

# CLOT WARS

*Episode 1: Unleashing the Force of Antithrombotics  
in Critically Ill Patients*

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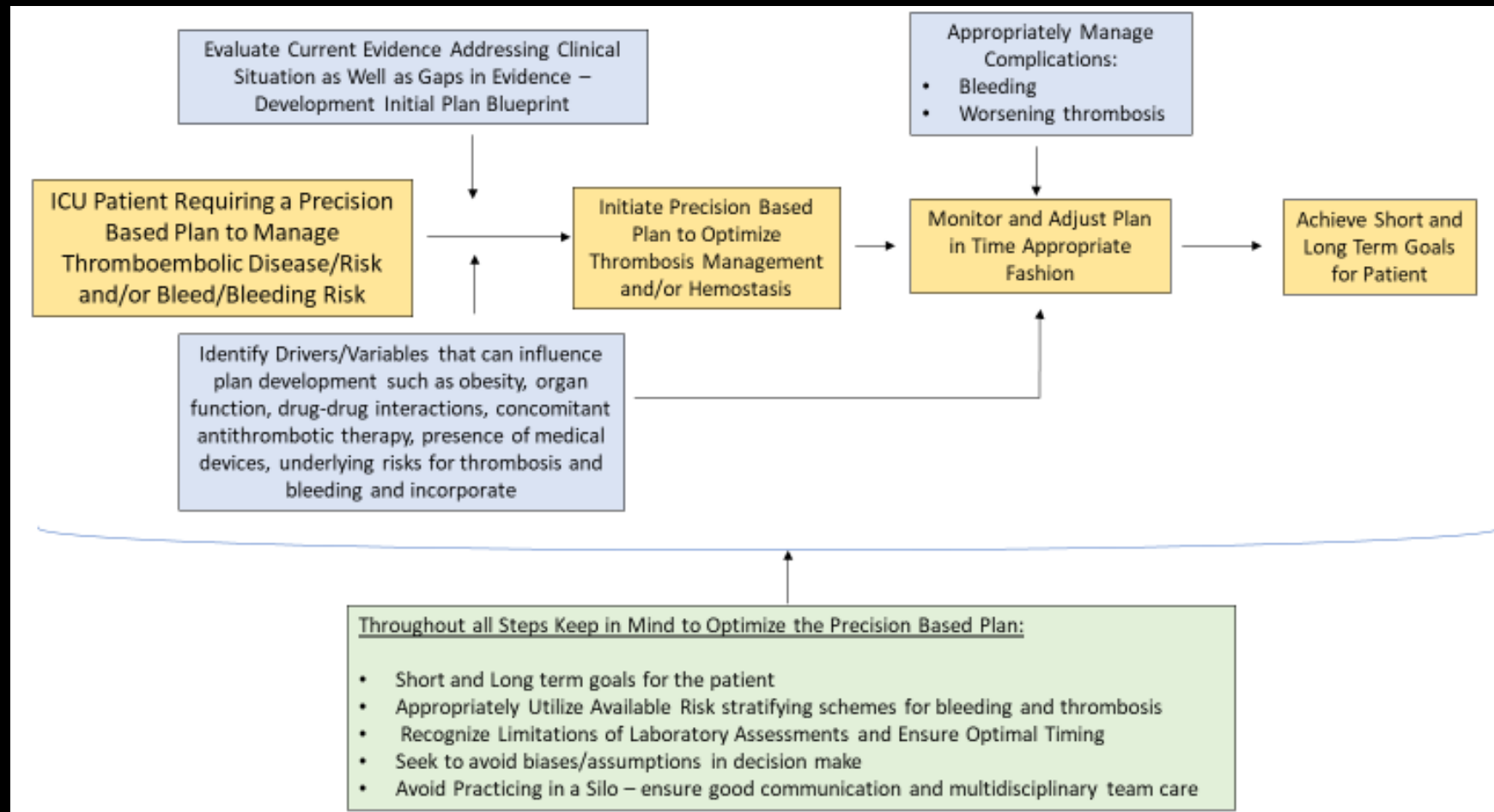
# Disclosures

- Speaker honorarium for this talk
- Speaker honoraria from Haemonetics
- Author is sole creator of slide content
- The medical opinions and products utilization are those of the speaker and not those of the organizers of this event

# Objectives

- Discuss the role of antithrombotic therapy in the critically ill
- Identify advantages and disadvantages of commonly used antithrombotics
- Apply knowledge acquired to complex critically ill patient cases

# Precision Based Approach to Management



# Coagulopathy in Critical Illness

Clotting Factor Alterations

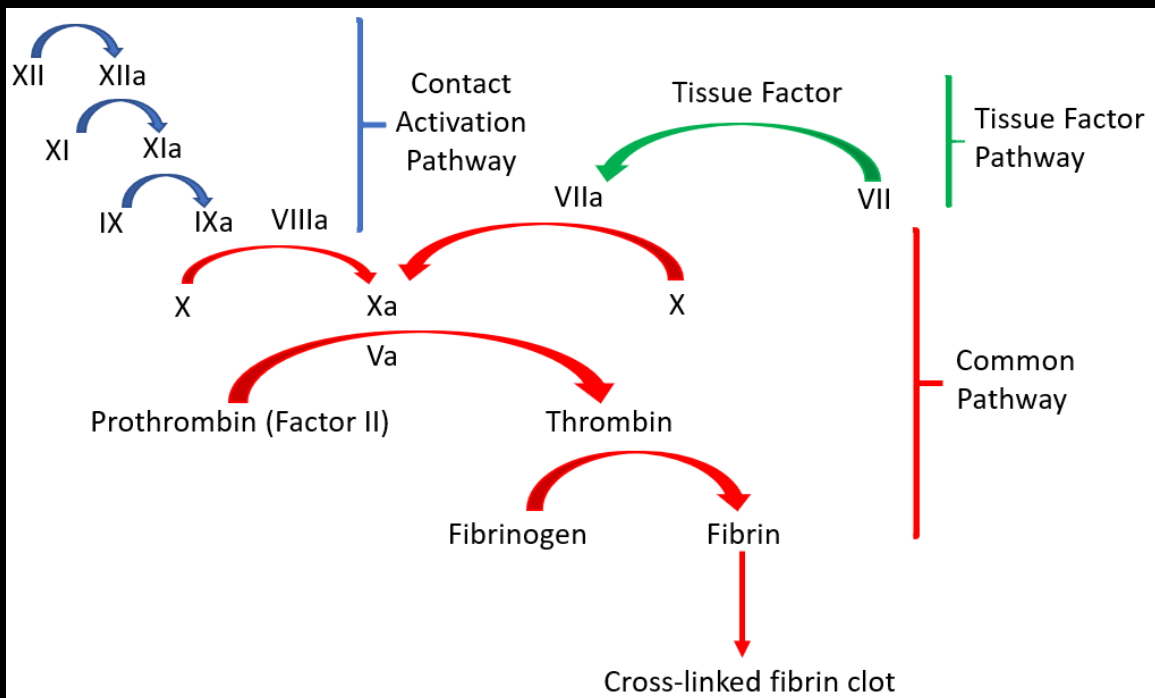
Platelet Inhibition or Aggregation

Hyperfibrinolysis or Fibrinolytic Shutdown

# Balancing Thrombosis and Hemorrhage

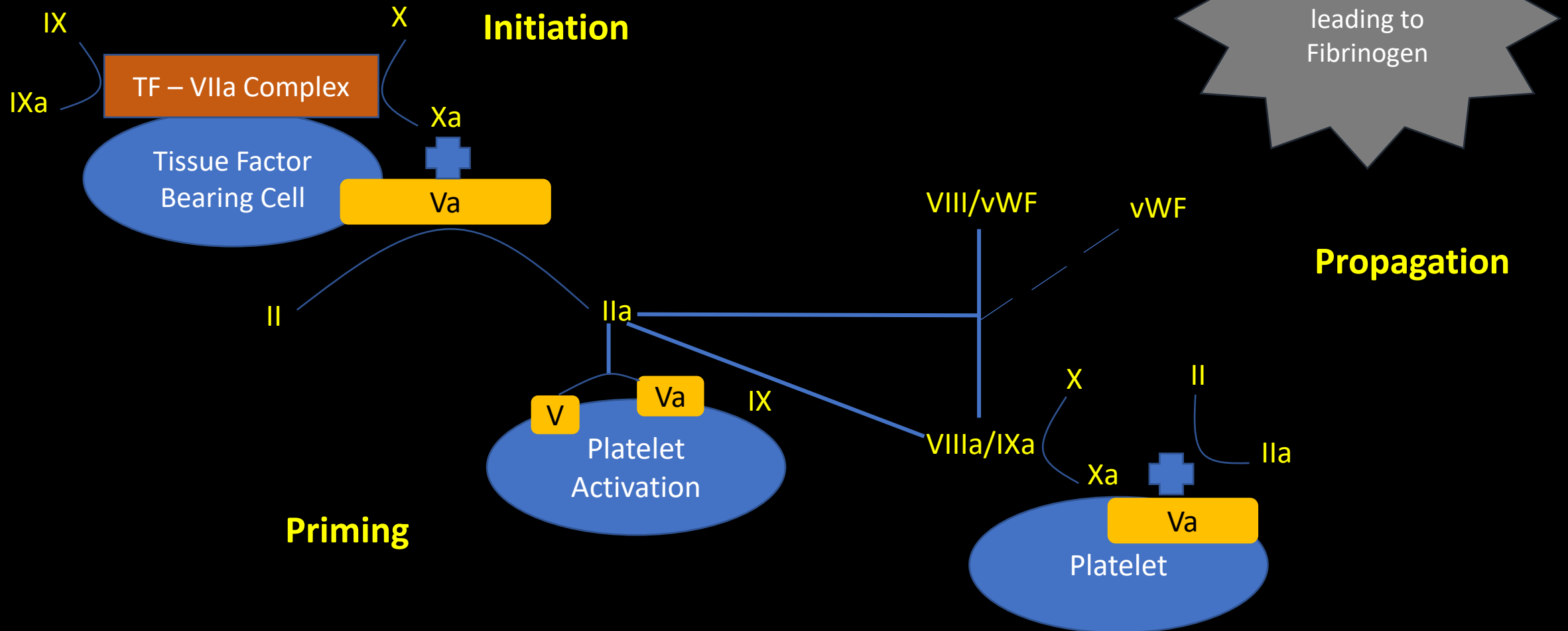


# Traditional Coagulation Measurement



- Platelet and fibrinogen values
- PT/INR (tissue factor and common pathways)
- PTT/aPTT (contact activation and common pathways)
- Less “traditional”
  - Thrombin time (TT)
    - Ecarin clotting time
    - Whole blood clotting

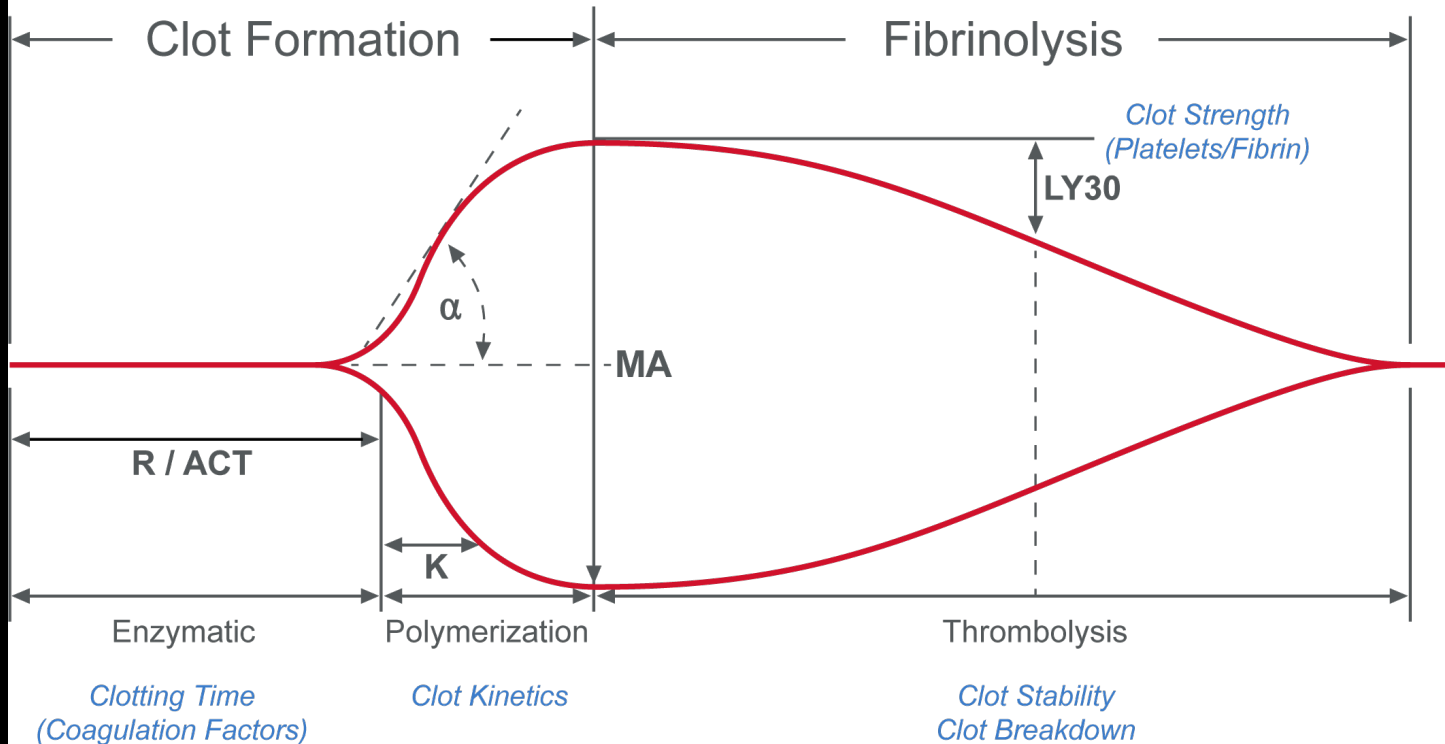
# Cell – Based Model of Coagulation





# Thromboelastography

Measure all phases of hemostasis in whole blood

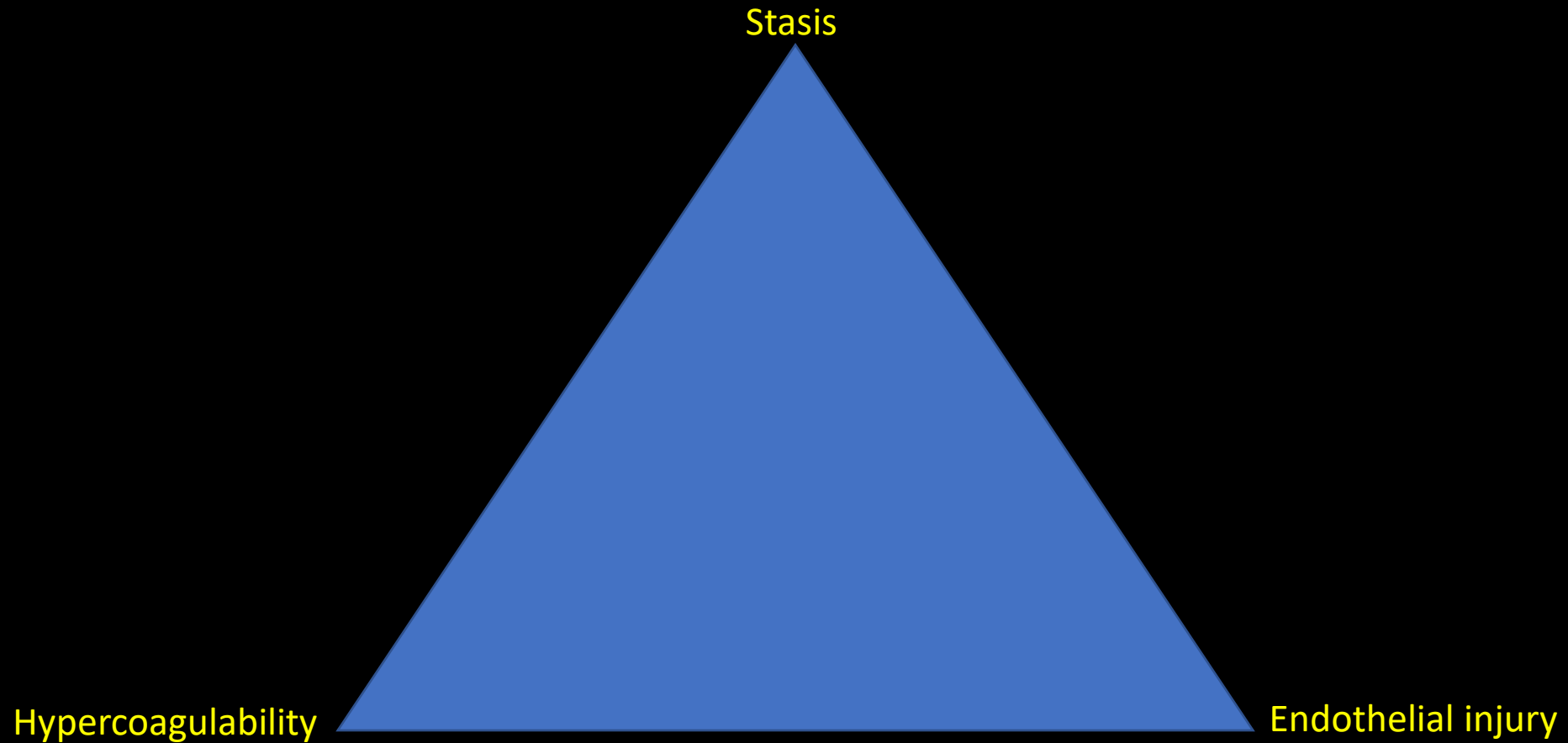


The TEG<sup>®</sup> hemostasis system continuously measures all phases of hemostasis as a net product of whole blood components.

# Hemostasis Beyond Coagulopathy

- Hypocalcemia
- Acidosis
- Hypothermia

# Virchow's Triad in Vascular Thrombosis



# Most Common Antithrombotics Utilized in the Intensive Care Unit

Anticoagulant	Antiplatelet
Unfractionated heparin (UFH)	Aspirin
Low molecular weight heparin (LMWH; enoxaparin)	Clopidogrel
Argatroban	Cangrelor
Bivalirudin	Tirofiban
Fondaparinux	Eptifibatide
Oral anticoagulants (warfarin, apixaban, rivaroxaban)	Abciximab

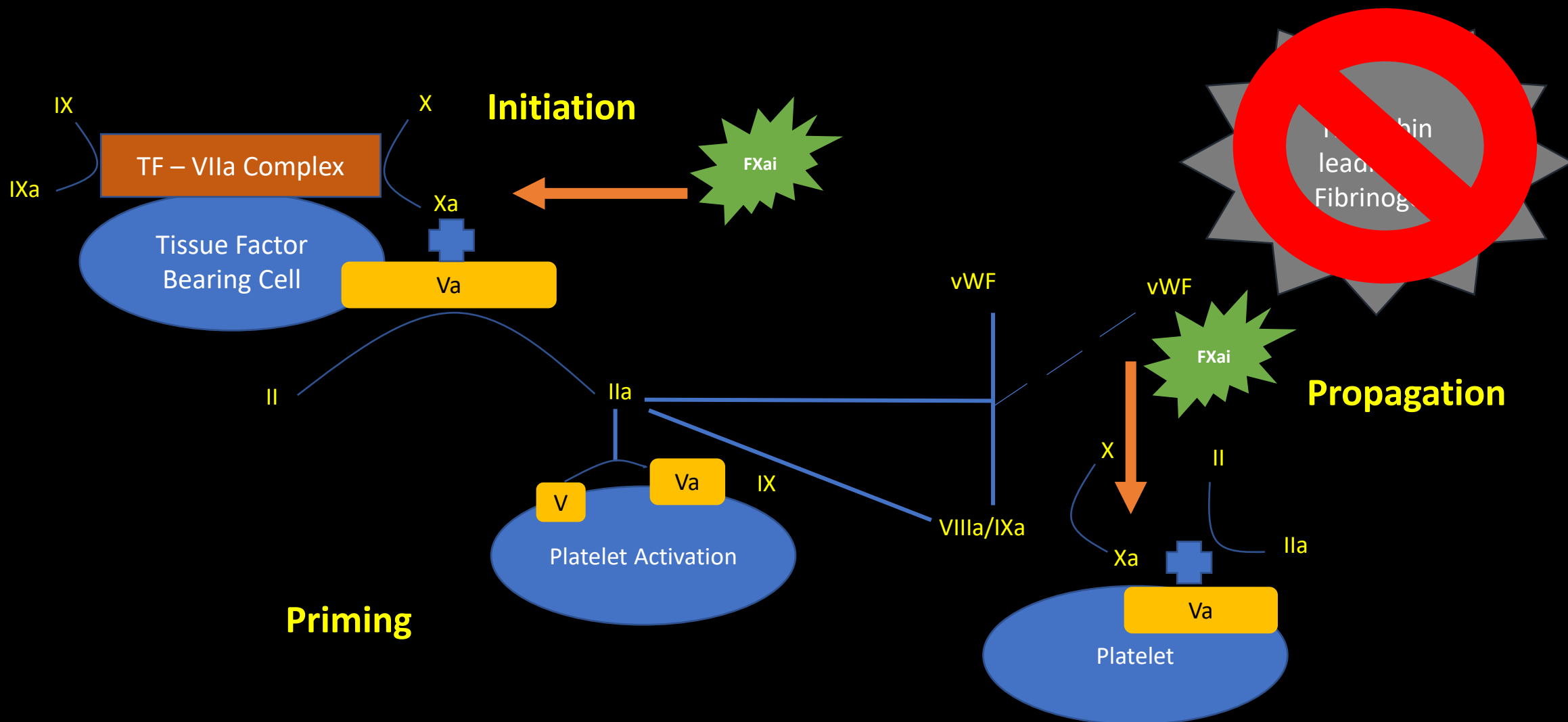
# Common Medications and Monitoring Strategies

- **Warfarin**: INR
- **Direct Oral Anticoagulant (DOACs)**: aPTT, TT, anti – Xa assays (chromogenic vs. non – calibrated), viscoelastic testing (VET)

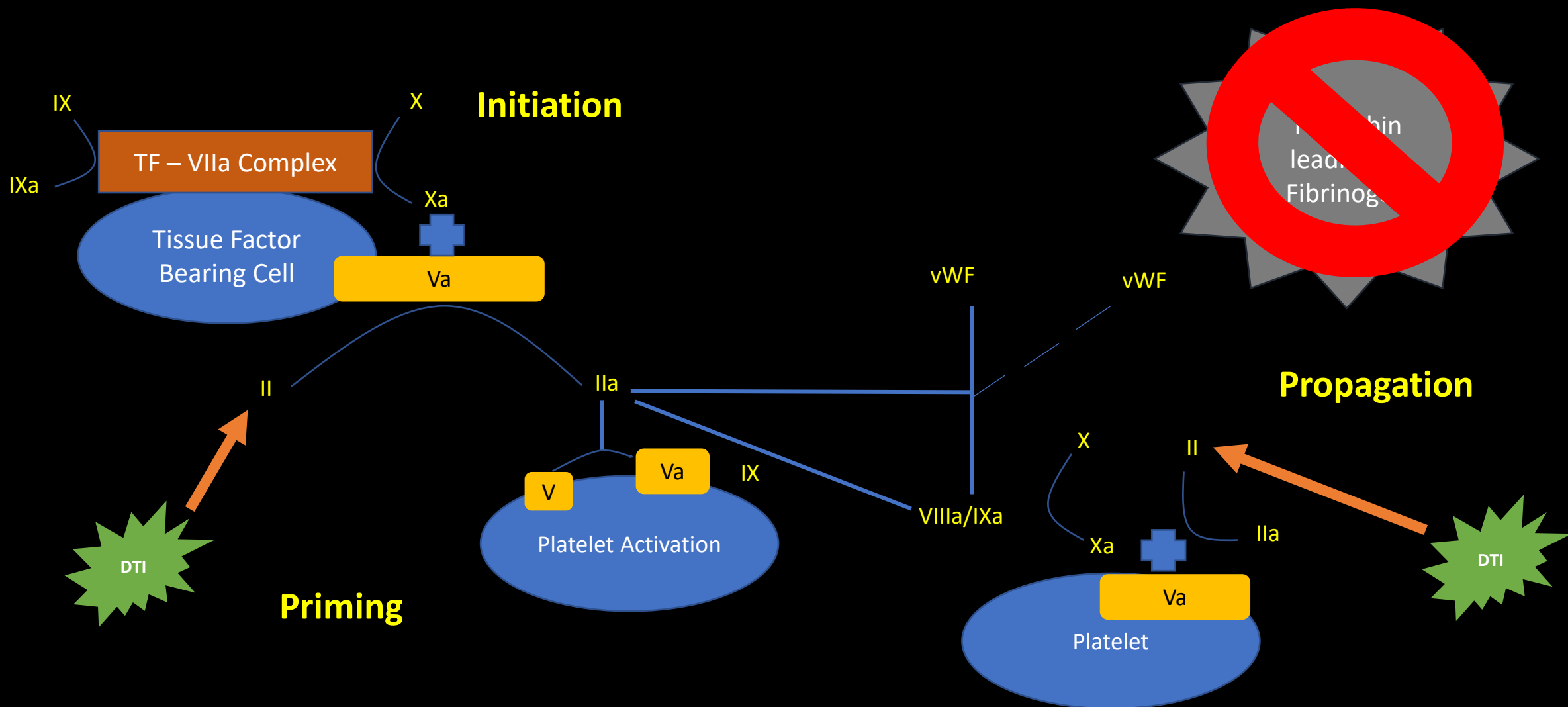
- **Aspirin**: Functional assays, VET
- **P2Y12 Inhibitors**: Functional assays, VET

- **Heparinoids**: aPTT, anti – Xa assays
- **Direct Thrombin Inhibitors**: aPTT, TT, activated clotting times, VET

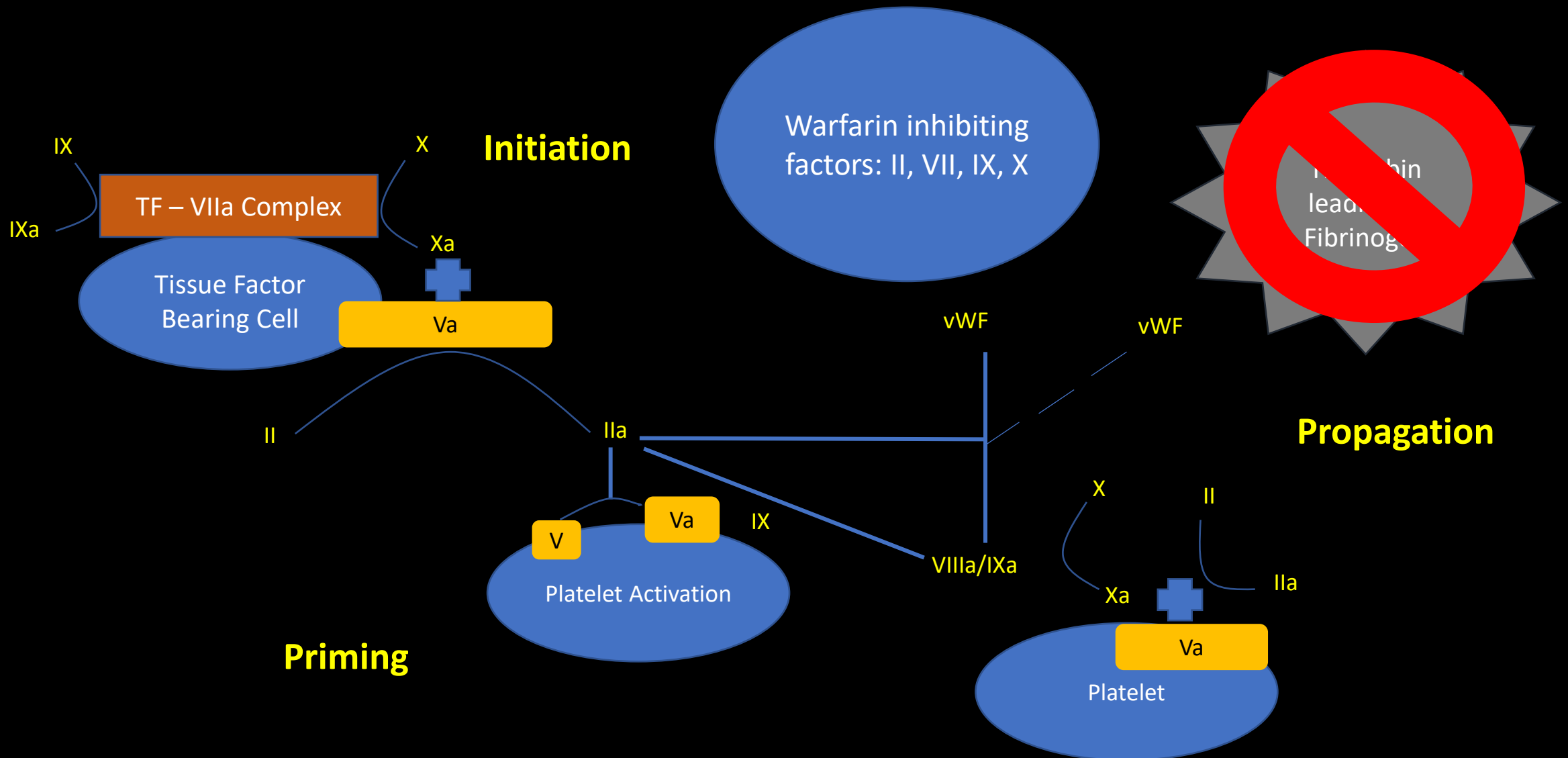
# Quick Overview of Factor Xa Inhibitors



# Quick Overview of Direct Thrombin Inhibitors (DTI)

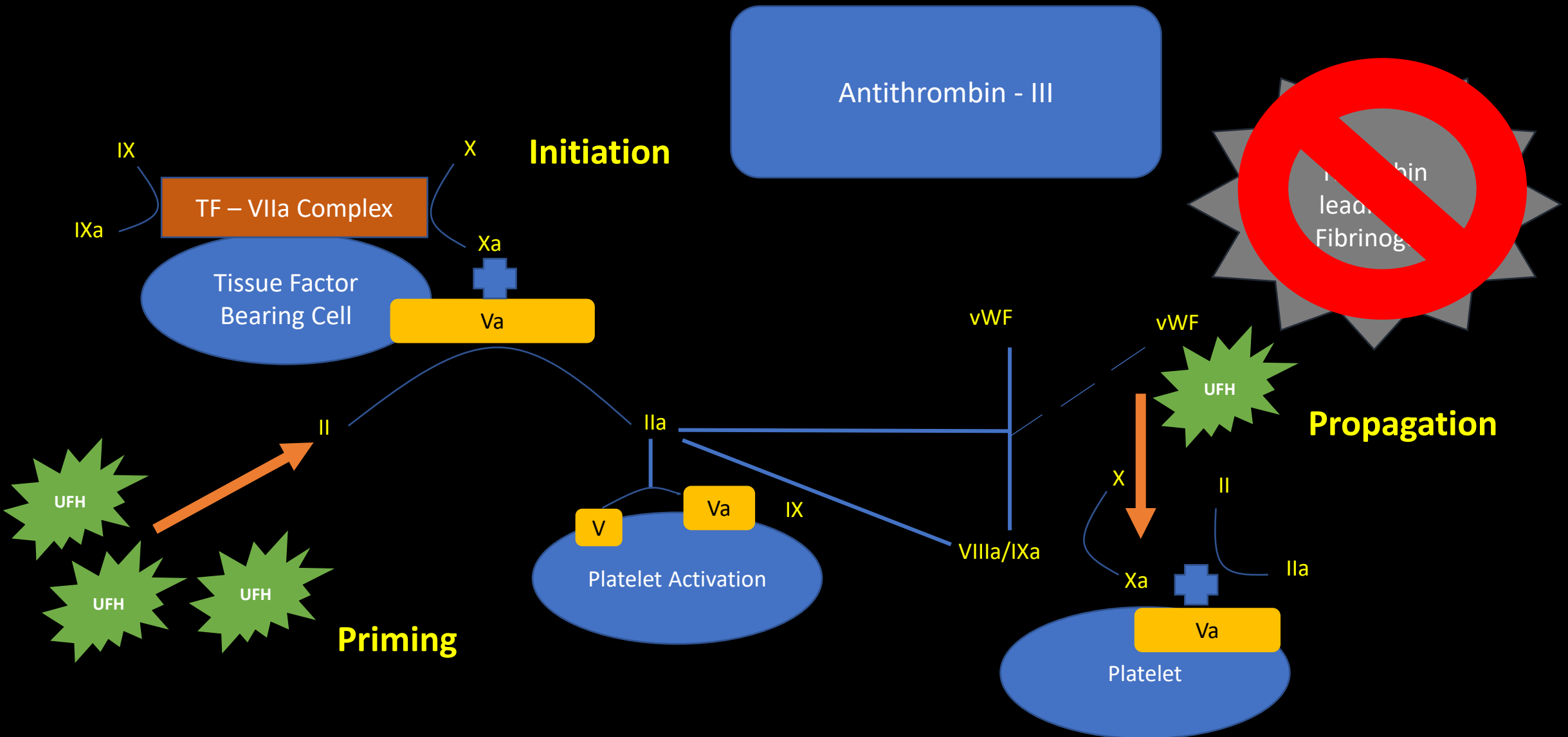


# Quick Overview of Warfarin

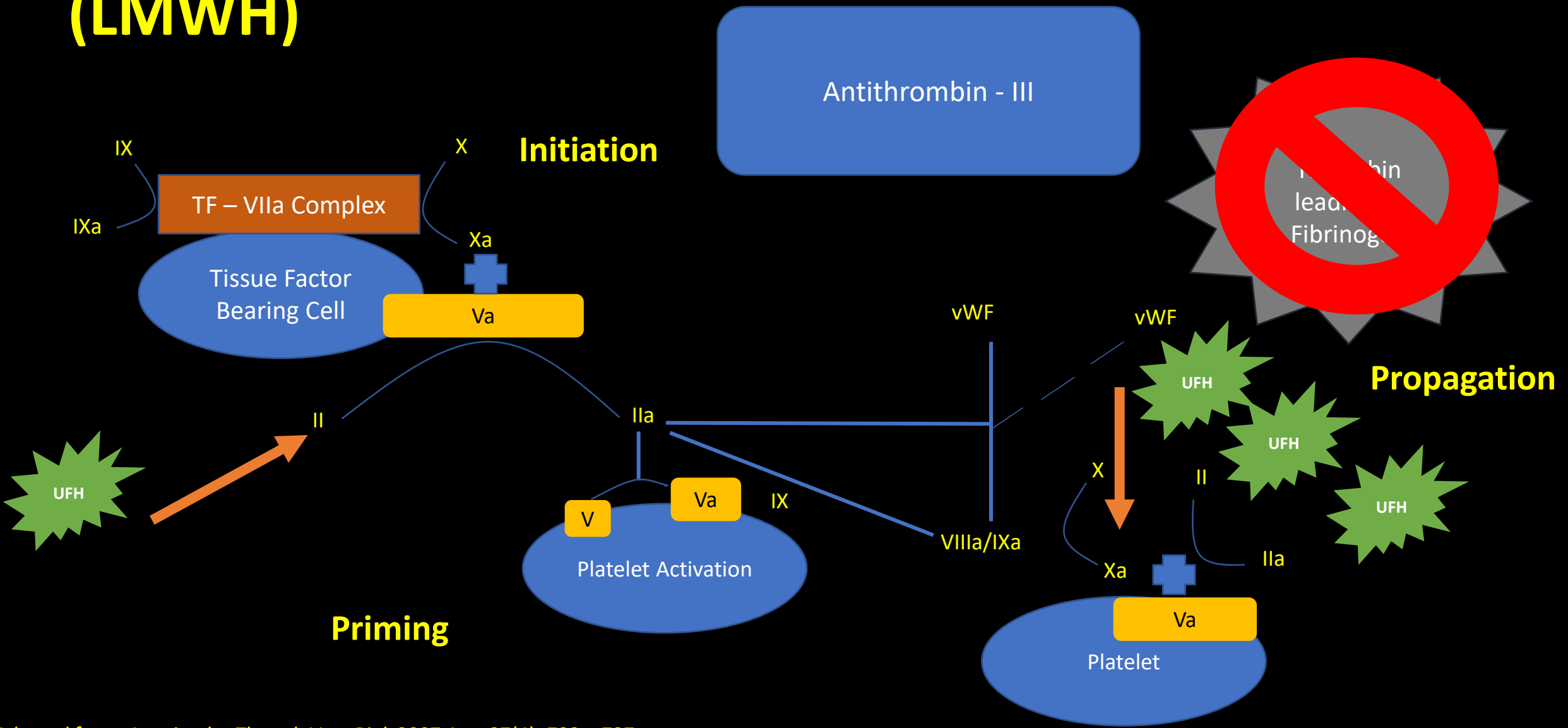




# Quick Overview of Unfractionated Heparin (UFH)



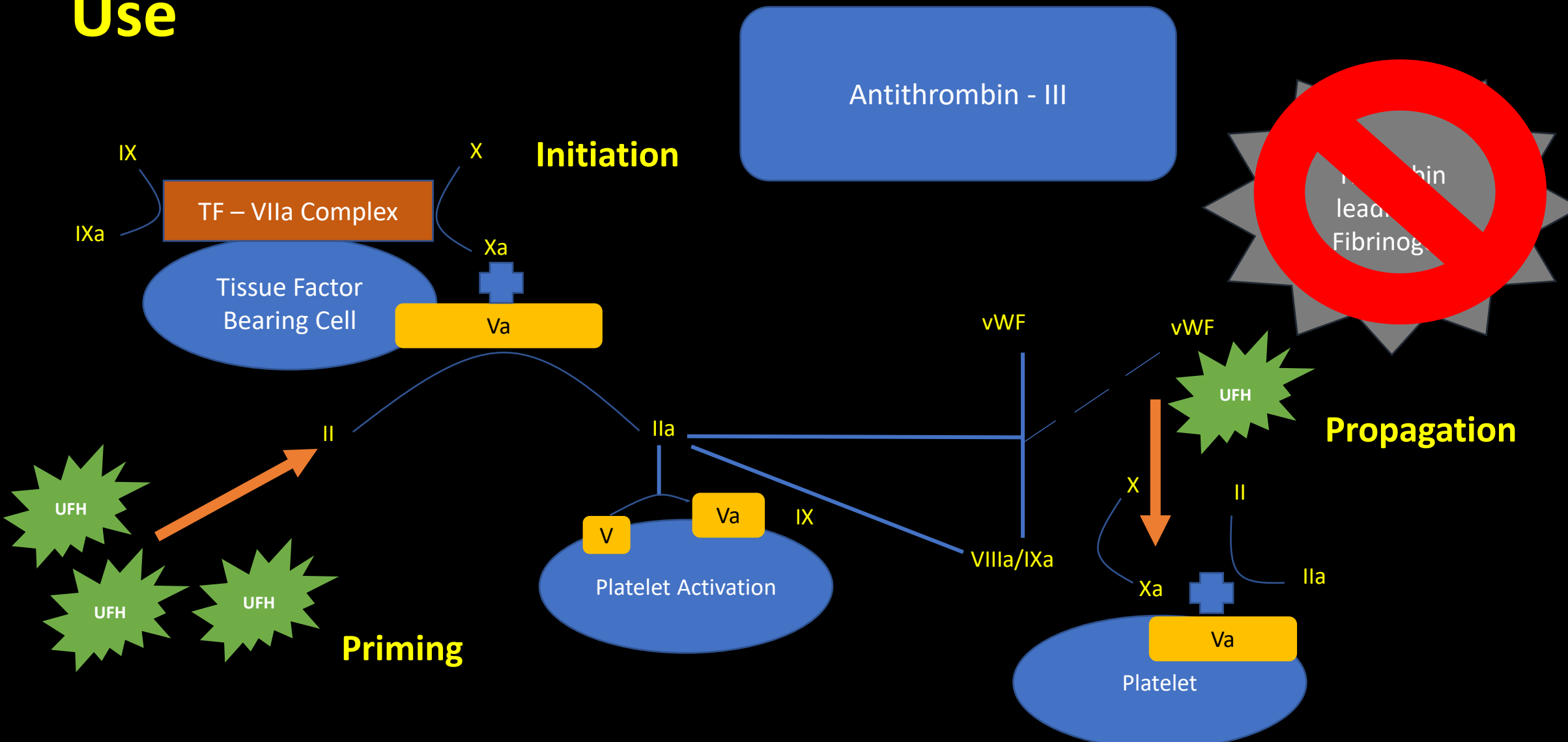
# Quick Overview of Low Molecular Weight Heparin (LMWH)



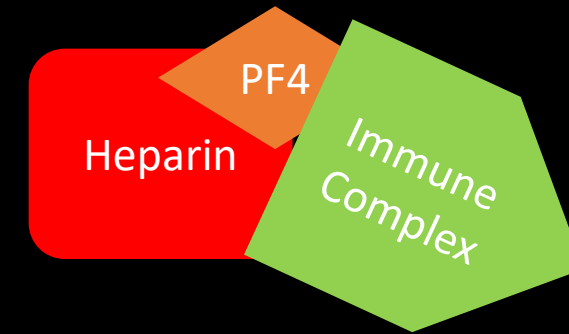
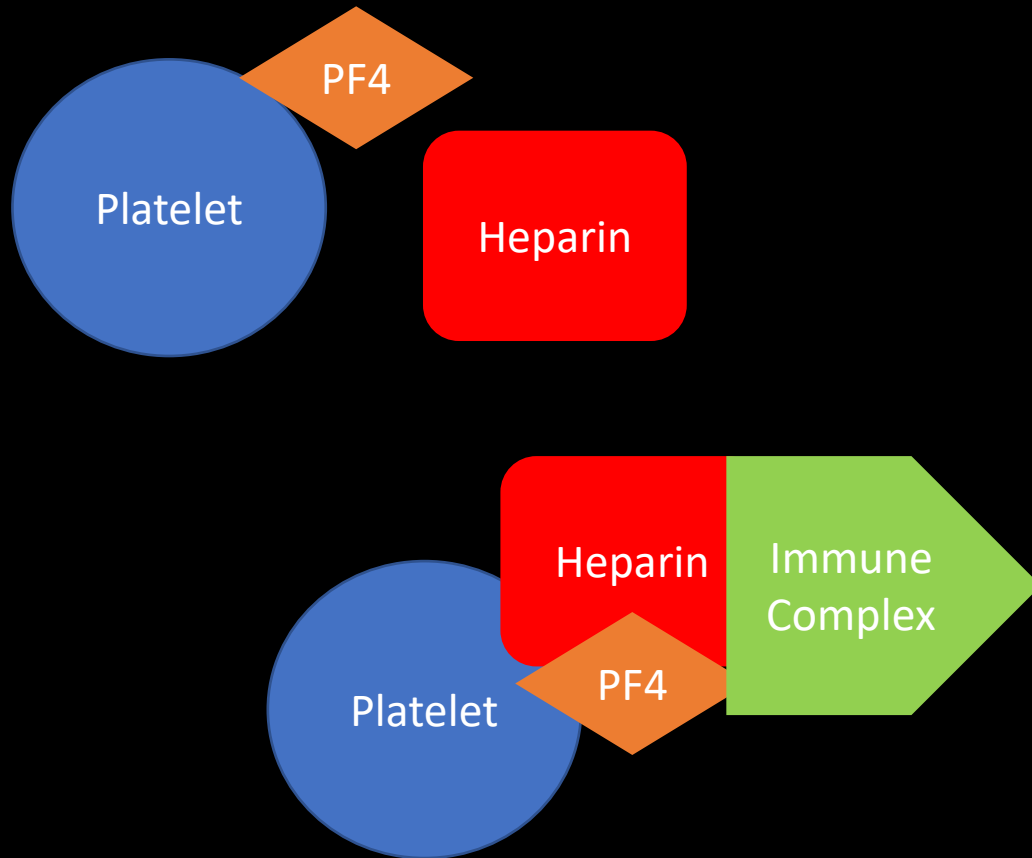
Adapted from: *Arterioscler Thromb Vasc Biol.* 2007 Apr; 27(4): 722 – 727.

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

# Antithrombin – III Deficiency with UFH & LMWH Use



# Heparin Induced Thrombocytopenia (HIT)



- Platelet removal by macrophages causing thrombocytopenia
- Platelet activation, release, aggregation and other procoagulant factors causing thrombosis
- Prothrombotic state that can lead to microvascular clots

# HIT Diagnosis

4T Score

PF4 Test

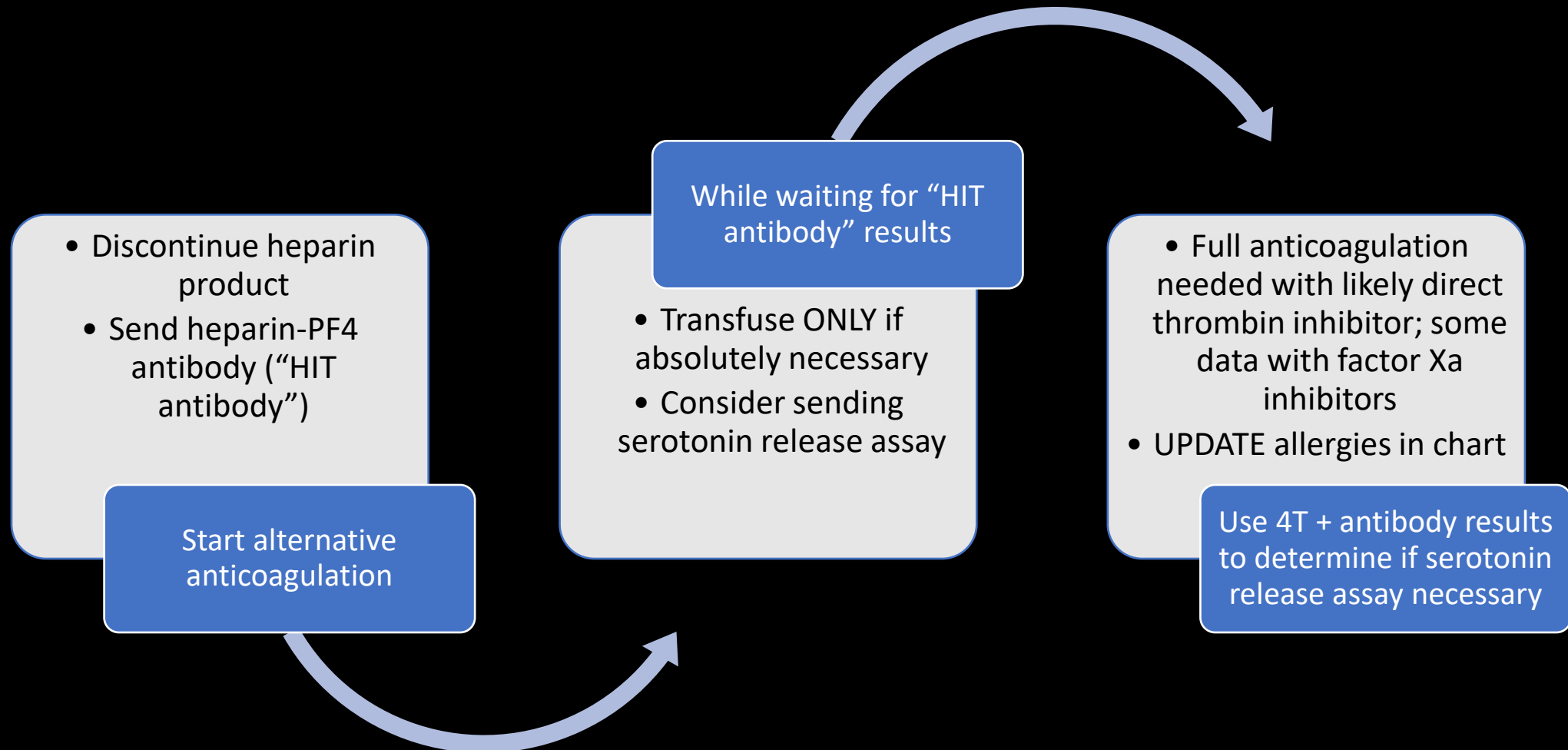
Serotonin  
Release Assay



# Bedside Scoring Tool: 4T Score

Parameter		Score	Total Score and Likelihood of Diagnosis
Thrombocytopenia	Platelet count fall >50%	2	<p>0 to 3 points: Low probability (&lt;1% risk of HIT)</p> <p>4 to 5 points: Intermediate probability (~10% risk of HIT)</p> <p>6 to 8 points: High probability (~50% risk of HIT)</p>
	Platelet count fall 30 – 50%	1	
	Platelet count fall <30%	0	
Timing of platelet count fall	Clear onset between 5 – 10 days	2	
	Consistent with days 5 – 10 days but not clear; onset after day 10	1	
	Platelet count fall <4 days	0	
Thrombosis	New thrombosis or skin necrosis	2	
	Progressive or recurrent thrombosis; non-necrotizing skin lesions	1	
Other causes of thrombocytopenia	None	2	
	Possible	1	
	Definite	0	

# Management if 4T has Intermediate to High Probability

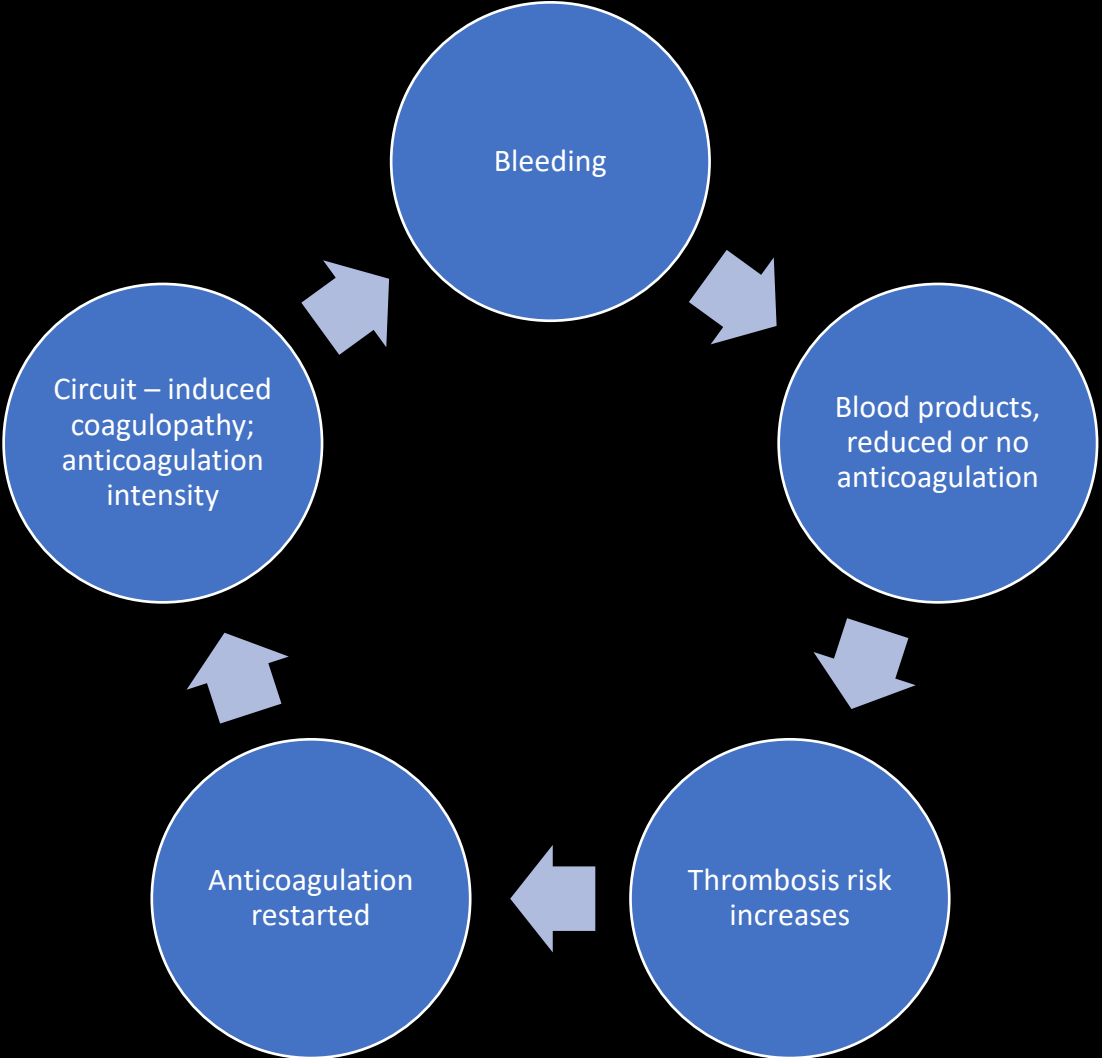


# Patient Case

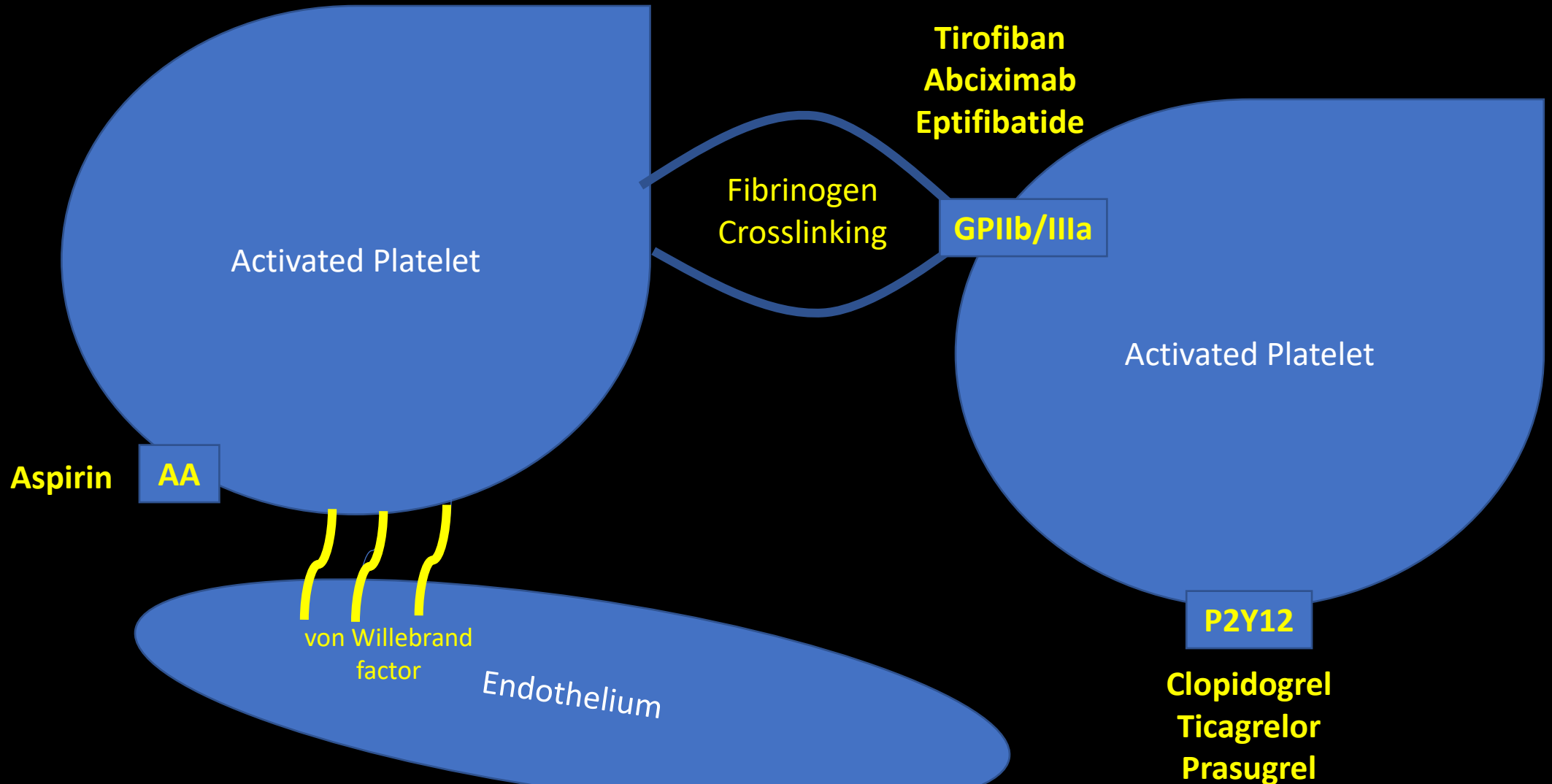
46 – year – old female receiving VV extracorporeal membrane oxygenation to support severe ARDs secondary to *streptococcus pneumoniae* infection; patient also has a submassive pulmonary embolism requiring unfractionated heparin for anticoagulation



# Hemostatic Changes During Extracorporeal Membrane Oxygenation



# Antiplatelet Effects



# Patient Case

52 – year – old male with history of atrial fibrillation receiving apixaban 5 mg twice daily; patient also has a history of chronic kidney disease (CKD) stage 2 and coronary artery disease who comes to your ED after experiencing an isolated traumatic brain injury; GCS 12

# Hemorrhage Management with Antithrombotics

Causative Agent	Hemostasis or Reversal Agent	Comment
UFH	Protamine	Dose is based upon total quantity of heparin units received + last administration time
LMWH	Protamine +/- PCCs	Dose is based upon total quantity of heparin units received + last administration time
Direct Thrombin Inhibitors (Argatroban, Bivalrudin)	Supportive Management	Such a short half-life reversal strategy has not been validated
Warfarin	Vitamin K +/- PCCs	Vitamin K must always be given concomitantly with PCCs
Rivaroxaban or Apixaban	Andexanet Alfa or PCCs	Both strategies tend to be effective most have PCCs on formulary
Fondaparinux	Supportive Management +/- PCCs	Minimal guidance on reversal
Antiplatelet Agents	Desmopressin, Platelets, Supportive Care	Many factors guide decision on antiplatelet reversal

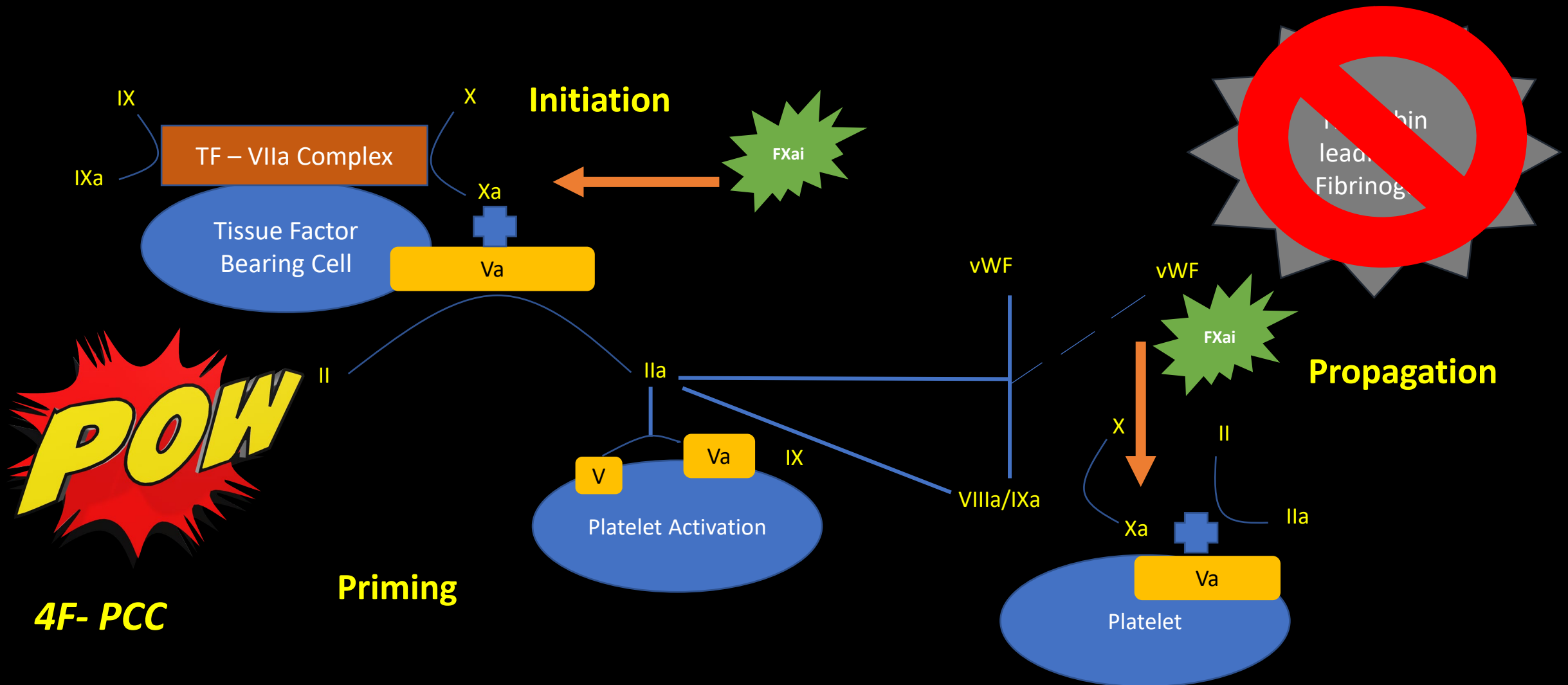
# Identifying DOAC Presence

Agent	Test and Limitations
<p>Factor Xa Inhibitors</p> <ul style="list-style-type: none"><li>• Apixaban</li><li>• Rivaroxaban</li><li>• Edoxaban</li></ul>	<ul style="list-style-type: none"><li>• PT/INR only capture supratherapeutic values</li><li>• aPTT will not be prolonged</li><li>• Anti-Xa assays are not always readily available; work with lab to reduce turn around times; uncalibrated are okay to qualitatively determine drug presence</li></ul>
<p>Direct Thrombin Inhibitors</p> <ul style="list-style-type: none"><li>• Dabigatran</li></ul>	<ul style="list-style-type: none"><li>• PT/INR/aPTT only capture supratherapeutic [ ]s</li><li>• Thrombin time or ecarin clotting time not widely available</li><li>• Limited dabigatran use will make drug specific assay unlikely</li></ul>

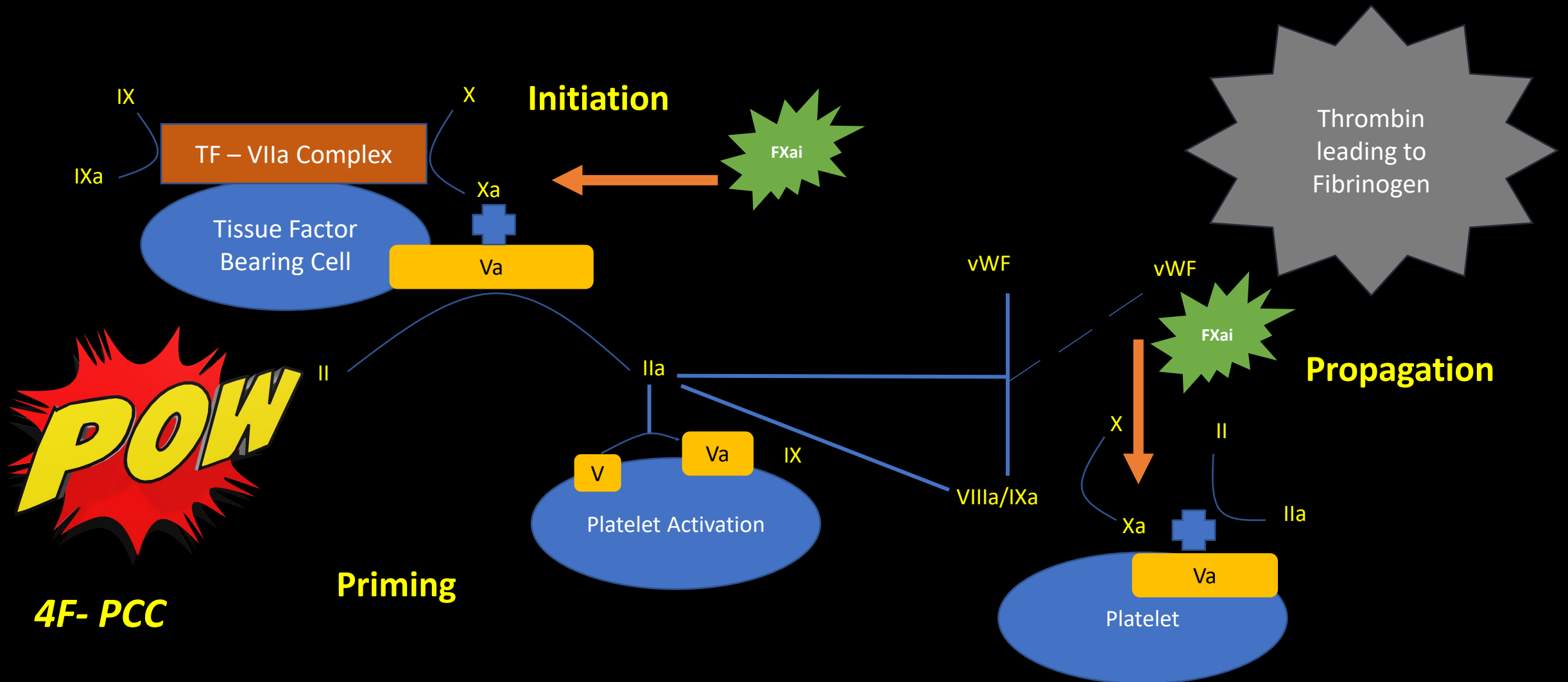
# TEG<sup>®</sup> 5000 and DOACs

- May not be as sensitive to detect lower serum concentrations of DOACs
- As with any coagulation test, TEG<sup>®</sup> 5000 should not be sole factor in monitoring for response, hemostasis, or hemorrhage
- Attempting to determine past medical history can be of extreme benefit

# 4F-PCCs Hemostatic Effects on Factor Xa Inhibitors

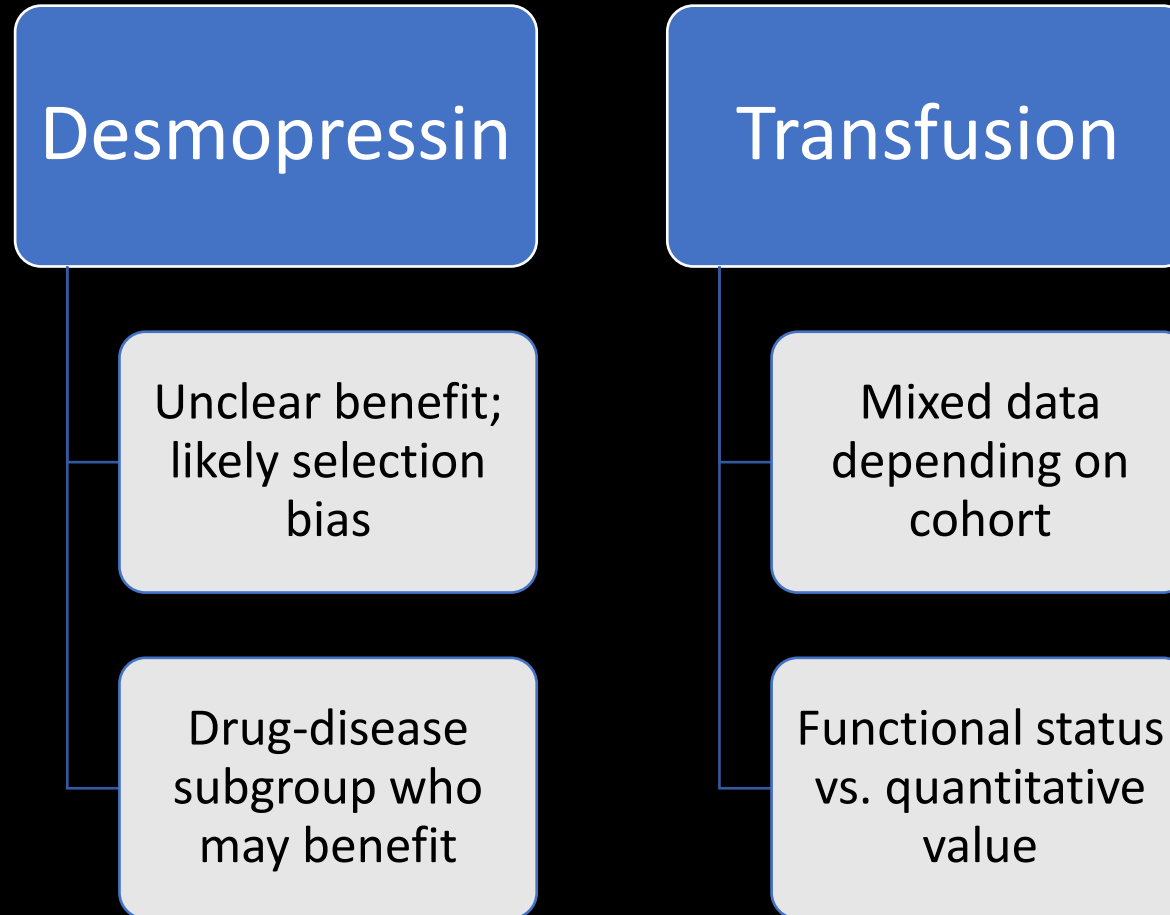


# 4F-PCCs Hemostatic Effects on Factor Xa Inhibitors





# Antiplatelet Bleed Management



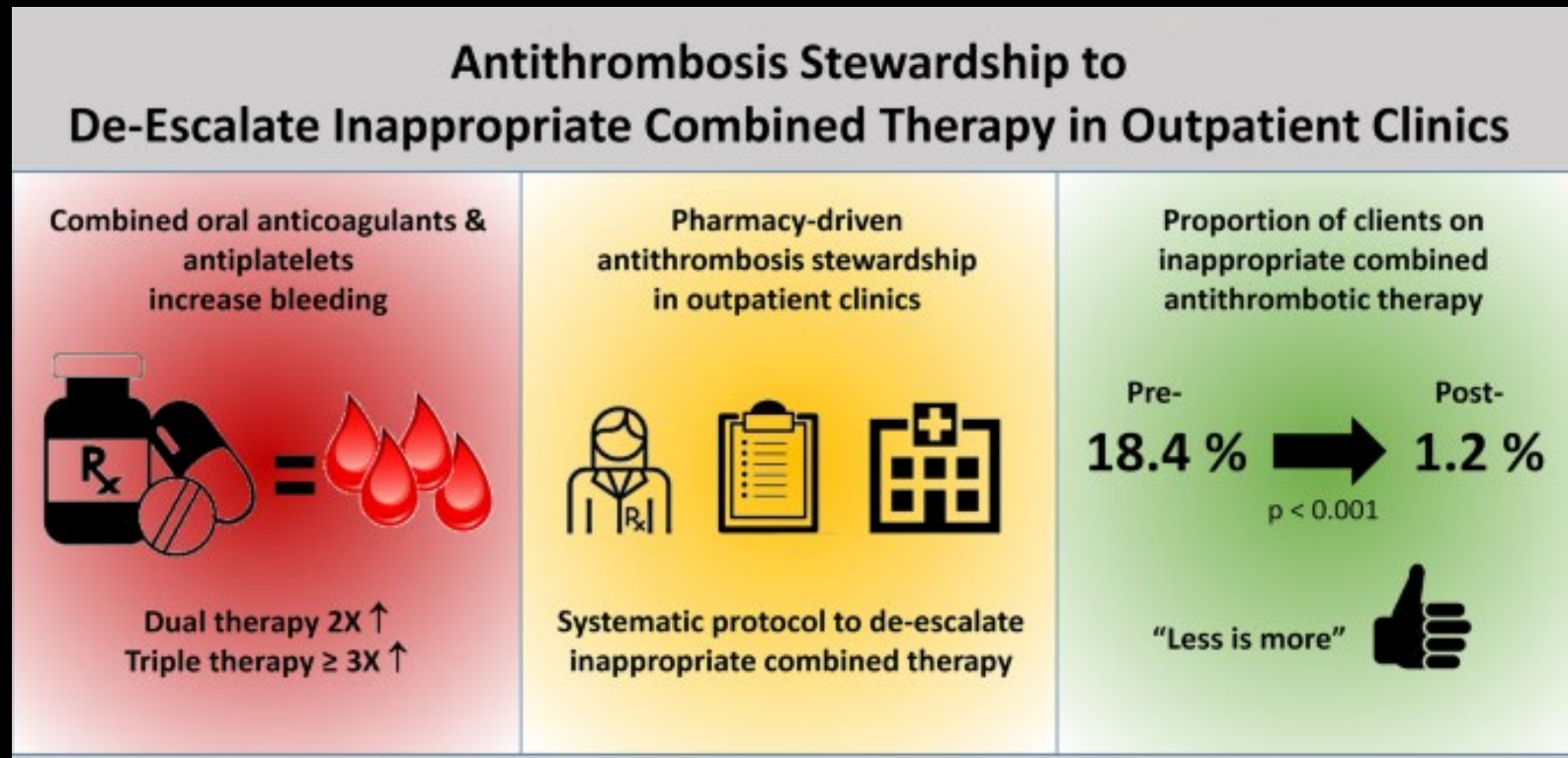
# Revisiting Clinical Case

- 52 – year – old male with history of atrial fibrillation receiving apixaban 5 mg twice daily; patient also has a history of chronic kidney disease (CKD) stage 2 and coronary artery disease who comes to your ED after experiencing an isolated traumatic brain injury; GCS 12
- UFH anti-xa elevated indicating drug present in serum
- TEG 5000k indicating clotting factor dysfunction
- PCC administered to help achieve hemostasis

# Considerations in Providing Precision Based Care to This Case

- Patient prior to injury was higher thrombotic risk given atrial fibrillation
- Important to identify once acute resuscitation has occurred the optimal time to restart at minimum VTE prophylaxis vs. full anticoagulation
- In this patient with history of TBI you may consider an option that is easily reversible or with a short half life for agent selection

# De-escalation Considerations



# Clinical Scenarios for De-escalation in Most Cases



Aspirin for primary prevention of cardiac and stroke events

De-escalation of dual antiplatelet therapy after myocardial stenting at 3 months

Consistently assessing need for both anticoagulation + antiplatelet regimens; rarely is triple therapy indicated

# Future Therapy Close to Approval

- Factor XI inhibitors are in active Phase 3 trials
- Ciraparantag as a “universal” anticoagulant reversal agent has active Phase 3 trials underway
- Further use of functional coagulation testing

# Conclusion

- Critically ill patients are hyperdynamic that can change their risk of thrombosis and bleeding rapidly
- Identifying the appropriate agent and monitoring strategy are essential
- Management of hemorrhage events will be dependent on the agent causing hemorrhage, pharmacokinetic properties, and any drug-disease variables

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