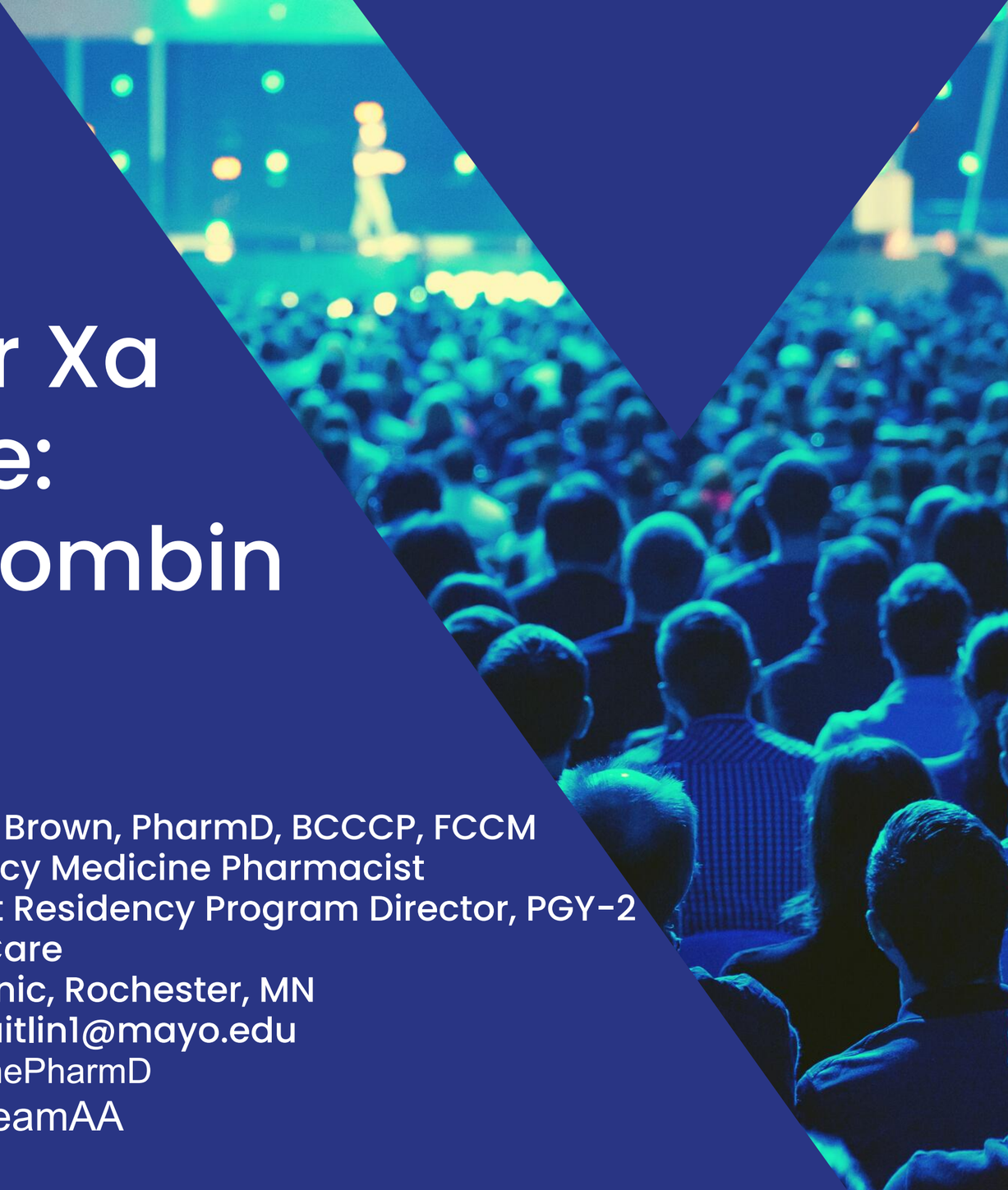

The Clot Thickens: Factor Xa Inhibitor Reversal Debate: Andexanet Alfa or Prothrombin Complex Concentrate?

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Disclosures

BG No relevant financial disclosures or conflicts of interest
CB Has received grant funding from Alexion/Astra Zeneca

Objectives

1) Describe the pharmacological characteristics of andexanet alfa (AA) and four – factor prothrombin complex concentrate (4F-PCC)

2) Compare and contrast literature and guidelines pertaining to hemostatic efficacy and safety of AA and 4F-PCC for life – threatening bleeding in patients on factor Xa inhibitors

3) Develop patient case based treatment plans based upon available literature

What do you currently use for factor Xa inhibitor reversal in your practice?

1) Andexanet Alfa
2) 4F-Prothrombin Complex Concentrate
3) Other

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4F-PCC – Efficacy

If you chose 4F-PCC why do you use it over Andexanet Alfa?

Baker's Not Mad Just Disappointed You're Thinking of AA over PCC

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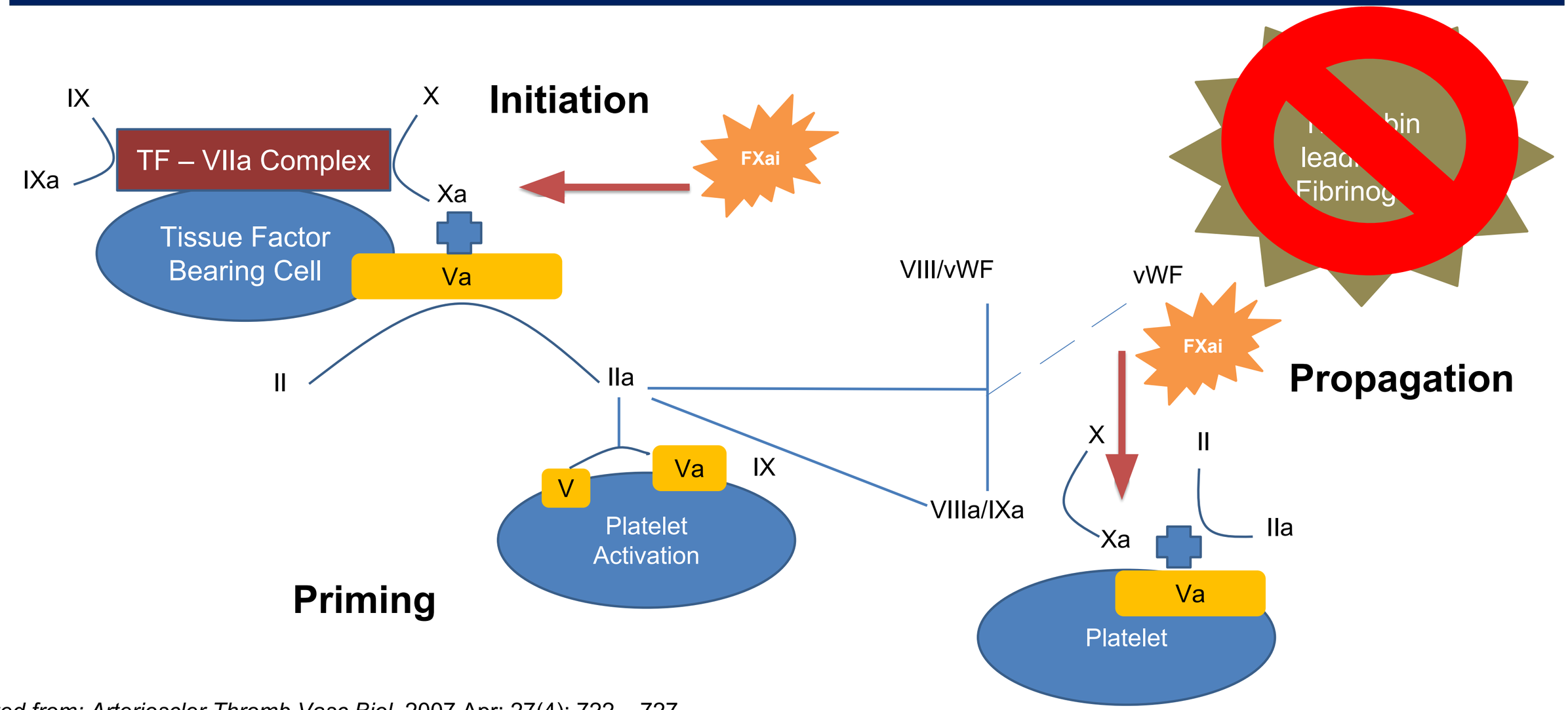
Quick Overview of Factor Xa Inhibitors (#NoClottingCascade)



Adapted from: Arterioscler Thromb Vasc Biol. 2007 Apr; 27(4): 722 – 727.
Tanaka. *Transfus Med Rev*. 2021 Oct; 35(4): 96 – 103.

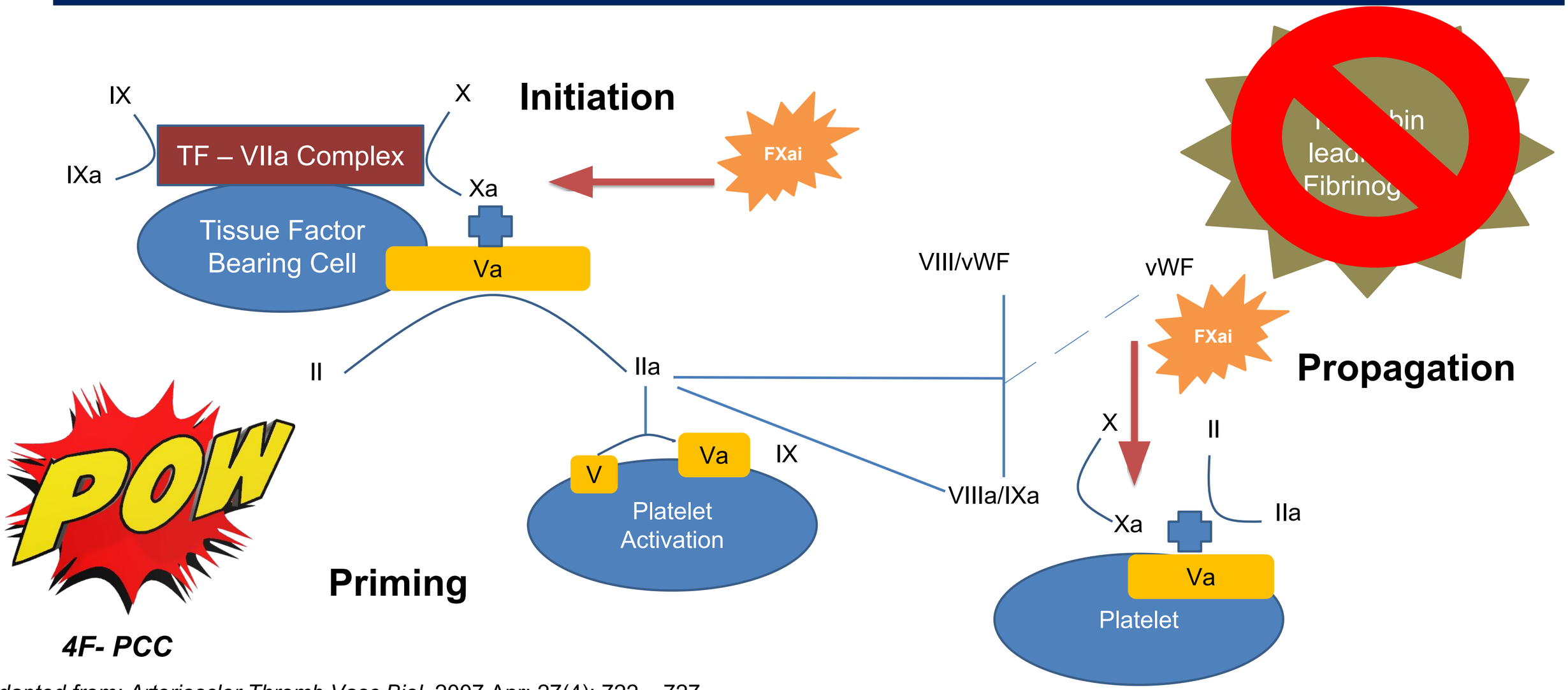
4F-PCC Contents

Component	Content	Half – Life
Factor II	380 – 800 units	60 hours
Factor VII	200 – 500 units	5 hours
Factor IX	400 – 620 units	18 hours
Factor X	500 – 1020 units	36 hours
Protein C	420 – 820 units	8 hours
Protein S	240 – 680 units	30 hours
Heparin	8 – 40 units	90 minutes

Per ~500 unit vial of Kcentra® (prothrombin complex concentrate human)

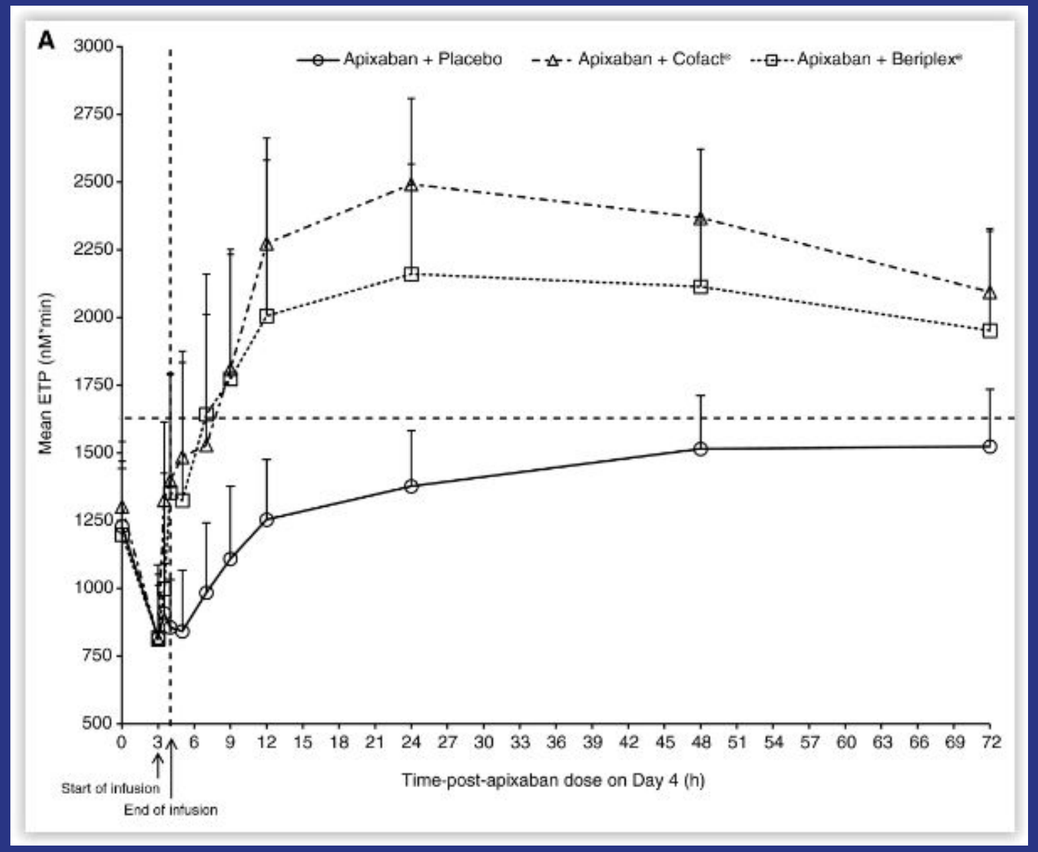
Kcentra (prothrombin complex concentrate human) [prescribing information]. Kankakee, IL: CSL Behring; October 2018.

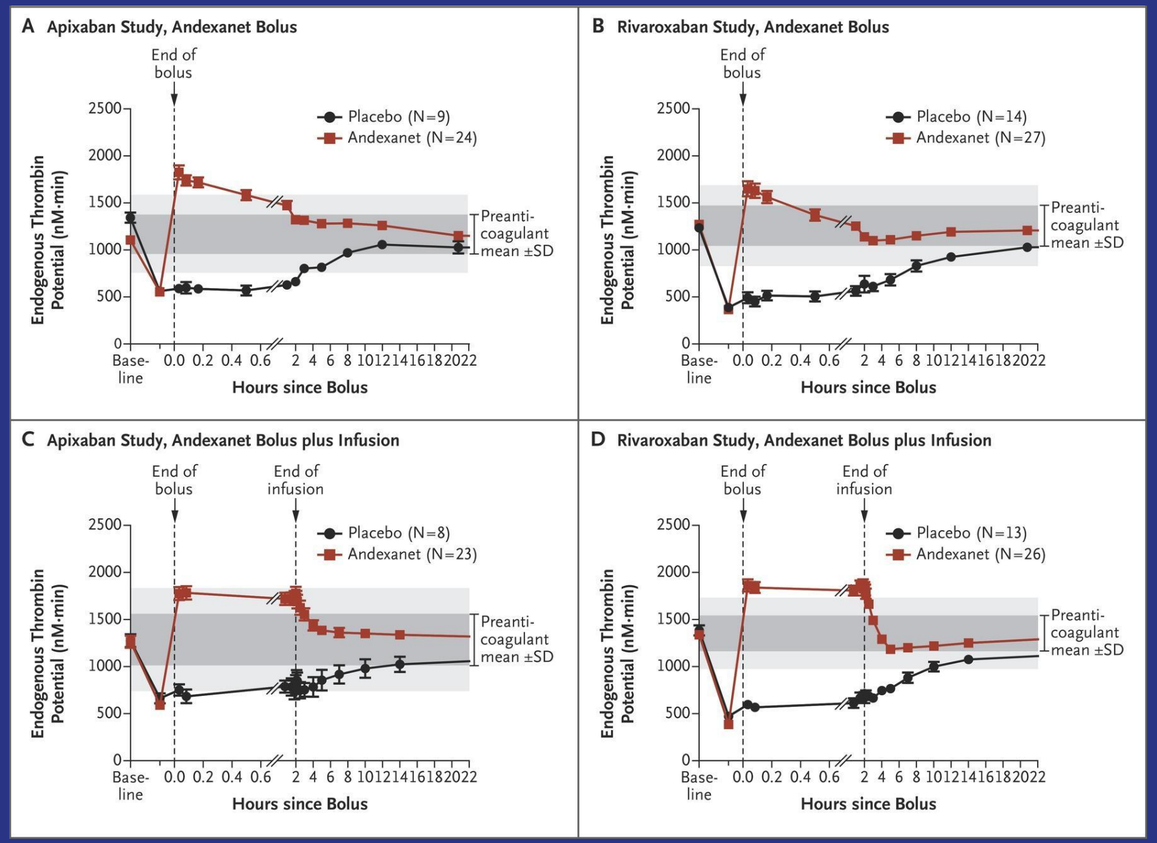
4F-PCCs Hemostatic Effects on Factor Xa Inhibitors



Adapted from: Arterioscler Thromb Vasc Biol. 2007 Apr; 27(4): 722 – 727.
Tanaka. *Transfus Med Rev*. 2021 Oct; 35(4): 96 – 103.

4F-PCC vs. Andexanet Alfa Effects on Thrombin Generation





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Song. *J Thromb Haemost*. 2017 Nov; 15(11): 2125 – 2137.
Siegal. *N Engl J Med*. 2015 Dec 17; 373 (25): 2413 – 2424.

4F-PCC vs. Andexanet Alfa in the Field

Nederpelt. *Crit Care Med*. 2021 Oct 1; 49 (10): e1025 – e1036.	
Patients	Studies evaluating management of factor Xa inhibitor – associated hemorrhage
Intervention	Meta – analysis of the two interventions comparing hemostatic effectiveness using ISTH criteria for 12 and 24 hours, and in – hospital mortality
Comparison	Andexanet alfa vs. PCC
Outcomes	A total of 554 unique entries was evaluated with 21 being included for a total of 1376 patients; 5 were prospective and 17 retrospective; median age was 77 in AA group and 76 in PCC group; majority of patients suffered an ICH (68.9% in AA vs. 87.7% in PCC); the primary indication for anticoagulation was atrial fibrillation; the majority of patients received a PCC dose of ≥ 30 units/kg (53.4%) where as patients in the AA group primarily received the lower dose algorithm (84%); antiplatelet use was similar between both groups with 35.9% in the AA group compared to 32.8% in the PCC group Mean hemostatic effectiveness for AA was 82% at 12 hours vs. 71% at 24 hours compared to PCC with 88% effectiveness at 12 hours and 76% at 24 hours ICH patients: 57% at 12 hours for AA, 89% at 24 hours vs. 88% at 12 hours for PCC, 73% at 24 hours Mean in – hospital mortality was 23.3% for AA compared to 15.8% for PCC
Conclusion	No available evidence supporting one agent over the other to manage factor Xa inhibitor – associated hemorrhage; non – commercially biased authorship

* ISTH, International Society of Thrombosis and Hemostasis; ICH, intracranial hemorrhage

Guideline Recommendations

Guideline or Guidance Organization	Recommendation	General Comments
Neurocritical Care Society / Society of Critical Care Medicine	• 4F-PCC 50 units/kg if last dose was in 3-5 half-lives time frame	Prior to AA approval
American College of Emergency Physicians	• AA use over 4F – PCC	Unrestricted educational grants funded by AA maker; literature review did not meet PRISMA standards
American Heart Association/ American Stroke Association	• AA over 4F – PCC (2a vs. 2b)	Unclear rationale why AA recommended over 4F – PCC
Anticoagulation Forum	• AA over 4F – PCC (2,000 units)	Prior to FiX – ICH Study

Frontera. *Neurocrit Care*. 2016 Feb; 24(1): 6 -46.
Baugh. *Ann Emerg Med*. 2020 Oct; 76(4):470 – 485.
Greenberg. *Stroke*. 2022 Jul; 53(7):e282 – 361.
Cuker. *Am J Hematol*. 2019 Jun; 94(6): 697 – 709.

Operational Considerations

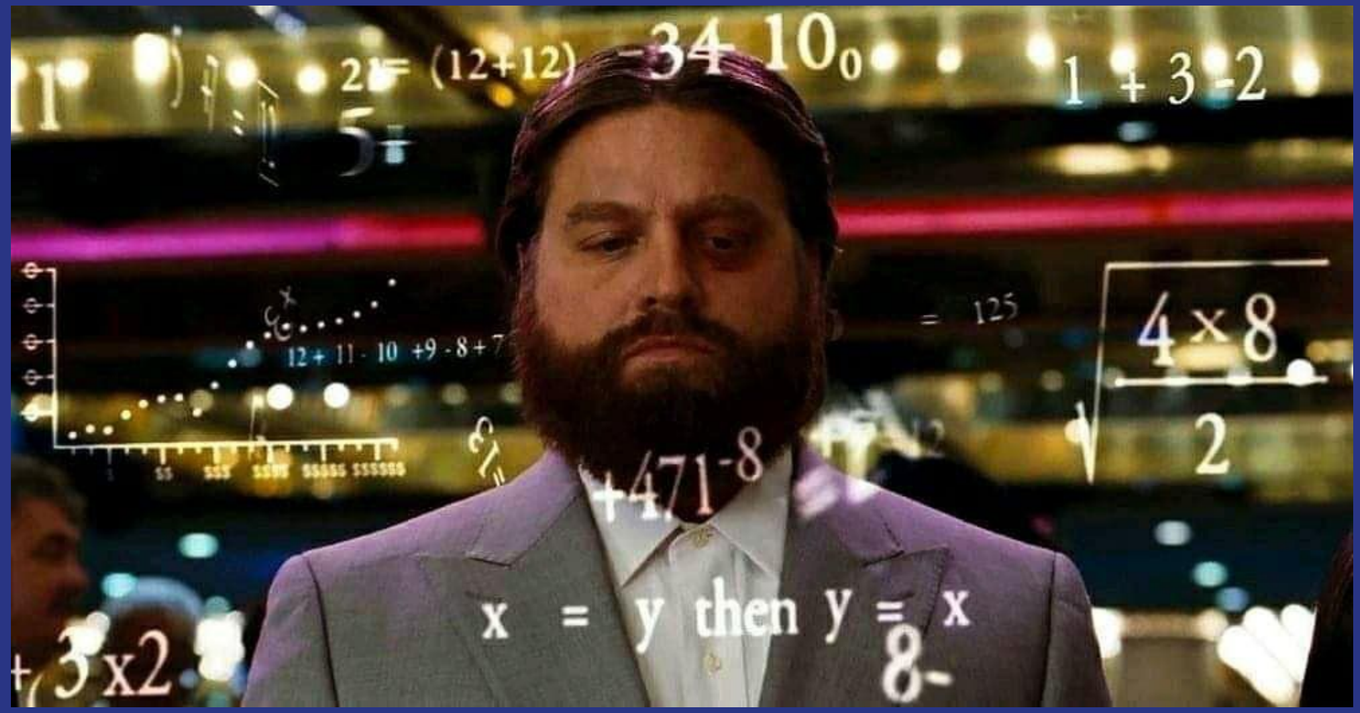
4F-PCC
- Expedited administration
- Usually stocked in ADC
- Easy reconstitution

AA
- Delayed administration
- Not stocked in ADC
- Complicated reconstitution

In this race, the hare wins

ADC, automated dispending cabinet

Live Look at Me Trying To Figure Out How To Dose AA



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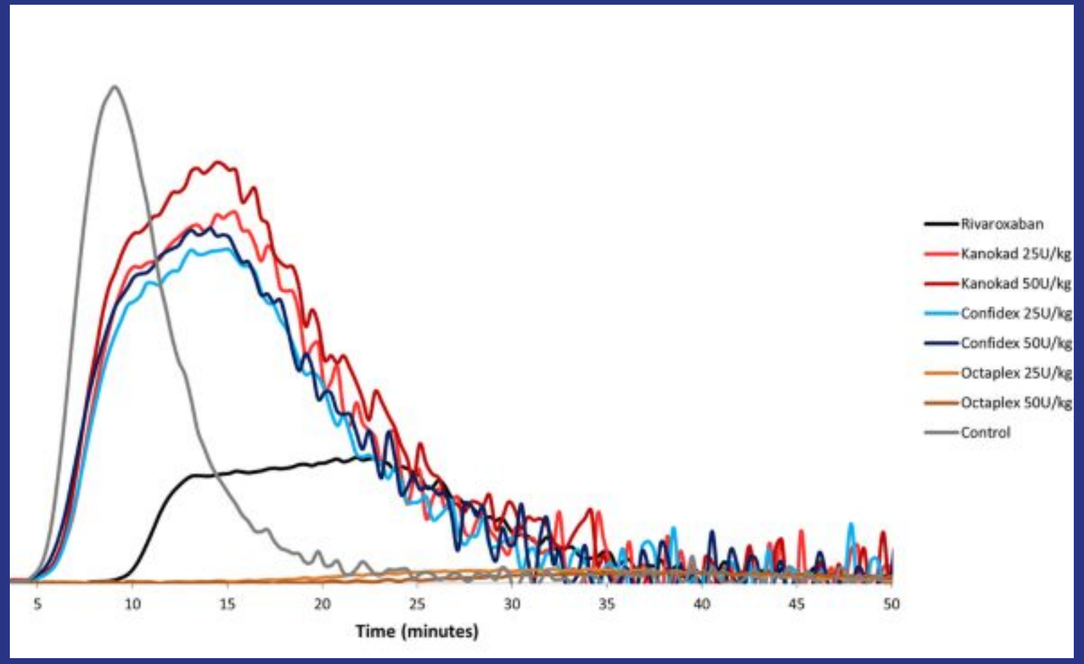
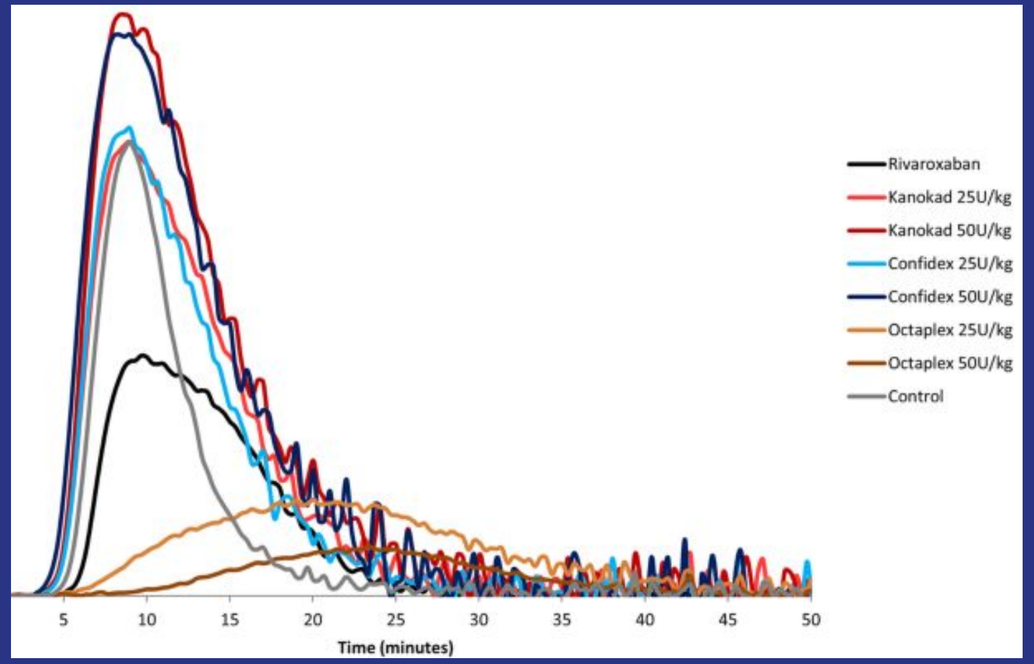
4F-PCC Dosing is Simple and Cost Effective



Rivaroxaban concentration of 89 ng/mL



Rivaroxaban concentration of 49 ng/mL

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Quillon. *Thromb J*. 2020 Aug 24; 18:15.

Example Case

52 – year – old male with history of atrial fibrillation receiving apixaban 5 mg twice daily; patient also has a history of CKD stage 2 who comes to your ED after experiencing an isolated TBI; GCS 12, UFH anti – Xa assay with a value of 0.98 IU/mL.

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PCC generates thrombin similar to andexanet alfa

- True
- False

Efficacy Bottom Line

- PCCs have the ability to generate thrombin at a rate similar to AA
- The sustained pharmacodynamic mechanism of PCCs is beneficial especially as we begin to see more patients with factors that can protract factor Xa inhibitor effects
- Operationally it is much simpler to dose and deliver PCCs in these highly acute situations that require expedited administrations

#EPRxTeamPCC

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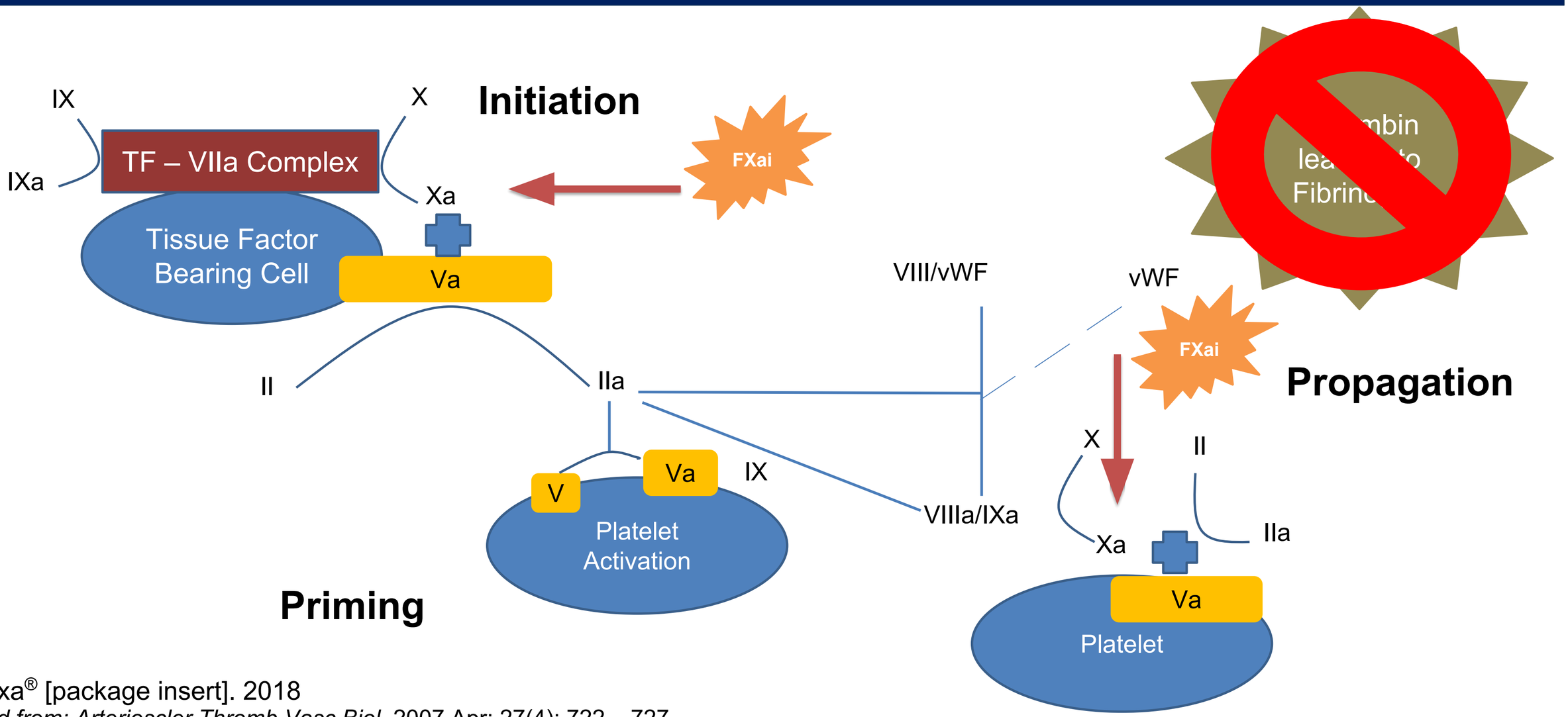
Andexanet Alfa(AA) Efficacy

If you chose Andexanet Alfa why do you use it over 4F-PCC?

Andexanet Alfa's Targeted Pharmacology
It's actually reversing…



Andexxa® [package insert]. 2018

Adapted from: Arterioscler Thromb Vasc Biol. 2007 Apr; 27(4): 722 – 727.

Tanaka. *Transfus Med Rev*. 2021 Oct; 35(4): 96 – 103.

Andexanet Alfa Pharmacology

Onset	Rapid (2-4 minutes)
Duration	?

- Anti-factor Xa activity returns to baseline in ~4 hours
- Thrombin generation sustained for 22 hours

Siegal D. *Blood Advances*. 2017;21:1827-1838.
Abramowicz M. *JAMA*. 2018;320:399-400.

Andexanet Alfa Dosing
It's not that hard...

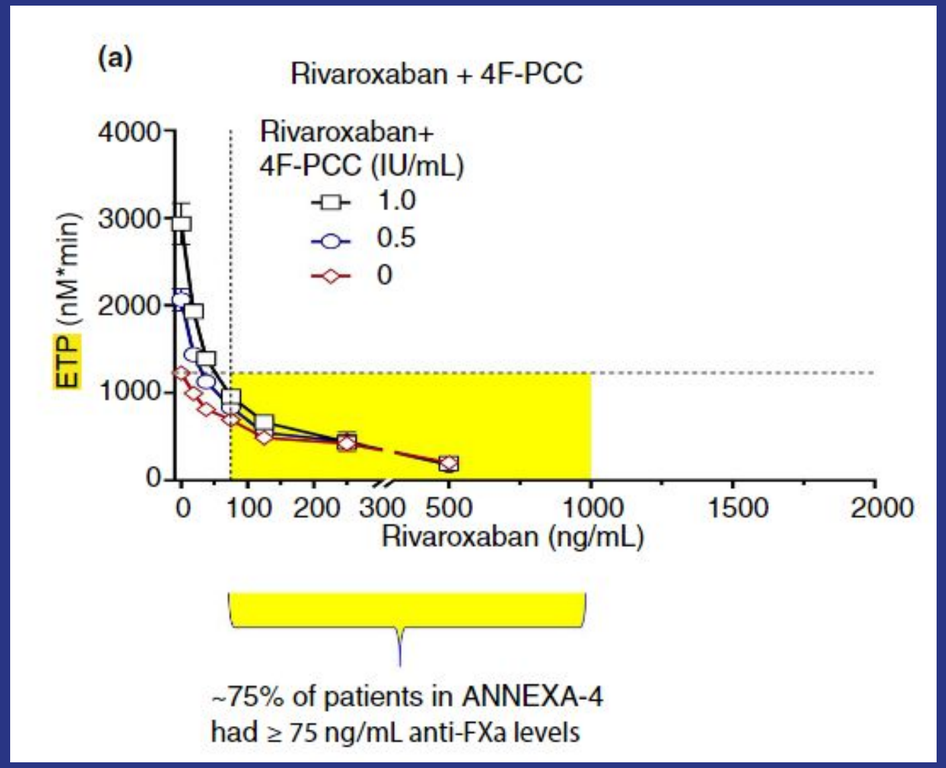
FXa inhibitor	Last dose	<8 hours or unknown	≥8 hours
Apixaban	≤5 mg	Low dose	Low dose
Apixaban	>5 mg or unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
Rivaroxaban	>10 mg or unknown	High dose	

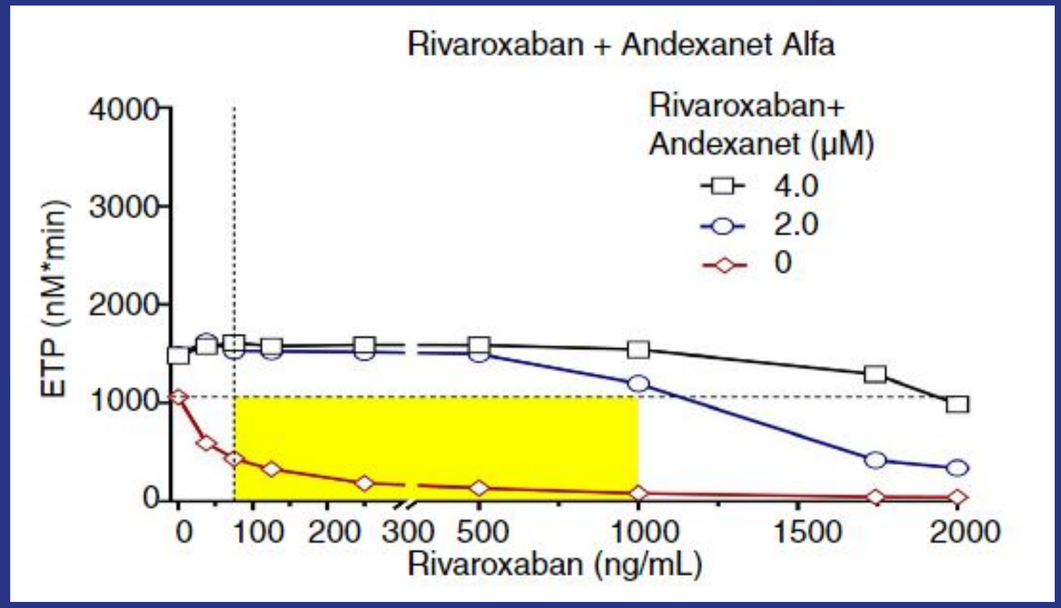
Dose	Initial IV bolus	IV infusion
Low dose	400 mg over ~15 minutes	4 mg/min for up to 120 minutes
High dose	800 mg over ~15 minutes	8 mg/min for up to 120 minutes

Andexxa® [package insert]. 2018

Endogenous Thrombin Generation

The Anti-Xa concentration matters





Dose	4F-PCC		Andexanet alfa	
	Units/kg	Plasma level (IU/mL)	mg	Plasma level (μM)
Low	25	0.5	400	2.0
High	50	1.0	800	4.0

ETP: Endogenous Thrombin Potential

Lu G, et al. *Res Pract Thromb Haemost.* 2020;4:1282–1294.

ANEXXA-4 "Updated" Study

Study Design 	Multicenter, prospective, open-label, single group study
Patient Population 	Adults, acute major bleeding, and received: • Apixaban • Rivaroxaban • Edoxaban • Enoxaparin (1mg/kg/day) within 18 hours
Intervention 	Andexanet alfa bolus & infusion
Primary Endpoints 	• Percent change in anti-Xa activity • Percent of patients with good or excellent hemostatic efficacy

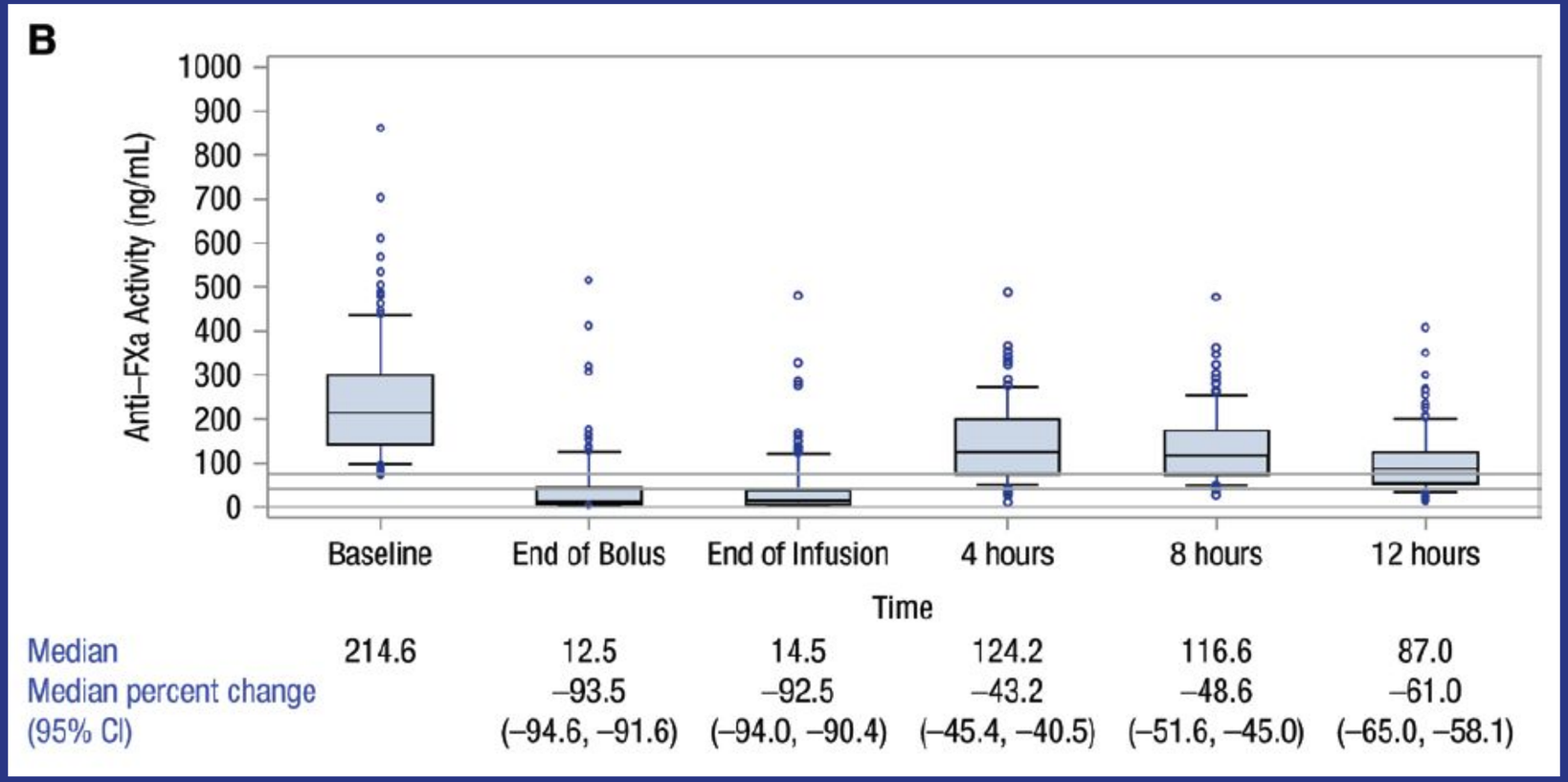
Milling TJ. *Circulation.* 2023;147:1026–1038.

ANEXXA-4: Baseline Demographics

Characteristics	Safety (N = 479)	Efficacy (N = 349)
Age, mean ± SD	77.9±10.7	77.7±10.6
Sex, male, n (%)	260 (54.3)	185 (53)
Factor Xa Inhibitor, n (%) Rivaroxaban Apixaban Edoxaban Enoxaparin	 176 (36.7) 245 (51.1) 36 (7.5) 22 (4.6)	 132 (37.8) 172 (49.3) 28 (68) 17 (4.9)
Site of bleeding, n (%) GI ICH Other	 109 (22.8) 331 (69.1) 39 (8.1)	 78 (22.3) 249 (71.3) 22 (6.3)

Milling TJ. *Circulation.* 2023;147:1026–1038.

ANEXXA-4: Anti-Xa Activity



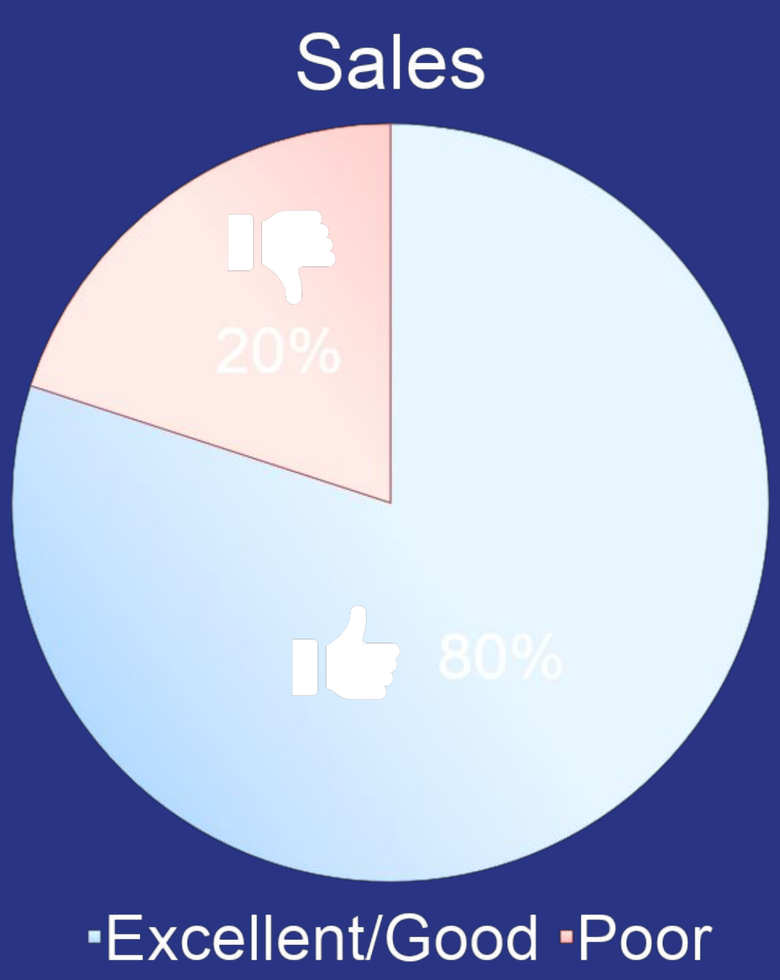
RAvpairaxaban

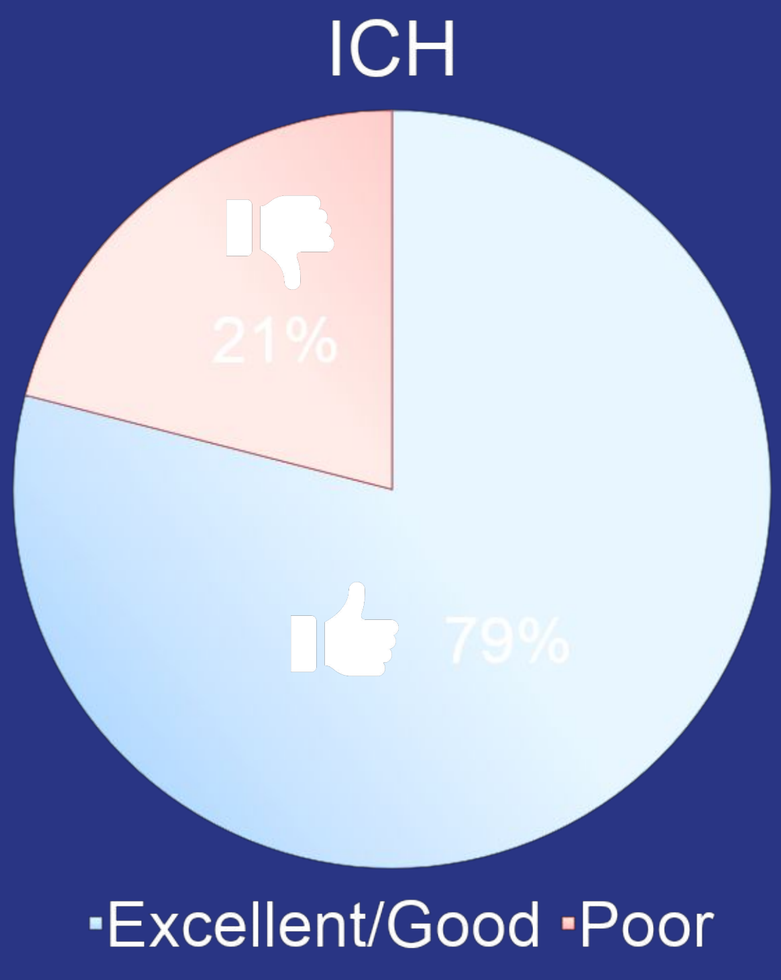
Milling TJ. *Circulation.* 2023;147:1026–1038.

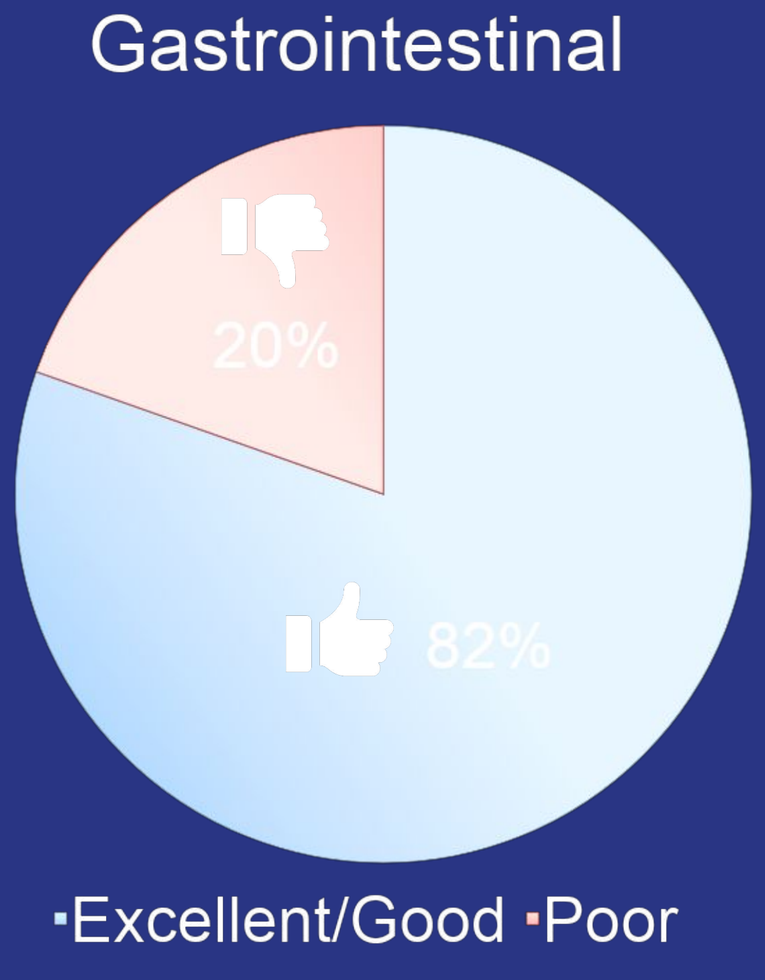
ANEXXA-4: Thrombin Generation

Milling TJ. *Circulation.* 2023;147:1026–1038.

Results: Hemostasis







Milling TJ. *Circulation.* 2023;147:1026–1038.

Comparative Trials

4F-PCC

- Most retrospective studies
- Heterogeneity of definitions
- No anti-Xa levels to confirm drug

Costa et al

- ANEXXA-4 patients propensity score matching to historic cohort for ICH
- Excellent/good hemostasis was 85.8% for AA and 68.1% for 4F-PCC [OR 2.73, 95% CI 1.16-6.42]
- 30 day mortality was better in AA (7.9%) vs 4F-PCC (19.6%) [OR 0.36, 95% CI 0.13-0.98]

Cohen et al

- ANEXXA-4 patients propensity matched to patients from ORANGE database
- 30-day mortality was 14.6% for AA vs 34.1% for PCC (RR 0.43, 95% CI 0.29-0.63)

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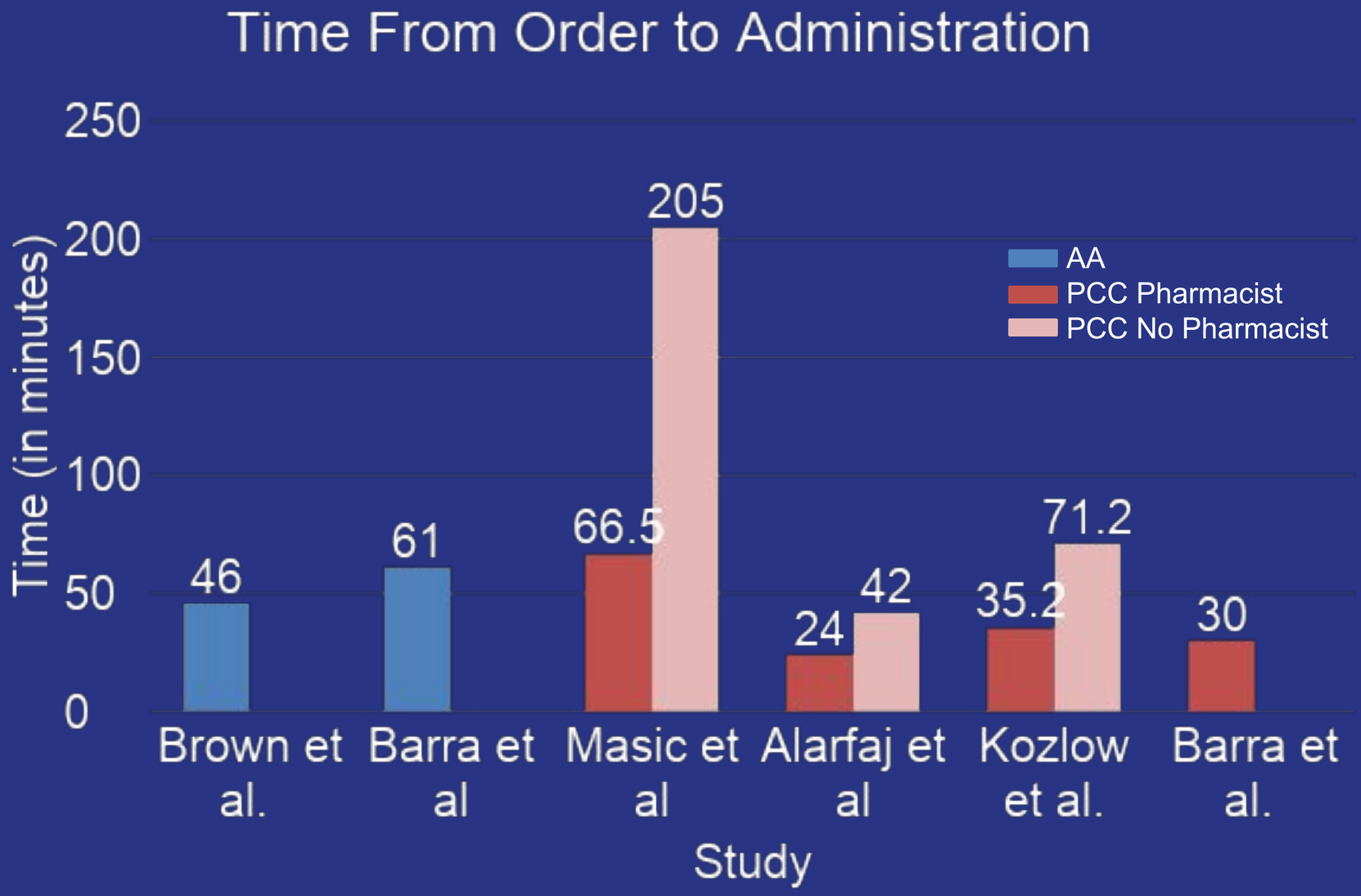
Majeed A. *Blood*. 2017;130:1706-1712.
Tao J. *Journal of Intensive Care*. 2018;6:34.
Shulman S. *Thromb Haemost*. 2018;118:842-851
Gerner ST. *Ann Neurol.* 2018;83:186-196
Smith MN. *J of Thrombosis & Hemostasis*. 2019;48:250-255.
Berger K. *Journal of Intensive Care.* 2020;35:1203-1208.
Reynolds TR. *J of Pharmacy Practice*. 2021;34:755-760.
Costa O. *Crit Care.* 2022;26:180
Cohen AT. *JACEP Open*. 2022;3:e12655.

Time to Administration



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Masic D et al. *J Emerg Med.* 2019;57:620-628.
Kozlow E et al. *JACCP.* 2020;4:33-39.

Brown et al. *AJEM.* 2020;38:827-848.
Alarfarj S et al. *AJEM.* 2018;36:2182-2186.
Barra et al. *J Thromb Haemost.* 2020;18:1637–1647.

Cost

4F-PCC

- 85 kg x 50 units/kg = 4,250 units
- 4,250 units x $2.62 unit = ~$11,135

Andexanet Alfa

- Low-dose regimen = ~$12,500

=

Fanikos J. *J Med Econ* 2022;25(1):309–20.
https://www.andexxa.com/access-reimbursement.html

Which agent is FDA approved and recommended by several guidelines

- Andexanet alfa
- 4F-PCC

Efficacy Bottom Line

- AA is approved by the FDA and endorsed by numerous guidelines
- AA has prospective trials with adjudicated endpoints to support it's use
- In propensity matched studies AA provided better efficacy
- Cost is now similar between agents

#EPRxTeamAA

Safety!

#EPRxTeamPCC

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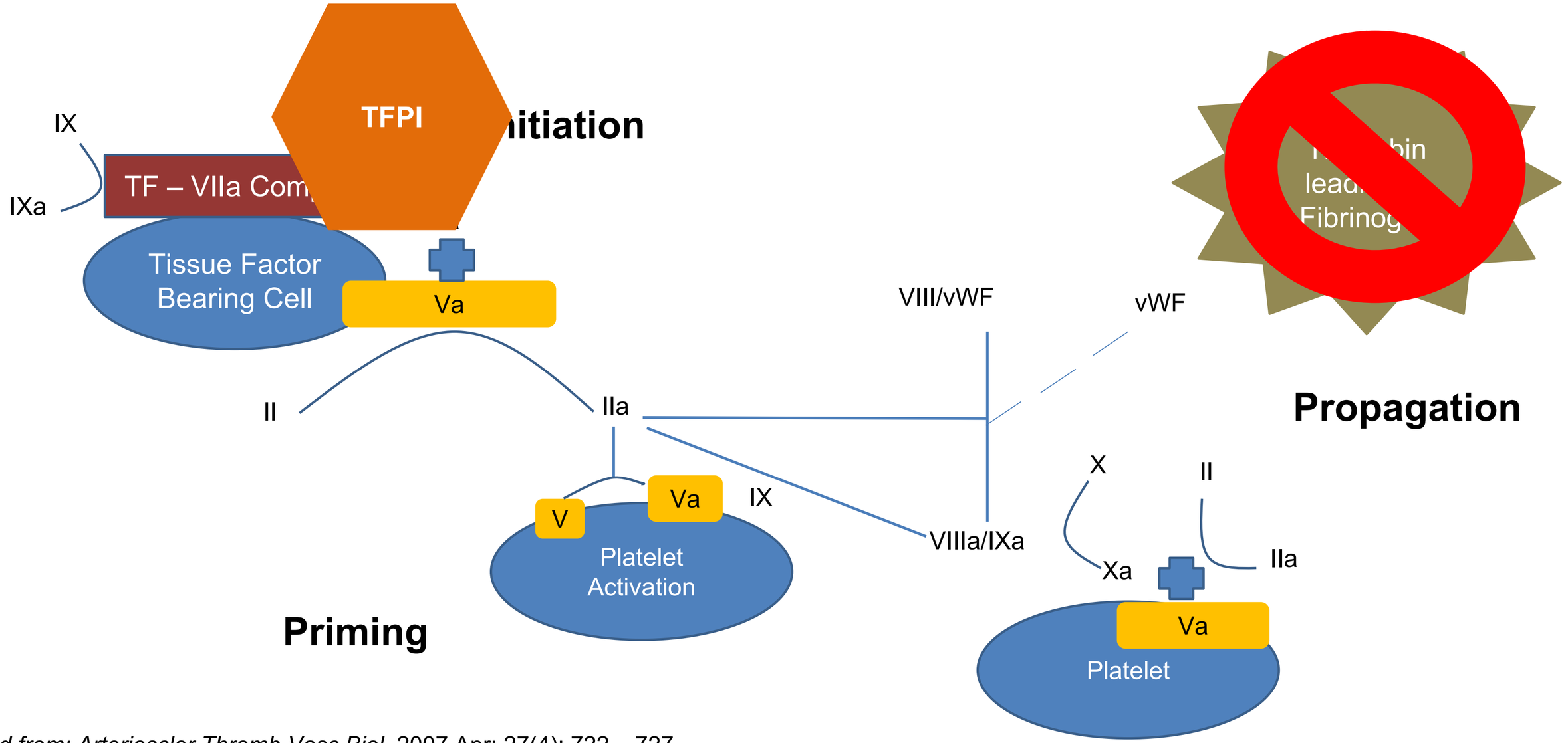
Tissue Factor Pathway Inhibitor (TFPI)



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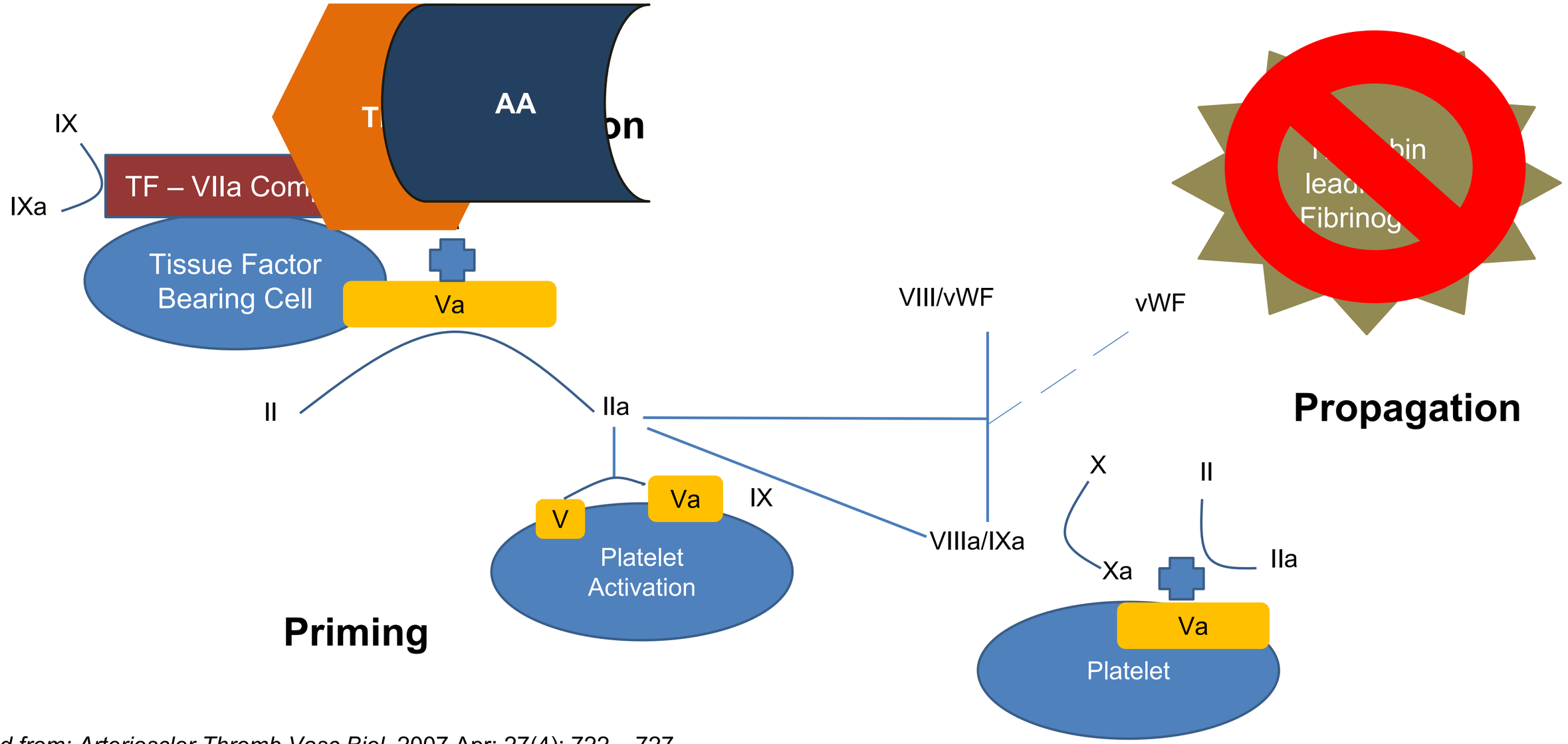
Tanaka. *Transfus Med Rev*. 2021 Oct; 35(4): 96 – 103.

AA Effects on TFPI



Adapted from: Arterioscler Thromb Vasc Biol. 2007 Apr; 27(4): 722 – 727.
Tanaka. *Transfus Med Rev*. 2021 Oct; 35(4): 96 – 103.

Heparin Resistance (Yeah I'm Going There)

- Increasing number of case reports describing excessive doses of UFH needed during cardiac surgery post utilization of AA

- This heparin resistance can have extremely detrimental outcomes for procedures where heparinization may be vital and may explain the increased thrombotic rates seen with AA over PCC

Levy. *N Engl J Med*. 2021 Aug 26; 385(9): 826 – 832.

4F-PCC vs. Andexanet Alfa in the Field

Nederpelt. *Crit Care Med*. 2021 Oct 1; 49 (10): e1025 – e1036.	
Patients	Studies evaluating management of factor Xa inhibitor – associated hemorrhage
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Outcomes	A total of 554 unique entries was evaluated with 21 being included for a total of 1376 patients; 5 were prospective and 17 retrospective; median age was 77 in AA group and 76 in PCC group; majority of patients suffered an ICH (68.9% in AA vs. 87.7% in PCC); the primary indication for anticoagulation was atrial fibrillation; the majority of patients received a PCC dose of ≥ 30 units/kg (53.4%) where as patients in the AA group primarily received the lower dose algorithm (84%); antiplatelet use was similar between both groups with 35.9% in the AA group compared to 32.8% in the PCC group 30-day VTE rates were 5.0% for AA and 1.9% for PCC 30-day thrombotic event rate was 10.7% for AA vs. 3.1% PCC
Conclusion	No available evidence supporting one agent over the other to manage factor Xa inhibitor – associated hemorrhage; non – commercially biased authorship

* ISTH, International Society of Thrombosis and Hemostasis; ICH, intracranial hemorrhage

Formulary Management

- While the cost of AA has been significantly reduced there are still pharmacoeconomic considerations with having both agents on formulary
- With both agents on formulary there is the possibility of increased confusion on which agent to use and errors if both are administered

Example Case

72 – year – old female with history of pulmonary embolism (45 days prior) receiving rivaroxaban 20 mg daily; who comes to your ED with signs and symptoms consistent with an ICH; the patient is managed with AA

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Safety Bottom Line

- Regardless of the agent utilized resumption or initiation of prophylaxis or anticoagulation is imperative for clinicians to prevent thrombotic events
- Both AA and 4F – PCC appear to have “similar” rates of thrombotic events however not all thrombotic events should be weighted equally (e.g. DVT vs. stroke)
- AA has an additional mechanism by which thrombotic risk are increased as well as resistance to heparinoid agents for prophylaxis

#EPRxTeamPCC

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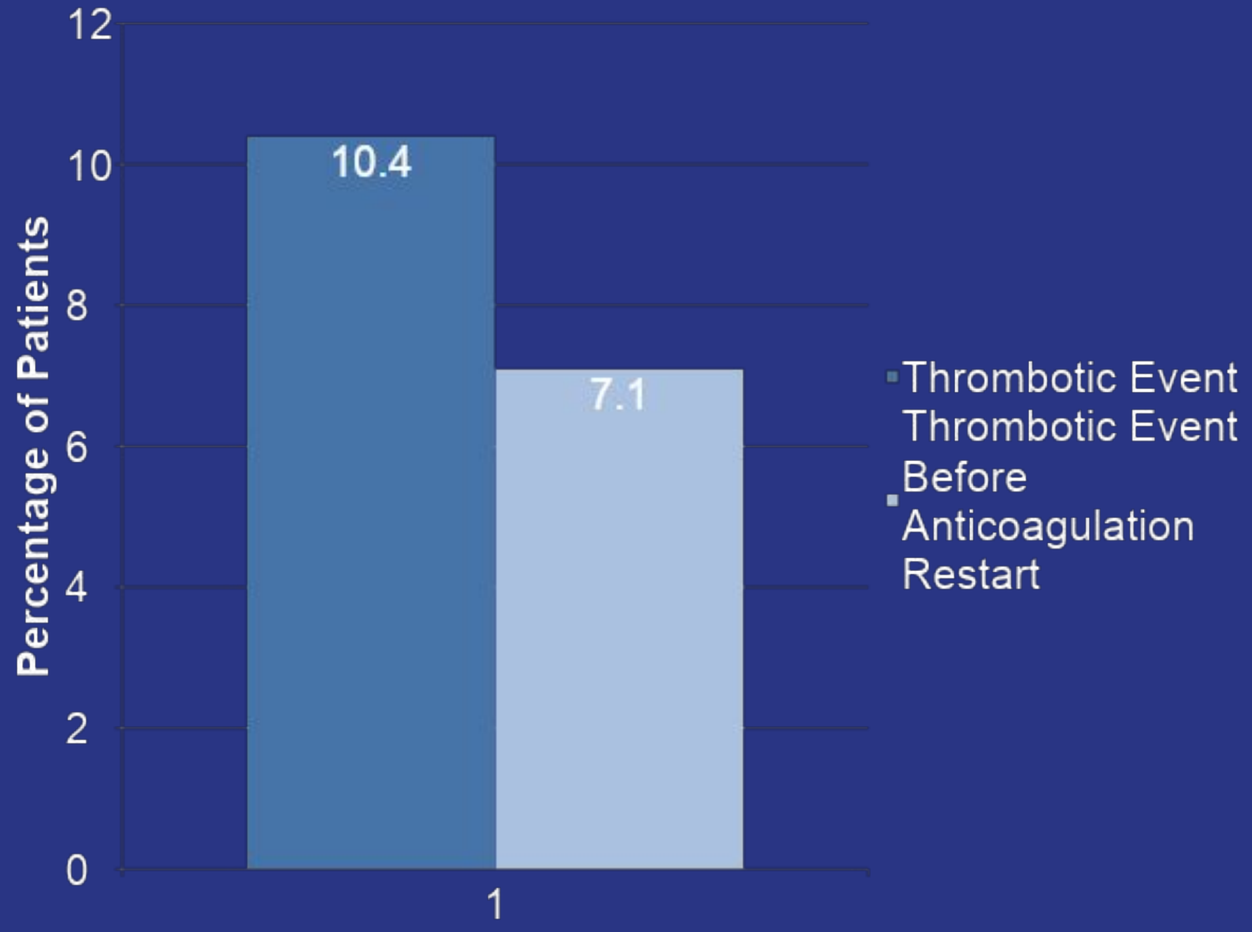
Andexanet Alfa Safety

AA Thrombotic Events



- 32% of thrombotic events occurred in 15-30 days
- No events occurred after resumption of oral anticoagulation

Meta-Analysis have not found a significant difference between thrombotic events with AA vs PCC

Heterogeneity in outcomes with PCC

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Milling TJ. *Circulation.* 2023;147:1026–1038.
Nederpelt C. *Crit Care Med*. 2021;49:e1025 – e1036.
Chaudhary R. *JAMA Open Network Neurology.* 2022;5:e2240145.

Safety Bottom Line

Anticoagulation should be resumed as soon as possible

No difference in thrombotic events between agents

#EPRxTeamAA

Case

GB is 62 year-old male (102 kg) on apixaban 5mg BID for atrial fibrillation. He comes in with altered mental status and is found to have a intraparenchymal hemorrhage (~15 mL in size). His last dose of apixaban was ~10 hours ago. His GCS is 12 and his ICH score is 1.

Your site has both andexanet alfa and 4F-PCC on formulary. What do you chose for anticoagulation reversal for GB?

- Andexanet alfa
- 4F-PCC
- Neither

ICH: Intracranial hemorrhage

AA or PCC?

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Overall Conclusion

- PCC generates thrombin at a rate similar to AA and has real – world efficacy demonstrating similar hemostasis rates
- Thromboembolic events might be more common in AA given several additional mechanisms which promote clot formation
- Operational and formulary considerations give the advantage to PCC

#EPRxTeamPCC

WAIT!!! Don’t Forget #EPRxTeamPCC

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Overall Conclusion

- AA is FDA approved and recommended by several guidelines
- AA has higher quality data to support its use and propensity matched studies have shown better outcomes with AA
- Cost is now comparable between agents
- Most thrombotic events happen before anticoagulation is re-initiated

#EPRxTeamAA

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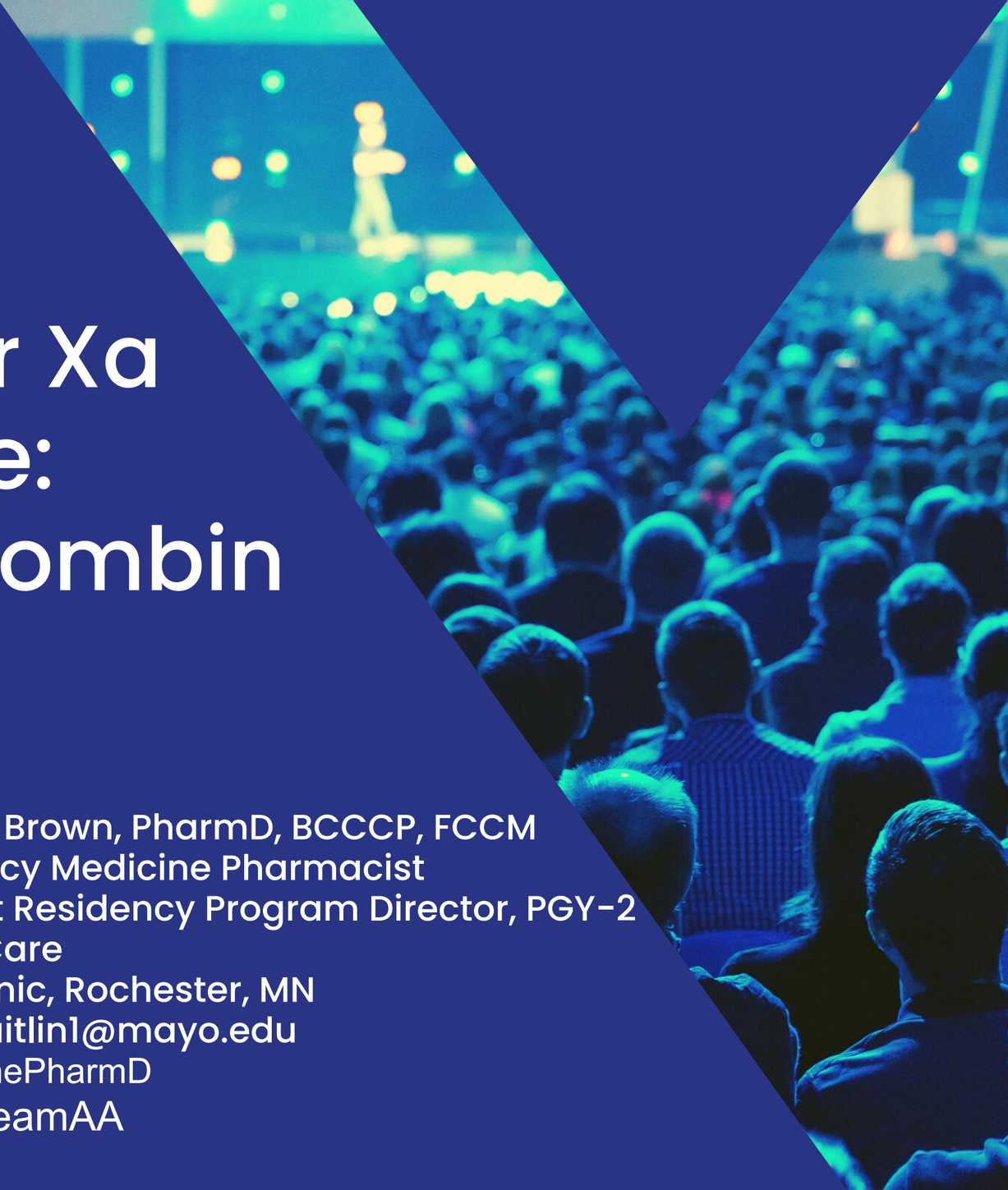

The Clot Thickens: Factor Xa Inhibitor Reversal Debate: Andexanet Alfa or Prothrombin Complex Concentrate?

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#EPRxTeamAA

Comparison of Reversal Studies

Study	Reversal Agent	N	Baseline Characteristics	% laboratory reversal	Hemostatic Efficacy		Thrombosis Rate	Mortality
					Excellent/ Good	Poor/ None		
Annexa-4	Andexanet alfa	67	42% ICH*	~90% decrease	79%	21%	18%	15%
Reverse-AD	Idarucizumab	90	35% ICH	89-98%	92%	8%	5.5%	20%
Sarode 2013	4F-PCC	98	12.1% ICH**	INR < 1.3 62.2%	72%	28%	7.8%	6%
	Plasma	104	11.5% ICH**	INR < 1.3 9.6%	65%	35%	6.4%	5%

*Excluded: GCS <7, ICH volume > 60 mL
**Excluded: GCS <7, ICH volume > 30 mL

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Connolly SJ. *NEJM.* 2016; 375:1131-1141.
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