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ANTICOAGULANT & ANTIPLATELET DRUGS

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify clinical uses for parenteral anticoagulants (including heparin, low molecular weight heparins, and direct thrombin inhibitors) and oral anticoagulants (direct oral anticoagulants, vitamin K antagonists).
2. Explain the mechanism of action of parenteral anticoagulants (including heparin, low molecular weight heparins, and direct thrombin inhibitors) and oral anticoagulants (direct oral anticoagulants, vitamin K antagonists).
3. State adverse effects and contraindications to parenteral anticoagulants (including heparin, low molecular weight heparins, and direct thrombin inhibitors) and oral anticoagulants (direct oral anticoagulants, vitamin K antagonists).
4. Describe the clinically important drug interactions of parenteral anticoagulants (including heparin, low molecular weight heparins, and direct thrombin inhibitors) and oral anticoagulants (direct oral anticoagulants, vitamin K antagonists).
5. List reversal agents for anticoagulants.

DRUG NAMES AND PRONUNCIATION

Alteplase AL te plase

Andexanet alfa an DEX a net AL fa

Aspirin AS pir in

Bivalirudin bi VAL I roo din

Clopidogrel kloh PID oh grel

Dabigatran etexilate da BIG a tran

ett EX ill ate

Enoxaparin ee noks a PA rin

Fondaparinux fon da PARE I nuks

Heparin HEP a rin

Idarucizumab eye da roo SIZ uh mab

Protamine PROE ta meen

Rivaroxaban riv a ROX a ban

Ticagrelor tye KA grel or

Warfarin War far in

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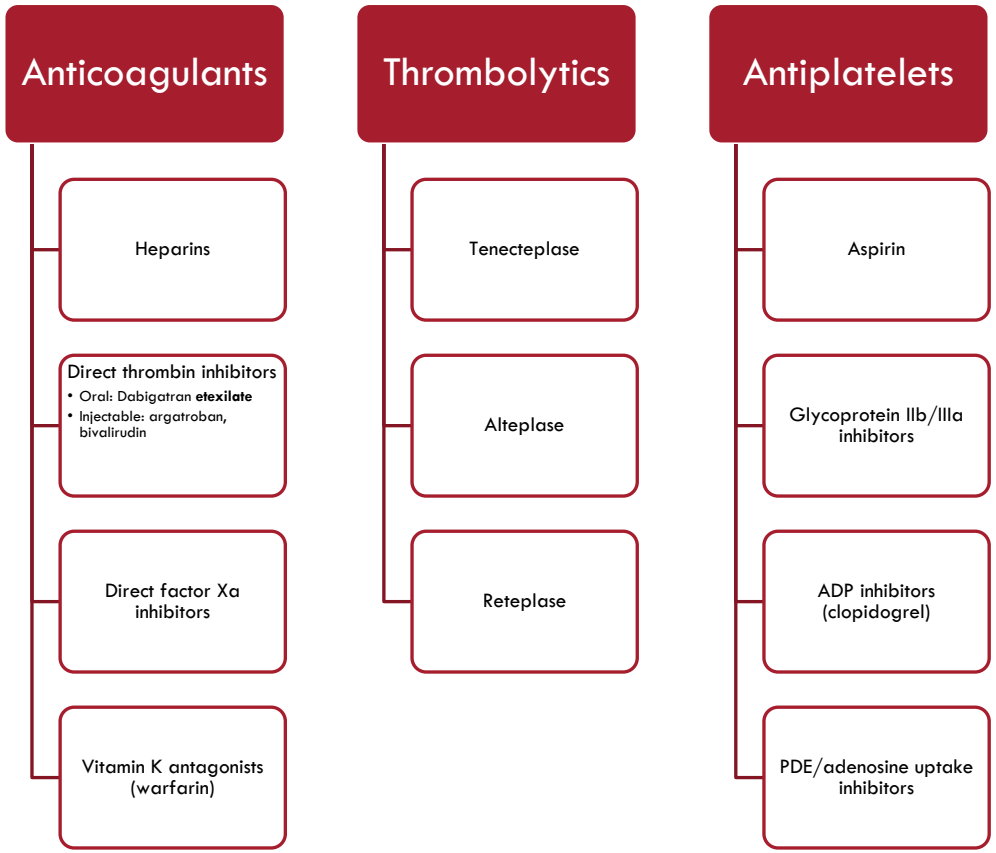
INTRODUCTION

ANTICOAGULANTS & ANTIPLATELETS



ACTIVE LEARNING

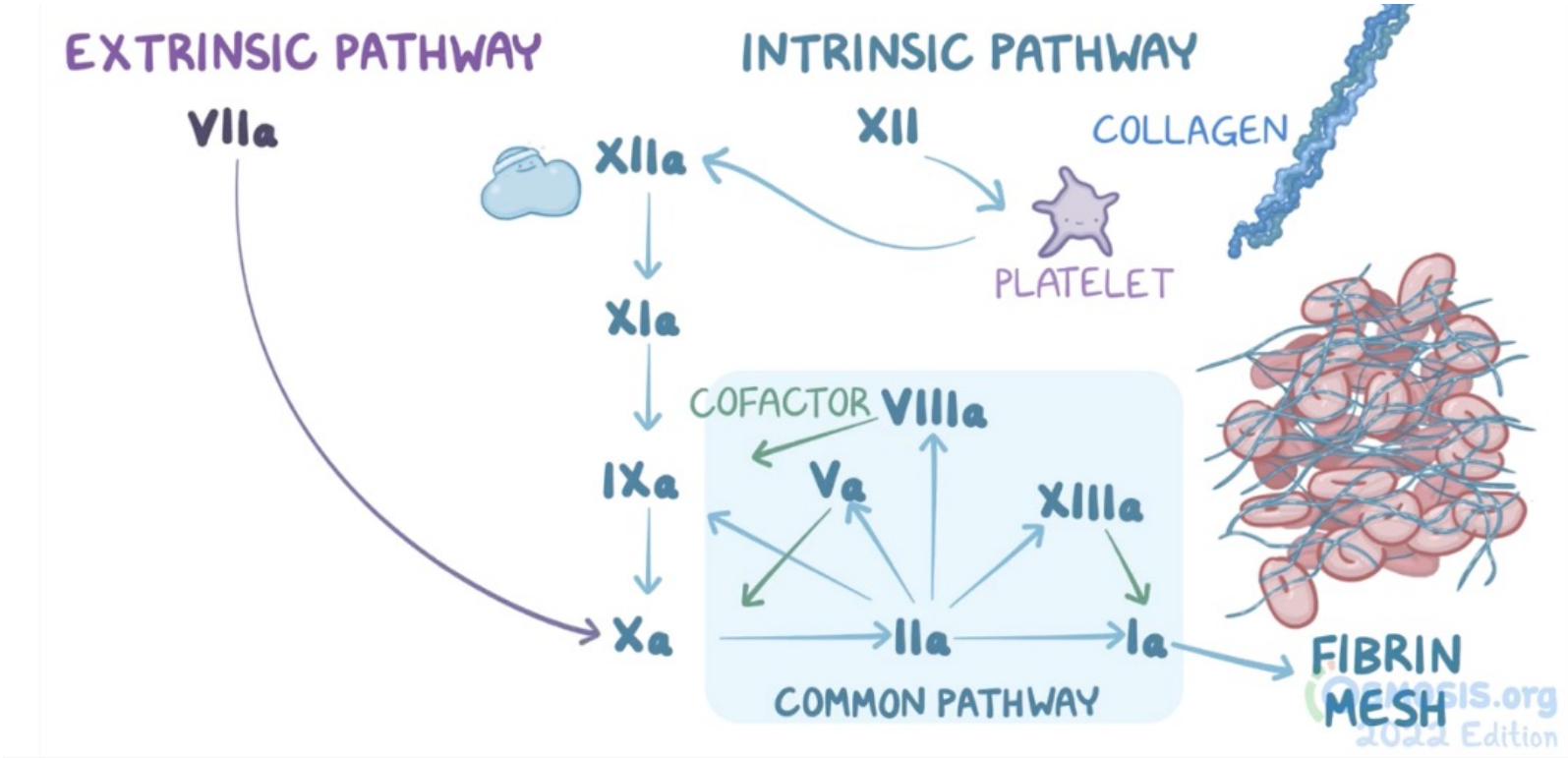
First, sketch the coagulation cascade.

Second, which factor is also called thrombin? How does thrombin contribute to coagulation?

COAGULATION CASCADE

Extrinsic (PT pathway)

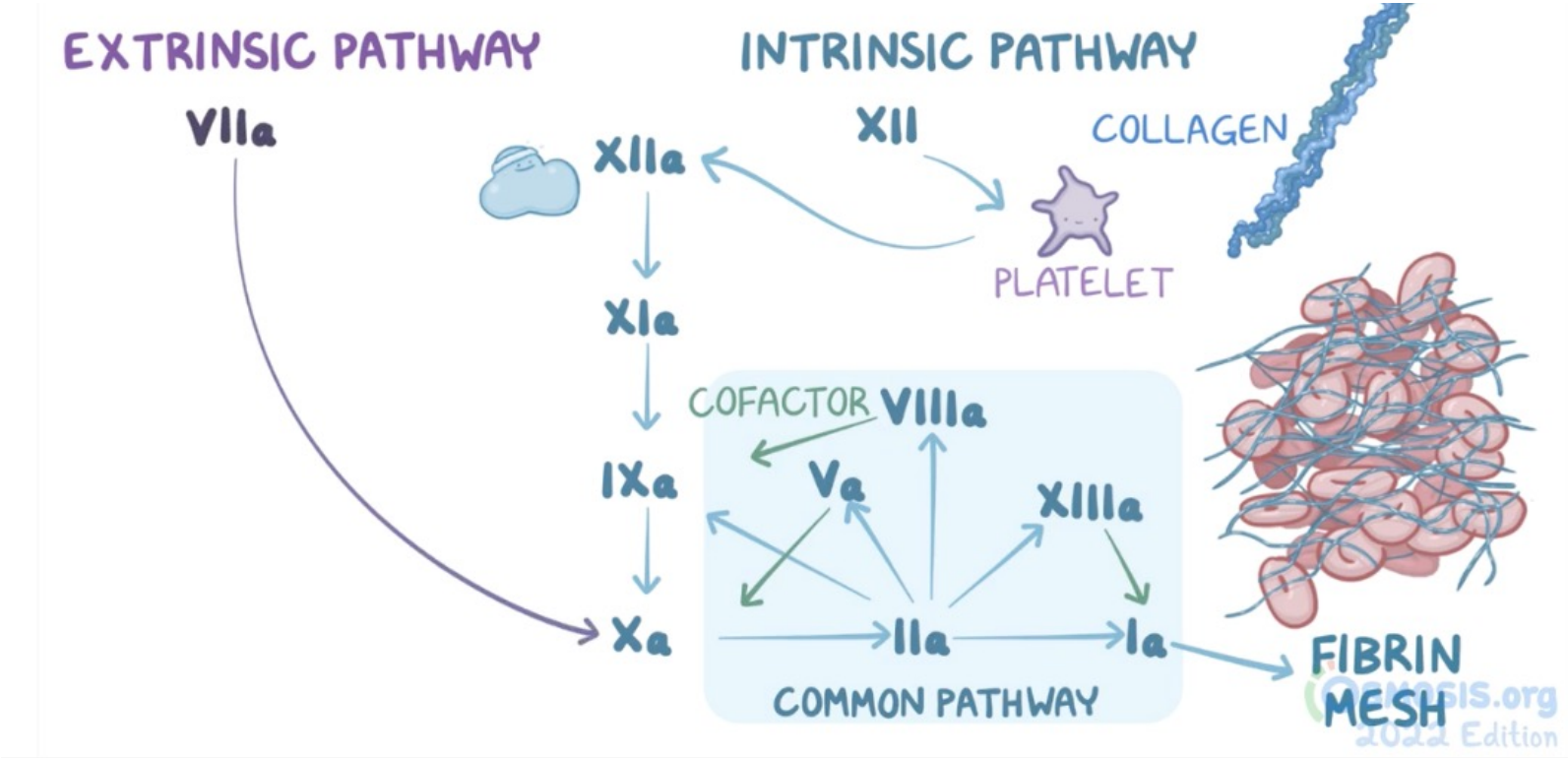
- Exposed tissue factor → VIIa → Xa → starts common pathway



COAGULATION CASCADE

Intrinsic (PTT pathway)

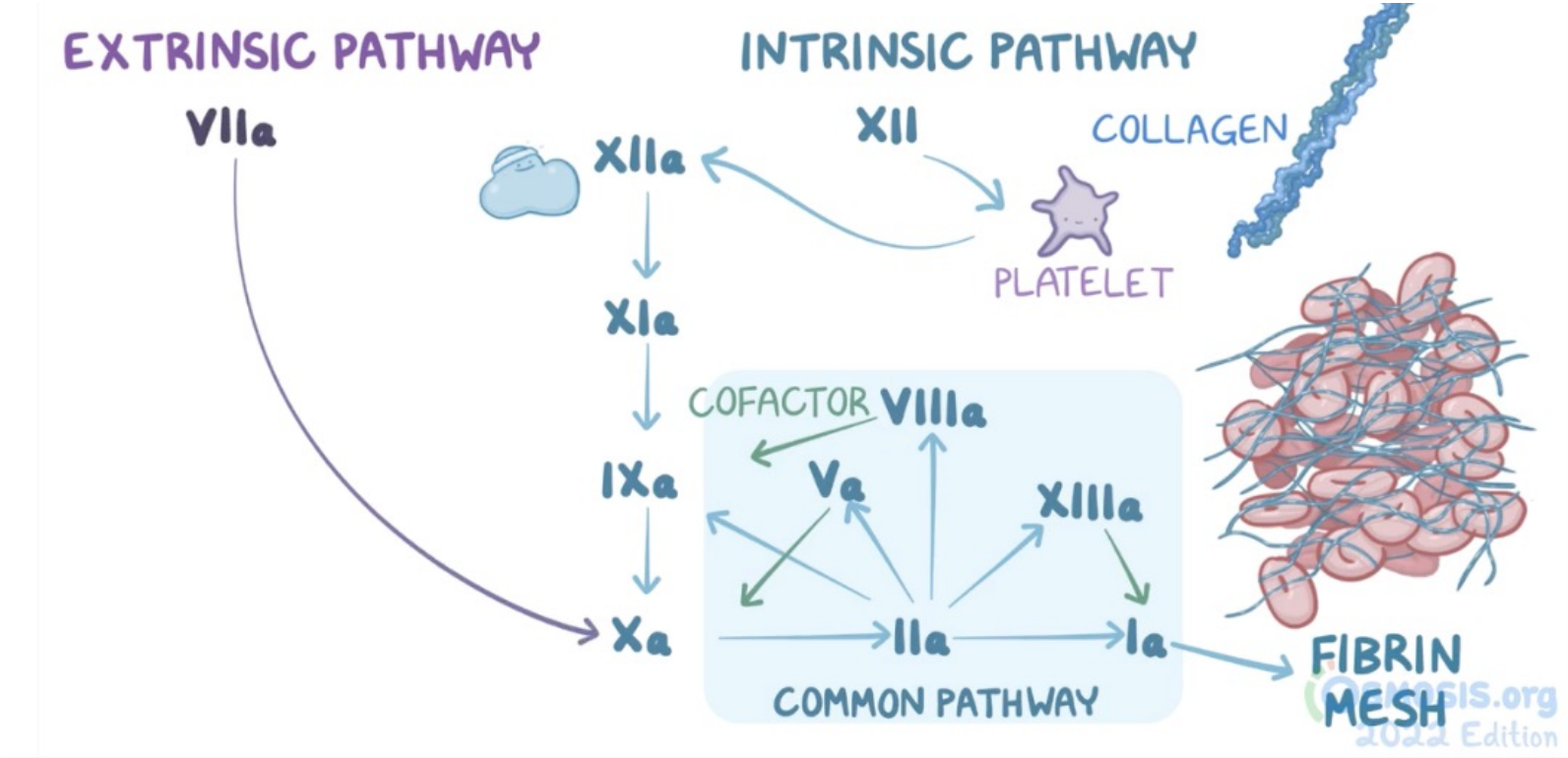
- Circulating factor XII encounters activated platelets or collagen
- XII ⟶ XII a ⟶ XIa ⟶ IXa ⟶ Xa ⟶ starts common pathway
  - IIa (thrombin) ⟶ Ia ⟶ builds fibrin mesh
  - IIa ⟶ V ⟶ co-factor for X
  - IIa ⟶ VIII ⟶ co-factor for IX
  - IIa ⟶ XIII ⟶ helps I (fibrin) form crosslinks



COAGULATION CASCADE

Common

- Factor X activated to Xa
- Factor Xa activates factor II (prothrombin) to IIa (thrombin)
- Factor IIa activates
  - Factor I (fibrinogen) → Ia (fibrin) → fibrin mesh
  - Factor V (co-factor for X)
  - Factor VIII (cofactor for IX)
  - Factor XIII (helps factor I [fibrin] form crosslinks)



COMPONENT/FACTORS, SYNONYMS, & TARGETS

Component or Factor	Common Synonym	Target of Action Of
I Ia	Fibrinogen Fibrin	 Thrombolytics (Fibrinolytics)
II IIa	Prothrombin Thrombin	Heparin, dabigatran (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	

COMPONENT/FACTORS, SYNONYMS, & TARGETS

Component or Factor	Common Synonym	Target of Action Of
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin, rivaroxiban, apixaban, edoxaban (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, aminocaproic acid

PROTHROMBIN TO THROMBIN

Prothrombin (factor II) is inactive

Factor Xa converts prothrombin to thrombin (factor IIa)

Presence of factor Va, negatively charged phospholipid surface, and calcium → more efficient factor Xa activation of prothrombin

- 10^9-fold greater efficiency

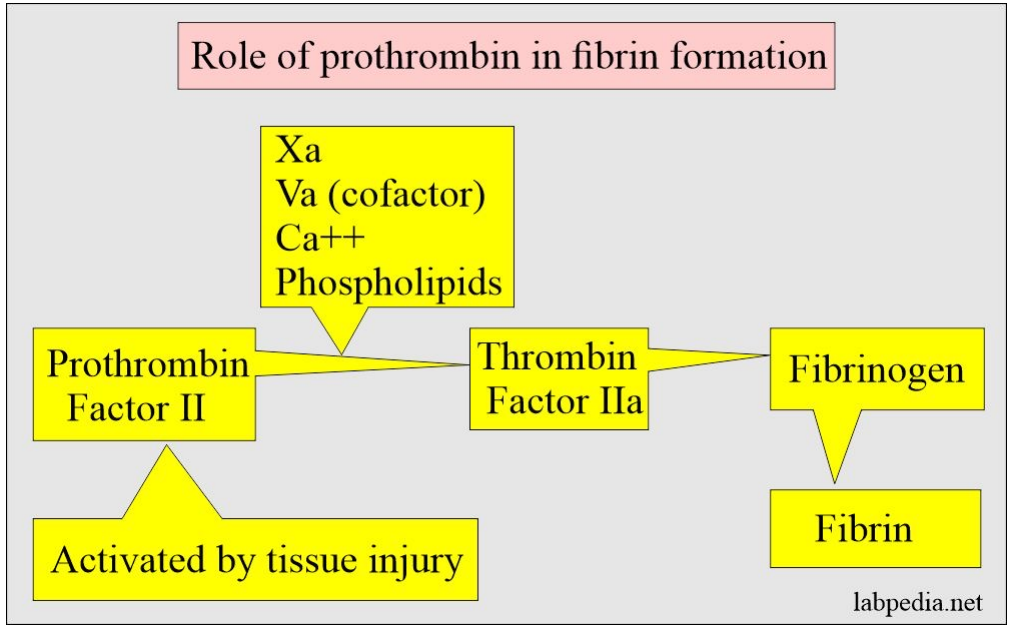
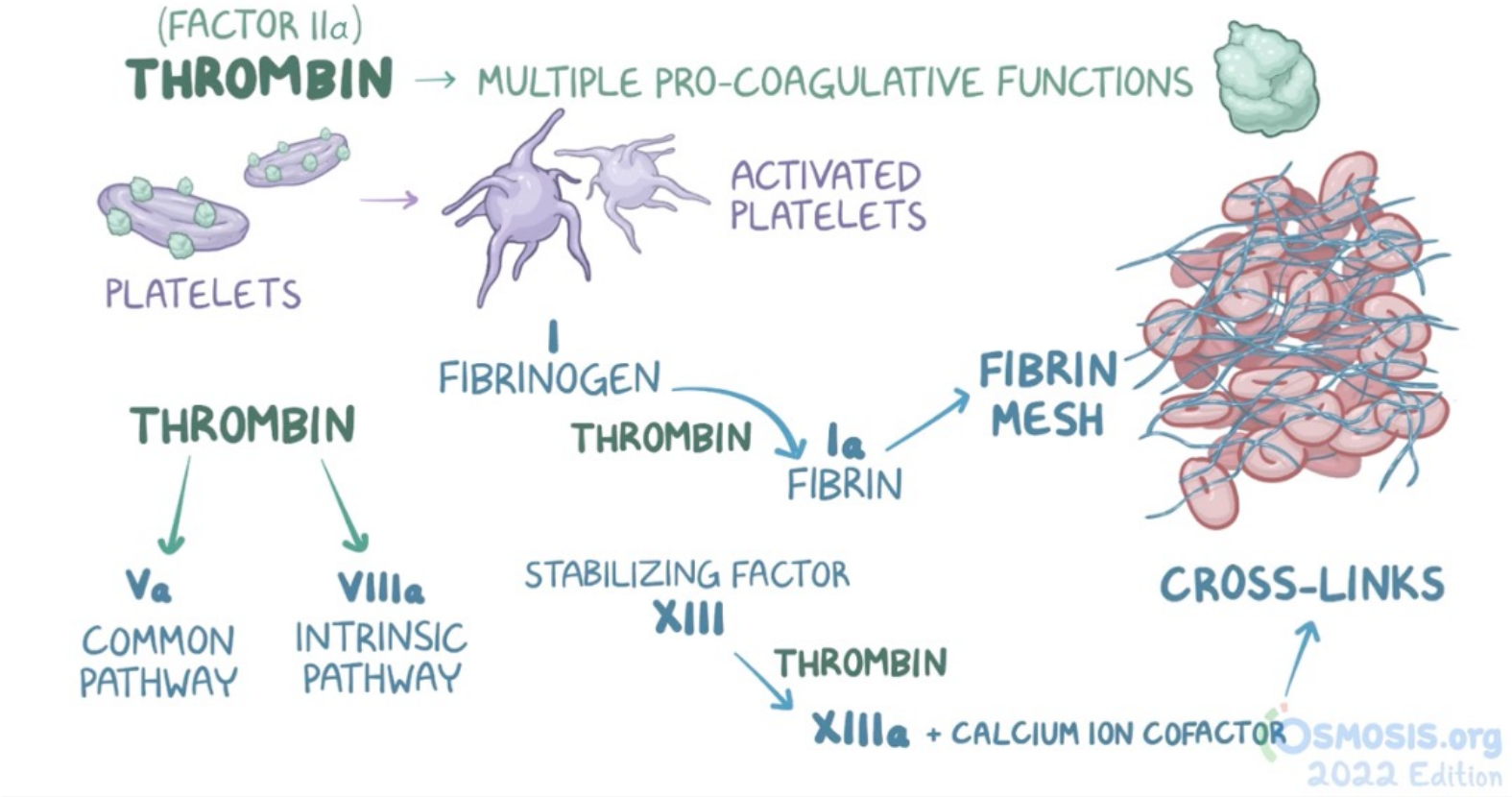


Image credit: https://labpedia.net/coagulation-part-7-blood-coagulation-factors-and-their-interpretations/

THROMBIN

Multiple pro-coagulative functions

- Activates platelets
- Activates factor V (common pathway)
- Activates factor VIII (intrinsic pathway)
- Cleaves fibrinogen (factor I) into fibrin (factor Ia) → forms fibrin mesh
- Cleaves stabilizing factor (factor XIII) into factor XIIIa
  - Combines with calcium ion co-factor to form cross-links between fibril chains → reinforces fibrin mesh



ANTITHROMBIN III ("ANTITHROMBIN")

Protein made by the liver

- Binds to thrombin (factor IIa)
  - Thrombin in blood can bind to antithrombin and become unavailable
- Binds to factor Xa
  - Prevents conversion of prothrombin to thrombin
- Inhibits factors VII, IX, XI, and XII with less affinity

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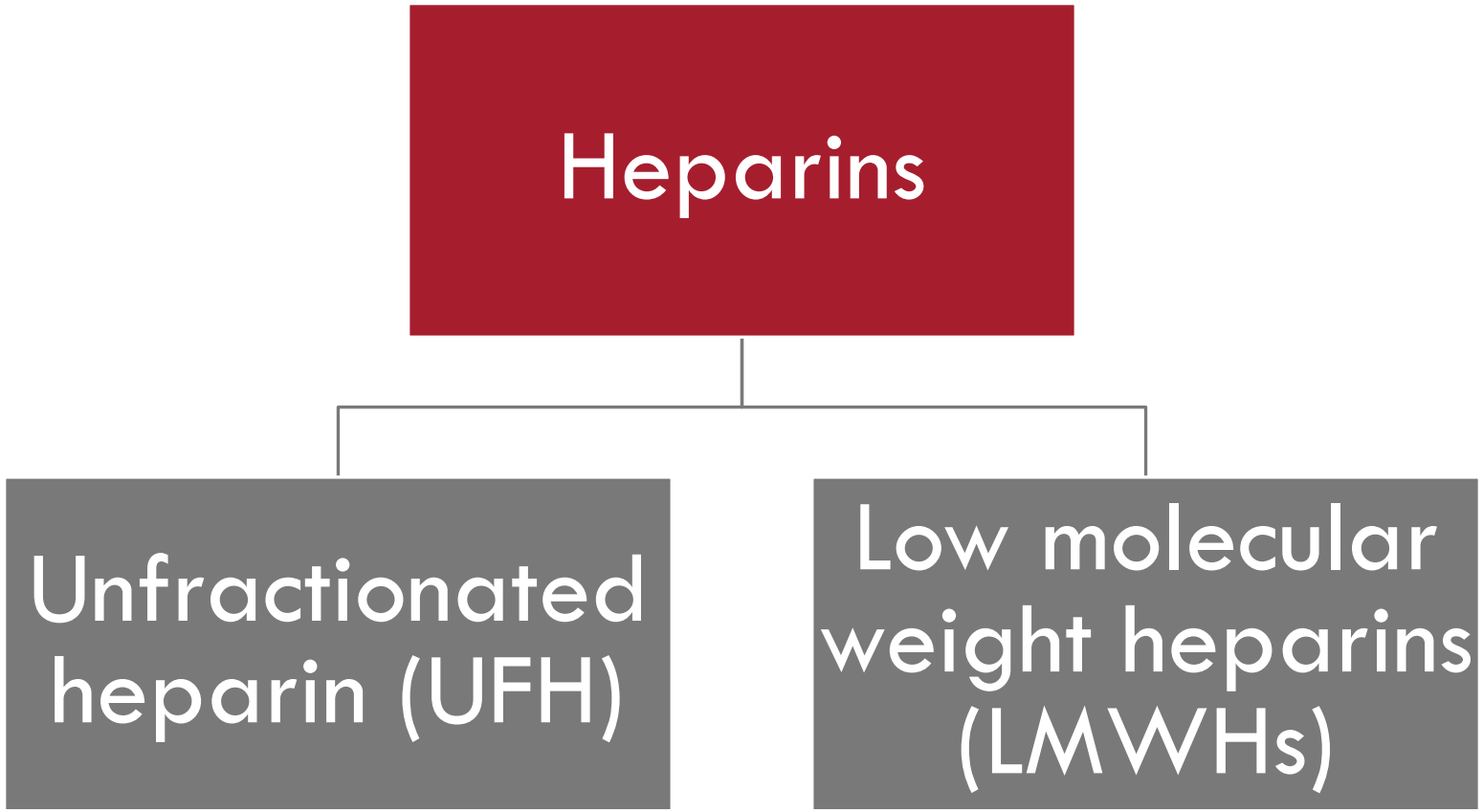
ANTICOAGULANTS: HEPARINS

HEPARIN CATEGORIES

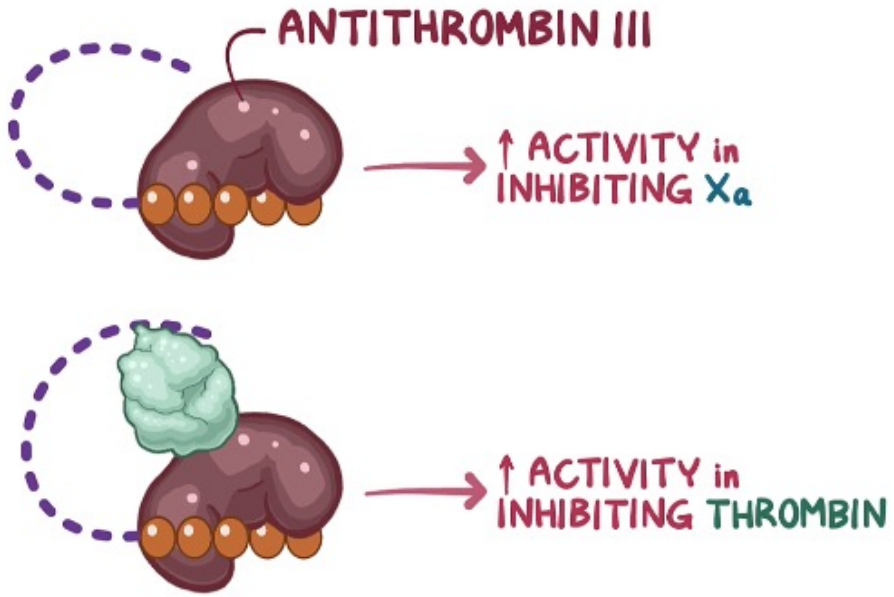


UNFRACTIONATED HEPARIN (UFH) MOA

Indirect thrombin inhibitor

- UFH complexes with endogenous antithrombin III via specific pentasaccharide sequence
- Heparin-antithrombin III complex irreversibly inactivates thrombin (factor IIa) and factor Xa

Derived from bovine lung or porcine intestinal mucosa



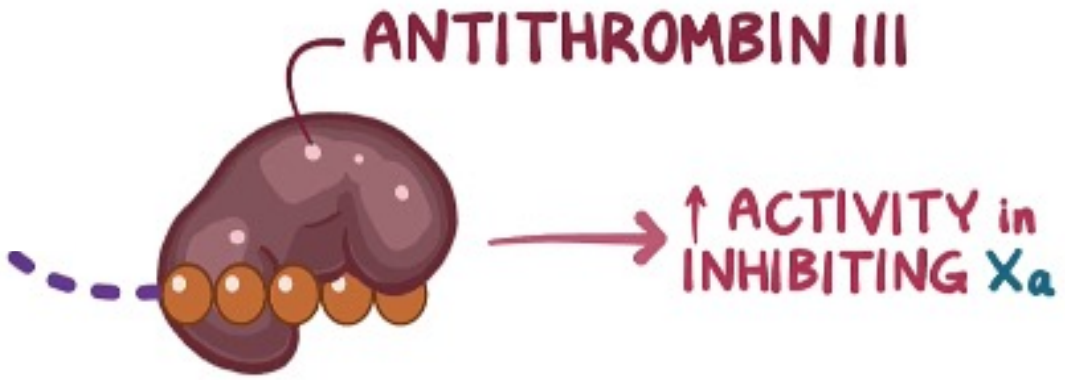
LOW MOLECULAR WEIGHT HEPARIN (LMWH) MOA

Like UFH, binds endogenous ATIII

Same inhibitory effect on factor Xa as UFH

Short chain LMWH–ATIII complex provides more selective action

- Do not directly affect thrombin (factor IIa)



ACTIVE LEARNING

Considering their differing mechanisms of action, which laboratory test(s) could be used to monitor efficacy of UFH? Which laboratory test(s) could be used to monitor efficacy of LMWH?

HEPARINS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Unfractionated heparin 💉	Known hypersensitivity to heparin, pork products, history of heparin-induced thrombocytopenia, severe thrombocytopenia, active bleeding	Bleeding Heparin-induced thrombocytopenia	Other anticoagulants can increase risk of bleeding
Low molecular weight heparins 💉 Enoxaprin (Lovenox) Dalteparin (Fragmin)			

LMWH Boxed Warning: Epidural or spinal hematomas may occur in those receiving neuraxial anesthesia or undergoing spinal puncture

CLINICAL USE & ADME

Prophylaxis and treatment of VTE and thromboembolic complications associated with atrial fibrillation

Prevention of clotting in arterial and cardiac surgery

Anticoagulant for blood transfusions, ECMO, and dialysis

Heparin

- Administered SQ (prophylaxis or acute) or IV (acute)
- Monitored with aPTT

LMWH

- Administered SQ
- Routine lab monitoring typically unnecessary
  - Anti-factor Xa is used when monitoring needed
- Renal dose adjustment may be needed

DOSING CONSIDERATIONS

Heparin

Dosed in units

Therapeutic indications monitored via aPTT (target 2 – 3 X normal)

- Anti-factor Xa levels may be monitored

LMWH

Dosed in mg (enoxaparin) or units (dalteparin)

Therapeutic monitoring not typically done

- Renal impairment may monitor anti-factor Xa levels

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Prothrombotic disorder caused by antibodies that recognize platelet factor 4 (PF4) and heparin

Life-threatening

Occurs after exposure to UFH or LMWH (less common)

Characterization
- Declining platelets
- Pain, redness, swelling of arm or leg
- Ecchymotic lesions
- Rash or sore where heparin was injected
- Weakness, numbness, painful extremity movement

Occurs in ~5% patients exposed to heparin

More commonly seen with UFH (versus LMWH)
- LMWH do not bind platelets to the same degree as heparin

Due to cross-reactivity with heparin antibodies, LMWH should NOT be used in patients with or history of HIT

PHARMACOLOGIC MANAGEMENT OF HIT

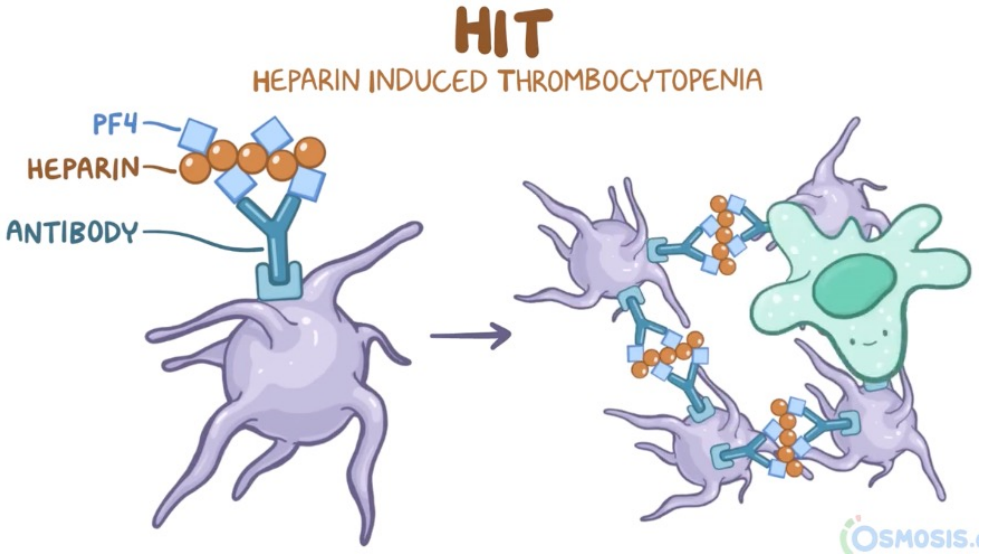
Discontinue ALL forms of heparin

- Includes LMWH

Start alternate anticoagulant to prevent/treat HIT-induced thrombosis

Permissible anticoagulants

- Argatroban
- Bivalirudin
- Fondaparinux (not FDA approved)
- Direct oral anticoagulants



FONDAPARINUX

Synthetic analogue of the pentasaccharide sequence that mediates interaction with antithrombin

Only Xa inhibition

- Too short to bridge antithrombin to thrombin → no direct effect on thrombin

Injectable

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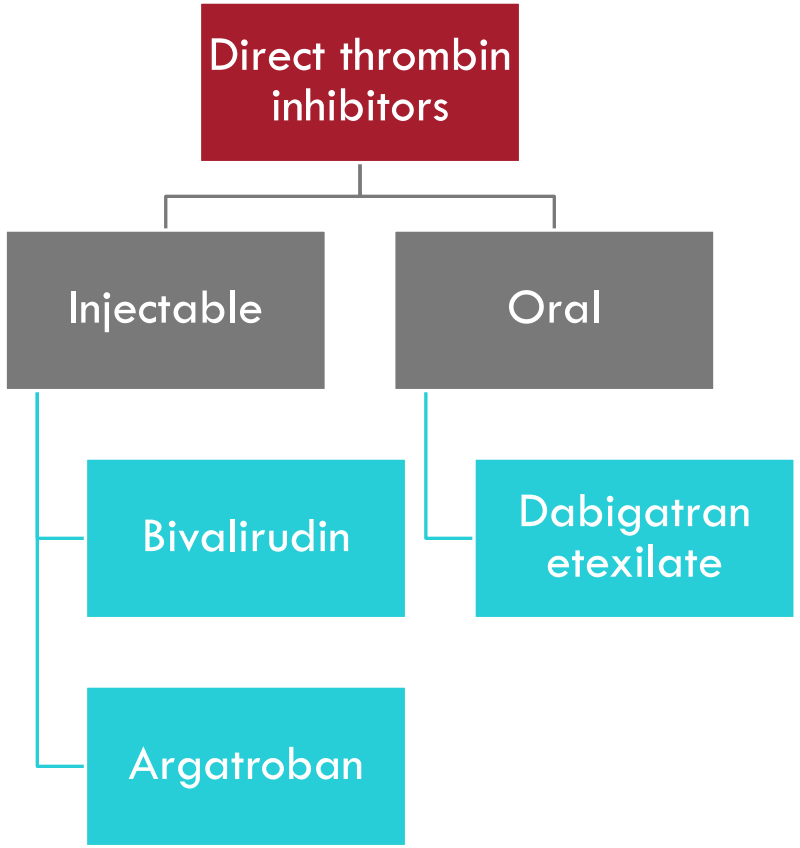
ANTICOAGULANTS: DIRECT THROMBIN INHIBITORS

DIRECT THROMBIN INHIBITOR CATEGORIES



DIRECT THROMBIN INHIBITORS MOA

Bind thrombin

- In circulation and already attached to forming clot

Inhibit enzymatic action of thrombin

DIRECT THROMBIN INHIBITORS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Dabigatran etexilate (Pradaxa) 💊	Active bleeding	Bleeding Dyspepsia Gastritis	Inducers of P-glycoprotein (P-gp) (ie, rifampin) ↓ serum concentrations of dabigatran P-gp inhibitors (ie, ketoconazole) may ↑ serum concentrations of dabigatran Other anticoagulants can increase risk of bleeding
Bivalirudin (Angiomax) 💉 **Argatroban** (Acova) 💉		Bleeding	Other anticoagulants can increase risk of bleeding

Dabigatran Boxed Warnings: Premature discontinuation increases risk of thrombotic events; Epidural or spinal hematomas may occur in those receiving neuraxial anesthesia or undergoing spinal puncture

CLINICAL USE & ADME

Dabigatran etexilate

- VTE treatment and prophylaxis
- Nonvalvular atrial fibrillation
- VTE prophylaxis in total hip arthroplasty

Bivalirudin

- Anticoagulant for use in patients undergoing PCI

Argatroban

- Anticoagulant for use in patients undergoing PCI
- HIT prophylaxis and treatment

Dabigatran etexilate

- Pro-drug that is converted by serine esterases to active dabigatran
- Eliminated in urine; use caution in patients with mild to severe renal impairment
- Routine lab monitoring typically unnecessary

Bivalirudin/argatroban

- Administered intravenously
- Monitor using aPTT

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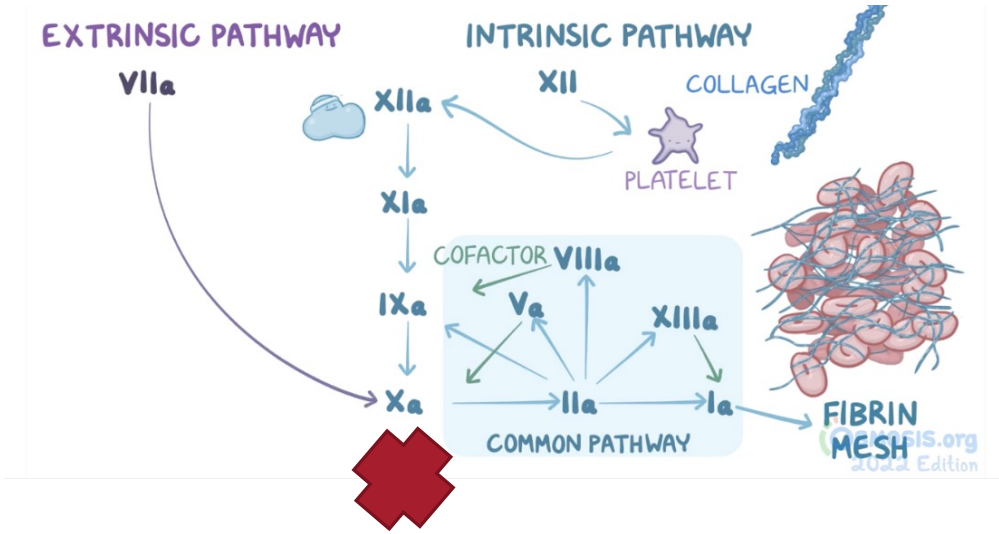
ANTICOAGULANTS: DIRECT FACTOR Xa INHIBITORS

DIRECT FACTOR Xa INHIBITORS MOA

Bind to the active site of factor Xa and inhibits its enzymatic action



DIRECT FACTOR Xa INHIBITORS (-XABAN)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Rivaroxaban (Xarelto) **Apixaban** (Eliquis) **Edoxaban** (Savaysa) **Betrixaban** (Bevyxxa) 💊	Active bleeding	Bleeding	Inducers of P-glycoprotein (P-gp) (ie, rifampin) ↓ serum concentrations of direct factor Xa inhibitors P-gp inhibitors (ie, ketoconazole) may ↑ serum concentrations of direct factor Xa inhibitors Other anticoagulants can increase risk of bleeding

Boxed Warnings: Premature discontinuation increases risk of thrombotic events; Epidural or spinal hematomas may occur in those receiving neuraxial anesthesia or undergoing spinal puncture

CLINICAL USE & ADME

Edoxaban
- VTE treatment
- Prevention of stroke in nonvalvular atrial fibrillation

Apixaban
- VTE treatment and prophylaxis
- Prevention of stroke in nonvalvular atrial fibrillation

Rivaroxaban
- VTE treatment and prophylaxis
- Coronary artery disease
- Prevention of stroke in nonvalvular atrial fibrillation

Rivaroxaban
- Increased exposure with mild-moderate renal dysfunction
  - Avoid in CrCl < 15 ml/min
- May not be appropriate with hepatic dysfunction
- 2023 Beers Criteria recommends avoiding use in older adults

Edoxaban
- Increased exposure with mild-moderate renal dysfunction
  - Avoid in CrCl < 15 ml/min

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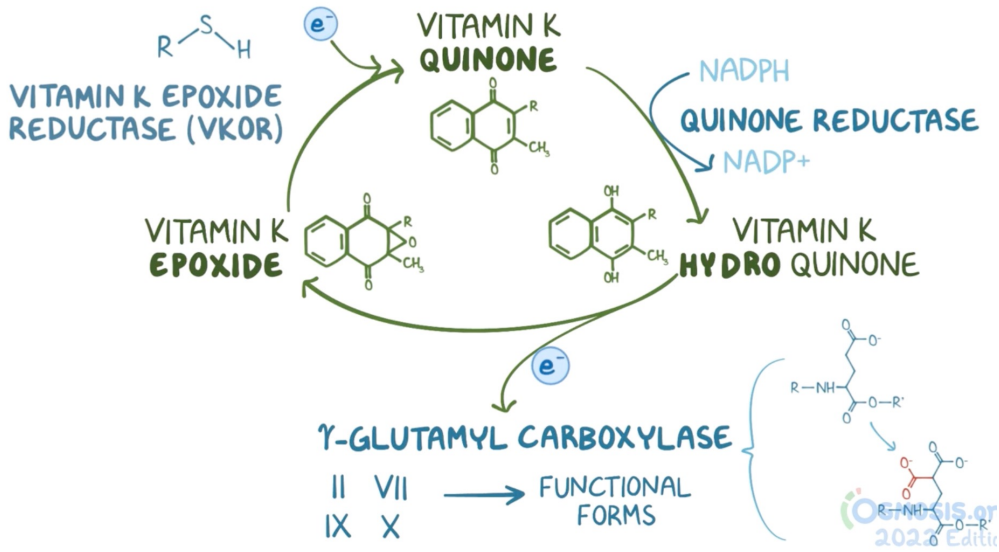
ANTICOAGULANTS: VITAMIN K ANTAGONISTS

VITAMIN K & COAGULATION

Dietary vitamin K = vitamin K quinone

- Reduced to vitamin K hydroquinone
- Vitamin K quinone donates electrons to gamma glutamyl carboxylase
- Gamma glutamyl carboxylase converts factors II, VII, IX, and X to functional forms
- Vitamin K epoxide converted back to vitamin K quinone via vitamin K epoxide reductase

Single molecule of vitamin K can be used many tines



ACTIVE LEARNING

How would inhibiting vitamin K epoxide reductase impact coagulation? Which clotting factors would be impacted by inhibition of vitamin K epoxide reductase?

PROTEIN C & S

Glycoproteins

Predominantly produced in liver

Important components of natural anticoagulant system in the body

Vitamin K dependent

Essential in maintenance of physiologic hemostasis

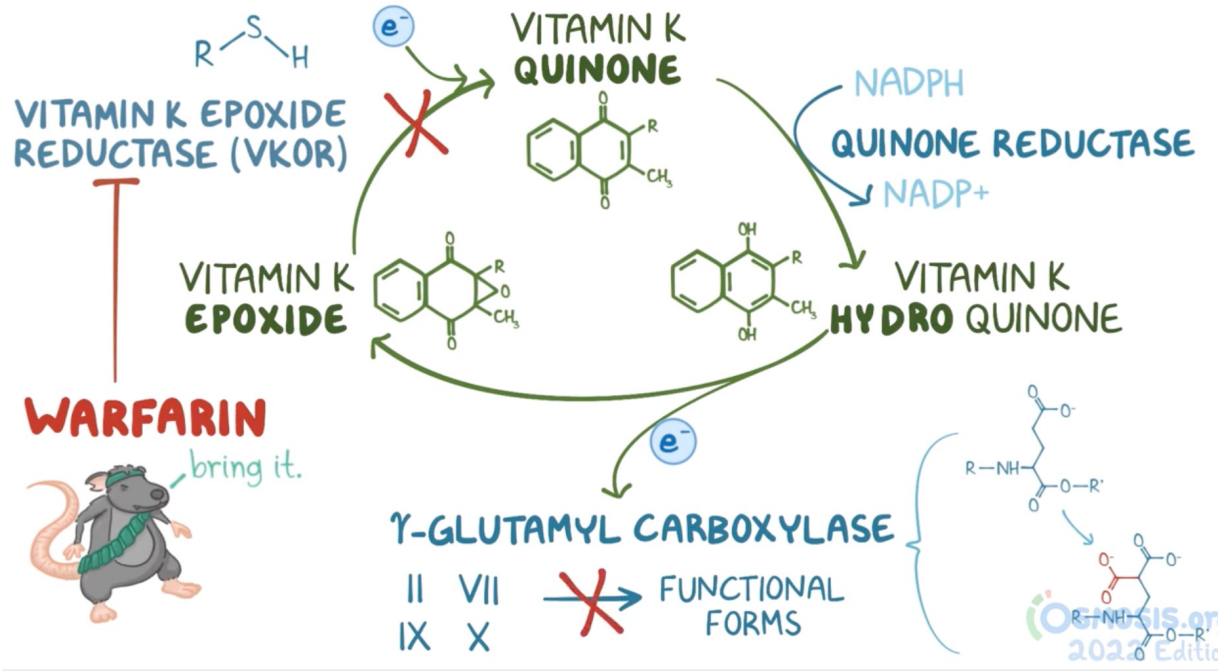
VITAMIN K ANTAGONISTS MOA

Inhibits vitamin K epoxide reductase

- Blocks enzyme that regenerates reduced vitamin K

Inhibits protein C and S

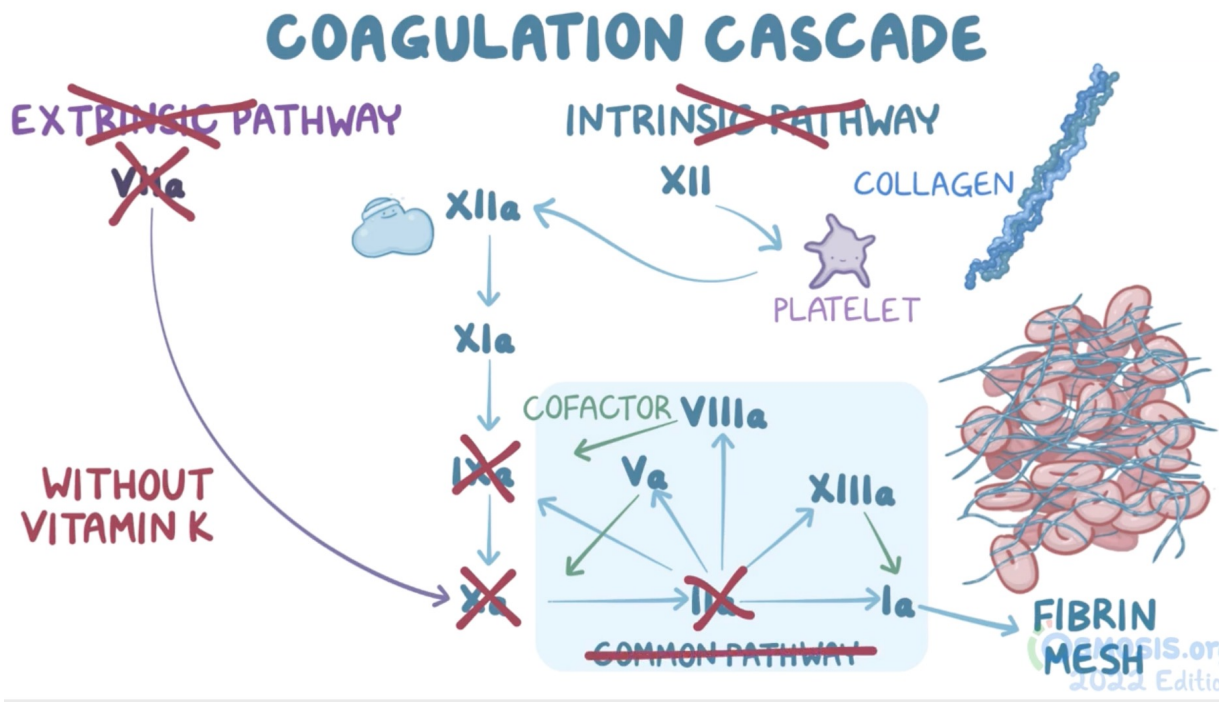
Action occurs in the liver



VITAMIN K ANTAGONISTS MOA

Has no effect on activity of already formed clotting factors

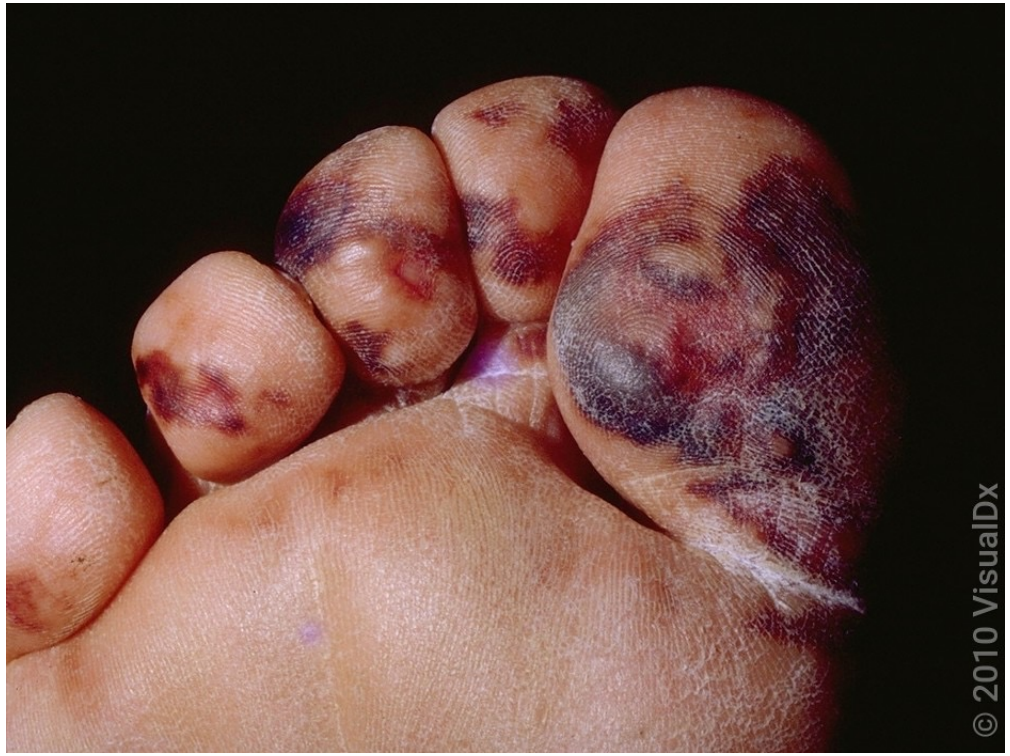
- Peak onset is delayed several days
- Depends on rate of metabolism of preformed factors
  - Factor II: 60 hrs, Factor VII: 8 hrs, Factor IX: 24 hrs, Factor X: 40 hrs, Protein C: 14 hrs)

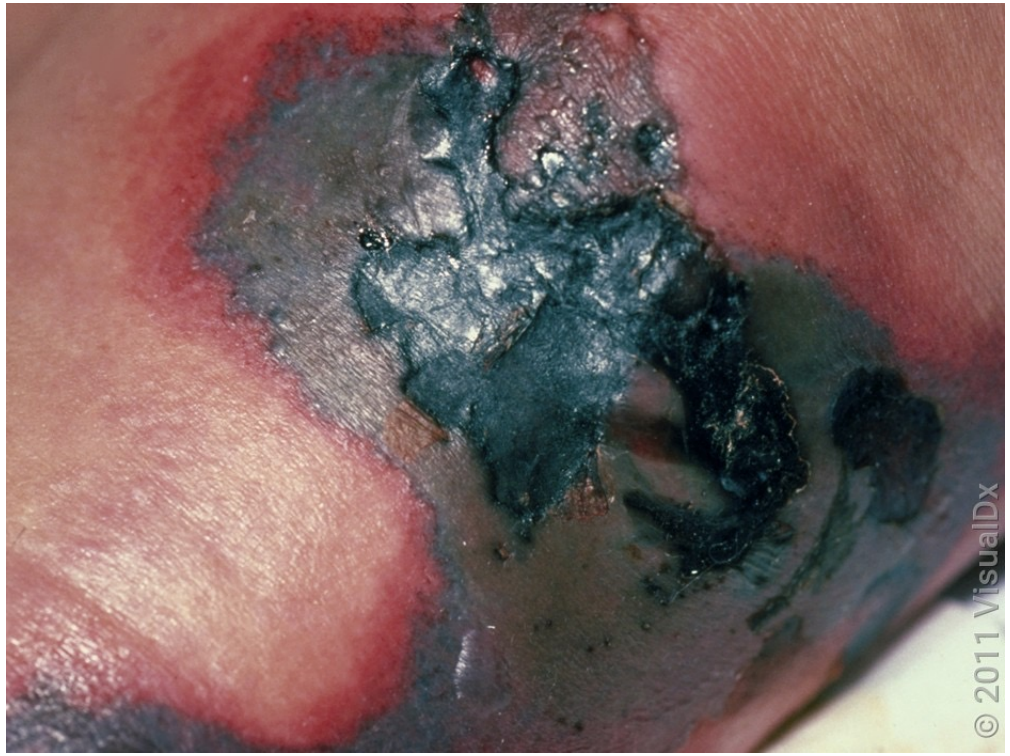


VITAMIN K ANTAGONISTS (WARFARIN)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Warfarin (Coumadin) 💊	Active bleeding Hemorrhagic tendencies Recent or potential surgery of eye or CNS Blood dyscrasias Malignant hypertension Pericarditis or pericardial effusion Bacterial endocarditis Patients with high potential for noncompliance Eclampsia/preeclampsia Pregnancy (teratogen)	Bleeding **Skin necrosis** Fetal toxicity	MANY CYP450 interactions **Notable drugs that increase warfarin levels:** **Sulfamethoxazole** **Amiodarone** **Metronidazole** **Fluconazole** Other anticoagulants can increase risk of bleeding
Boxed Warnings: Fatal bleeding risk			

WARFARIN NECROSIS





CLINICAL USE & ADME

Adjunct to reduce risk of systemic embolism after myocardial infarction

VTE prophylaxis and treatment

Prevention of thromboembolic complications of atrial fibrillation or cardiac valve replacement

Limitations: warfarin has NO direct effect on established thrombi

- Used to prevent further extension of already formed thrombi and prevent secondary thromboembolic compilations

Metabolized in liver

- MANY drug interactions
- Genetic variations in CYP2C9 isozyme and vitamin K epoxide reductase (VKOR) correlate with warfarin dose requirements

Individualized dosing (tremendous variability)

Routine monitoring is necessary

- INR (International Normalized Ratio) used
- Target is typically 2-3 or 2.5-3.5, depending on indication

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BLEEDING MANAGEMENT & REVERSAL AGENTS

MANAGEMENT OF BLEEDING

Any anticoagulant associated with bleeding

Major bleeding

- Intensive care setting
- Anticoagulant drug removal (reversal agent, activated charcoal, hemodialysis)
- Hemodynamic support

GENERAL ANTICOAGULANT REVERSAL STRATEGY

Discontinue all antithrombotic agents

Specific reversal agent/antidote

Nonspecific agents (such prothrombin complex concentrates or PCCs)

Antifibrinolytic agent (tranexamic acid, epsilon-aminocaproic acid)

Desmopressin (DDAVP)

Drug removal from circulation (ie, dialysis) or GI tract (activated charcoal)

REVERSAL AGENTS

Medication	Reversal Agent
Unfractionated heparin 💉	Protamine
Low molecular weight heparin 💉	Andexanet alfa Protamine (partial reversal)
Direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban) 💊	Andexanet alfa Prothrombin complex concentrate (PCC)
Direct thrombin (IIa) inhibitors (bivalirudin 💉, argatroban 💉, dabigatran etexilate 💊)	Dabigatran etexilate – Idarucizumab (Fab fragment) Bivalirudin, argatroban – PCC, tranexamic acid

Medication	Reversal Agent
Vitamin K Antagonist (warfarin) 💊	Vitamin K1 (phytonadione) 4-factor PCC, fresh frozen plans (FFP)
Thrombolytics (alteplase, reteplase, tenecteplase) 💉	FFP, cryoprecipitate
Glycoprotein IIb/IIIa inhibitor (GP IIb/IIIa) (abciximab, eptifibatide, tirofiban) 💉	None; dialysis
ADP inhibitors (clopidogrel) 💊	Controversial – some may use platelet transfusion

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CLINICAL CONSIDERATIONS

PREGNANCY

Pregnancy creates a hypercoagulable state

- Progesterone-induced venodilation → venous stasis
- Venous compression by uterus
- ↓ protein S activity, ↑ protein C resistance
- Increased thrombin production

Pregnancy risks

- Early miscarriage
- Excessive bleeding
- Placenta hemorrhage

ACTIVE LEARNING

Which anticoagulants would be most appropriate in pregnancy? Which anticoagulants would be least appropriate in pregnancy?

ANTICOAGULATION IN PREGNANCY

LMWHs (do not cross placenta)

UFH (does not cross placenta)

If patient has HIT, consider fondaparinux

AVOID

- Direct oral anticoagulants (small molecules → likely cross placenta)
  - Oral direct thrombin inhibitors (dabigatran)
  - Oral direct Xa inhibitors (rivaroxaban, apixaban, edoxaban)
- Warfarin (crosses placenta; teratogen)

POSTPARTUM ANTICOAGULATION

Postpartum may also be hypercoagulable

American Society of Hematology recommend certain anticoagulants during breastfeeding

- LMWH
- UFH
- Fondaparinux
- Warfarin
- Low-dose aspiring for vascular indications

AVOID direct oral anticoagulants

- Oral direct thrombin inhibitors (dabigatran)
- Oral direct Xa inhibitors (rivaroxaban, apixaban, edoxaban)

OLDER ADULTS

Oral anticoagulant recommendations per the 2023 American Geriatric Society's Beer's Criteria for long-term treatment of VTE or nonvalvular atrial fibrillation

- AVOID using warfarin (unless alternative agents are contraindicated)
  - For older adults who have been using warfarin long-term, may be reasonable to continue
- AVOID using rivaroxaban
- USE CAUTION in selecting dabigatran over other DOACs (such as apixaban) for

REFERENCE LIST

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ANY QUESTIONS?