

# Pharmacology



Sheet No. 4

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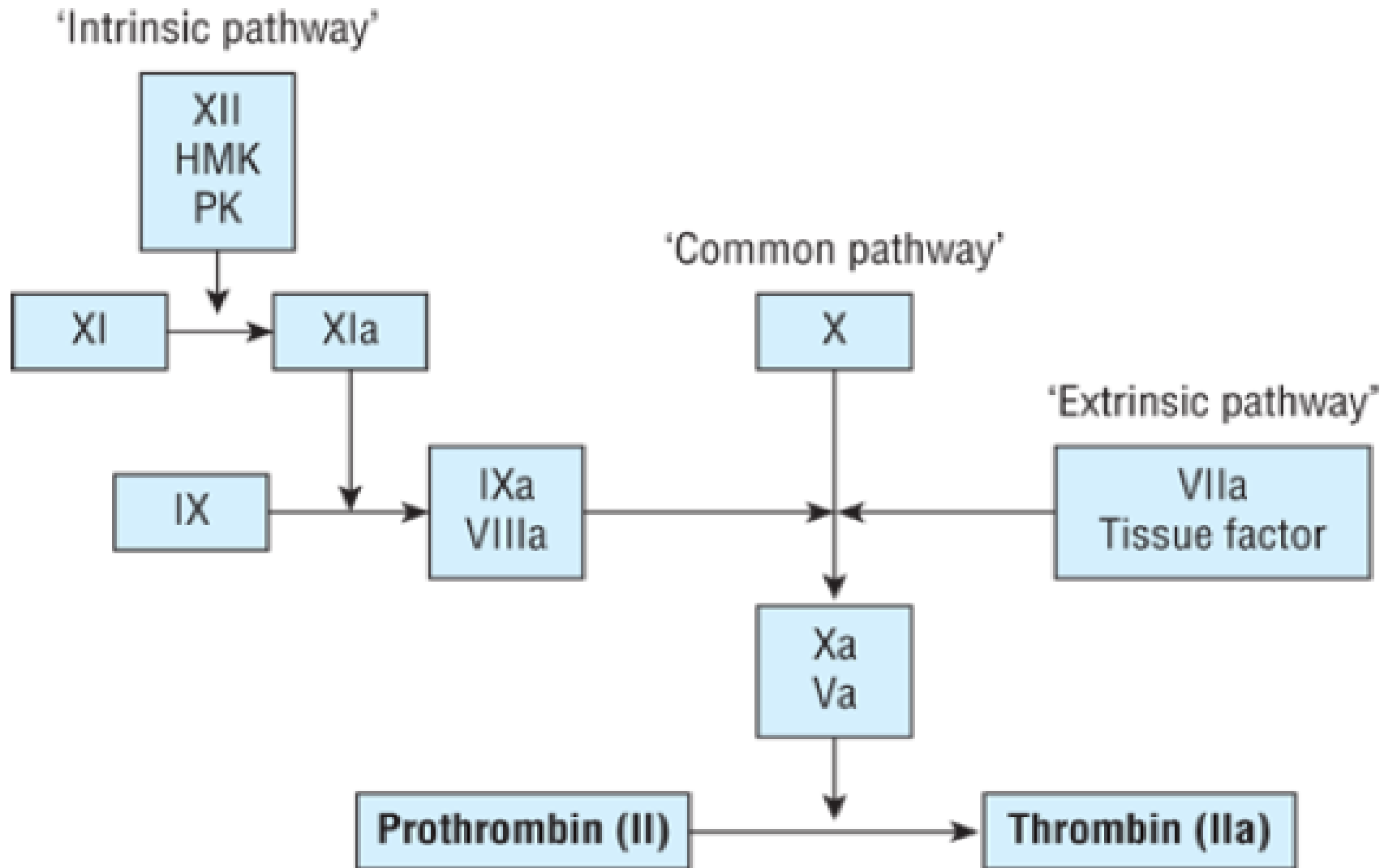
# Anticoagulants, Thrombolytics, and Antiplatelet Drugs

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Original text is black, what the doctor added is **in this color**  
**Good luck**

*Modified by: Ahmad AlHurani*

Classic depiction of the coagulation cascade.



HMK = high molecular weight kininogen; PK = prekallikrein

# Unfractionated Heparin - UFH

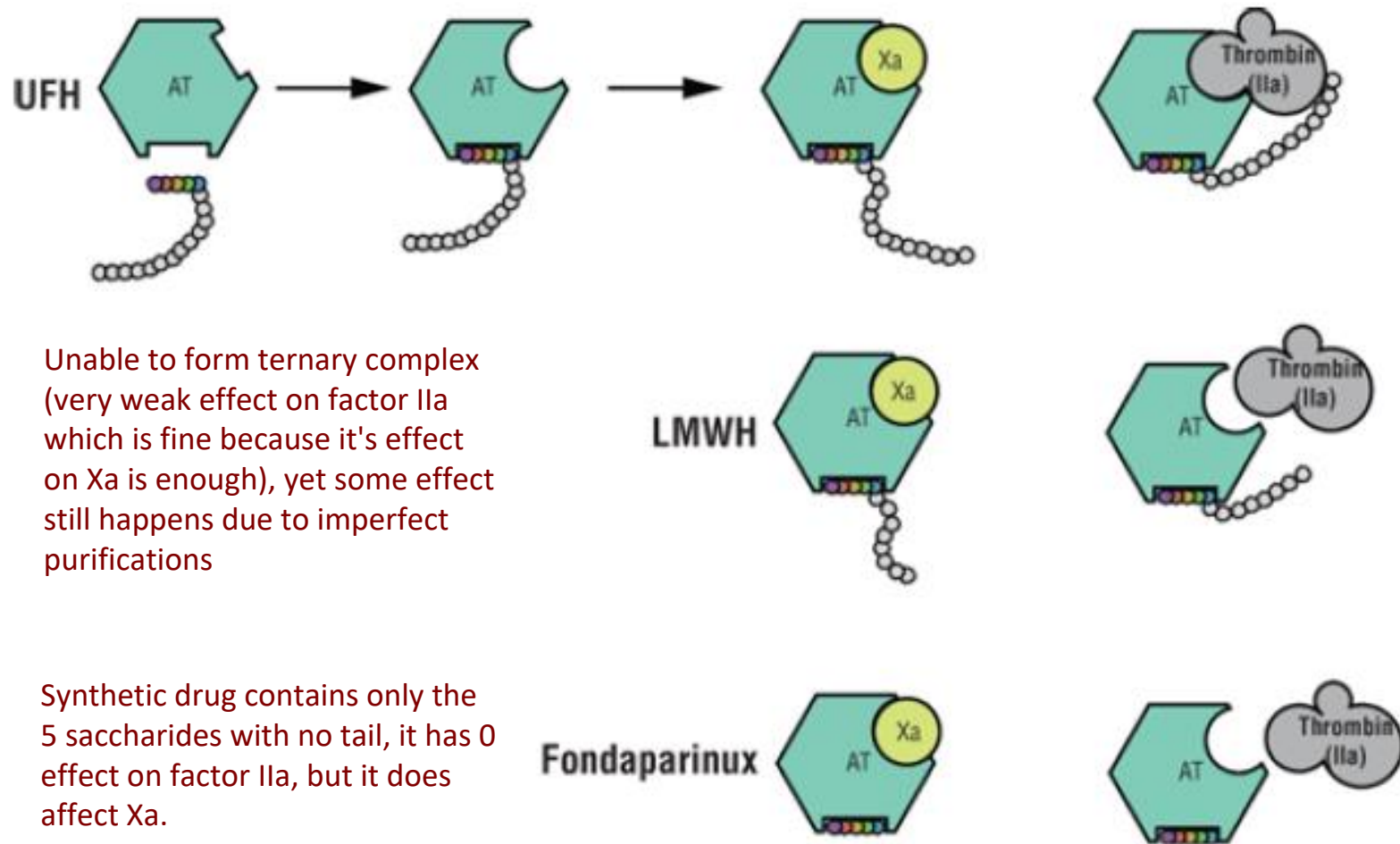
## Pharmacology/Mechanism of Action:

- Unfractionated heparin is a heterogeneous mixture of sulfated mucopolysaccharides of variable lengths.
- The anticoagulant effect of UFH is mediated through a **specific pentasaccharide sequence that binds to antithrombin.**
- UFH accelerates the anticoagulant action of antithrombin 100-1,000 times.
- Antithrombin inhibits factor **IIa**, IXa, **Xa**, and XIIa activity.
- **30% bioavailability, even though it's given IV infusions, and that's because it's metabolized by endothelial cells.**

# Unfractionated Heparin

- **UFH prevents thrombus growth and propagation** allowing endogenous thrombolytic systems to dissolve the clot.
- **Heparin doesn't affect the already formed thrombus**
- **Thrombin (IIa) and Xa are most sensitive to UFH–antithrombin complex inhibition.**
- **To inactivate thrombin (IIa), the heparin molecule must form a ternary complex bridging between antithrombin and thrombin.**
- **The inactivation of factor Xa does NOT require UFH to form a bridge with antithrombin, but requires only UFH binding to antithrombin via the specific pentasaccharide sequence.**

# Pharmacologic activity of unfractionated heparin, low-molecular-weight heparins (LMWHs), and fondaparinux



Unable to form ternary complex (very weak effect on factor IIa which is fine because it's effect on Xa is enough), yet some effect still happens due to imperfect purifications

Synthetic drug contains only the 5 saccharides with no tail, it has 0 effect on factor IIa, but it does affect Xa.

Cannot be given orally, as a saccharide, it's digestion starts by the saliva, not absorbed

# Unfractionated Heparin

- It is preferred to administer UFH by continuous intravenous infusion.
- The onset of action of UFH after SC injection is 1 - 2 hours, peaking at 3 hours.
- Intramuscular administration should **NOT** be used because of the risk of bleeding & hematomas. (**Absolute contraindication**)
- UFH has a dose-dependent half-life of ~ 30 - 90 minutes, because **its elimination follows zero-order kinetics** - dose dependent.  
Zero order: elimination is amount/unit time ex: 2mg/day  
First order: elimination is percentage/ unit time ex: 10%/day
- Given IV, Subcutaneous administration is only used for 2 cases:  
1) Pregnant woman 2) Prophylaxis of thrombosis (obese people face deep vein thrombosis after long operations)

# Unfractionated Heparin

## Adverse Effects:

### 1. bleeding:

Most serious adverse effect of heparin

Don't commit such **fatal** mistakes, like the most serious effect of insulin: (hypoglycemia)

- **Protamine sulfate (antidote of heparin) in a dose of 1 mg per 100 units of UFH (maximum of 50 mg) can be administered via slow intravenous infusion to reverse the anticoagulant effects of UFH.**
- This will only neutralize half of the heparin. If a patient has taken 10,000 unit, we try to neutralize 5,000 and that's by giving him a does of 50mg.
- We can't give more than that, because protamine sulfate itself has some anti coagulation effects at high doses (Only in the absence of heparin) (This effect doesn't happen with the presence of heparin as it's much weaker)
- **Protamine sulfate neutralizes UFH in 5 minutes, and action persists for 2 hours.**



# Unfractionated Heparin

## 2. Heparin-induced thrombocytopenia (HIT):

- HIT is caused by antibodies that bind to complexes of heparin and platelet factor 4 (PF4).
- These antibodies are **prothrombotic and activate platelets** **this will cause thrombotic thrombocytopenia due to platelet consumption.**
- Leads to arterial thromboembolic events.
- Occur in 5 - 10 days after initiation of UFH. **It takes this much time to produce these antibodies.**
- **If a patient develops HIT, this patient cannot take any heparin in the future, not even LMWH or fondaparinux. (HIT will develop even faster due to memory B cells, more severe)**

## 3. Significant bone loss and osteoporosis when used for more than 6 months (**pregnancy is the only reason why we would use it for that much time**)

# Unfractionated Heparin

- When using unfractionated heparin, 2 parameters require monitoring, APTT (Activated partial thromboplastin time) and **platelet count to detect HIT as early as possible.**
- APTT shouldn't increase more than two/three times normal, and not more than that depending on the severity of the thrombosis

## Drug–drug Interactions:

- **Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.**

# Note

- [Thrombosis seen with some Covid-19 vaccines is similar to HIT.
- It is mediated by antibodies to platelet factor 4-polyanion complexes.
- It represents vaccine-related variant of HIT, and called “**vaccine-induced immune thrombotic thrombocytopenia**”].

# Low-Molecular-Weight Heparins (LMWHs)

Same things to be said here, the only difference is that we have some advantages after the fractionation of heparin.

All are given subcutaneously, unit here is mg, because we are sure of the molecular weights, unlike heparin that uses units.

## (Enoxaparin, Dalteparin):

- LMWH is produced by depolymerization of UFH.
- Have ~ one-third the mean UFH molecular weight.

## Advantages include:

- a) predictable anticoagulation dose response.
- b) improved subcutaneous bioavailability.
- c) dose-independent elimination (first-order).
- d) longer half-life.
- e) reduced need for routine laboratory monitoring. unlike unfractionated heparin which requires continuous monitoring, also they claim that HIT development is not as common using LMWH.

# LMWHs

- **Low-molecular-weight heparin prevents thrombus growth and propagation by enhancing and accelerating the activity of antithrombin against factor Xa.**
- **Because of smaller chain lengths, LMWH has limited activity against thrombin (IIa).**
- The parameter used here is **(Anti activated factor X activity) - Anti-Xa assay.**
- No routine monitoring required, only 3 groups of patients are monitored here (not routinely as we said), **obese individuals, children and pregnant ladies.** (for pregnant lady that has thrombosis, we give UFH as subcutaneous still, but if UFH was ineffective or not possible to administrate, LMWHs are used.
- We don't use APTT here, because it's affected by factor II activity more than X, so we use it for unfractionated heparins only.

# LMWHs

- The bioavailability of LMWH is ~ 90% after SC injection.
- The peak anticoagulation at 3 - 5 hours.
- Mainly eliminated by renal excretion.
- The half-life of LMWHs is ~ 3 - 6 hours.
- Half-life may be prolonged in patients with renal impairment. **We need to reduce the dose for these patients.**

# LMWHs

## Adverse Effects:

### 1. Bleeding.

- IV protamine sulfate can be administered as antidote.

### 2. HIT is three times lower than that observed with UFH.

- LMWH should be avoided in patients with HIT, because of cross reactivity with antibodies.

### 3. Osteoporosis and osteopenia.

# LMWHs

## **Drug–drug Interactions:**

- **Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.**



# Fondaparinux

- Fondaparinux is a synthetic molecule consisting of the active pentasaccharide units that bind reversibly to antithrombin.
- It inhibits only factor Xa activity.
- It is effective in prevention of venous thromboembolism (VTE).
- It is rapidly and completely absorbed following SC administration, peak concentrations ~ 2 hours after a single dose and 3 hours with repeated once-daily dosing.
- It is eliminated unchanged in the urine, elimination half-life is ~19 hours.

# Fondaparinux

- The anticoagulant effect of fondaparinux persists for 2 - 4 days following discontinuation of the drug in patients with normal renal function. **persists even more than that with renal dysfunction.**

# Fondaparinux

## Adverse Effects:

1. Bleeding.
  2. Rare cause of HIT. *But it still happens, so we don't give it to patients with previous HIT anyway*
- No antidote to reverse its antithrombotic activity.

## Drug–drug Interactions:

- Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.

# Lepirudin

- **Hirudin** is derived from Leech.
- **Lepirudin** is from recombinant DNA technology.
- **Irreversible inhibitor**, inactivates fibrin-bound thrombin.
- Used IV or SC.
- Monitored by aPTT.
- Eliminated by hepatic metabolism and renal excretion, accumulates in renal failure.
- Used for thrombosis related to HIT.
- No antidote is available.

# Bivalirudin

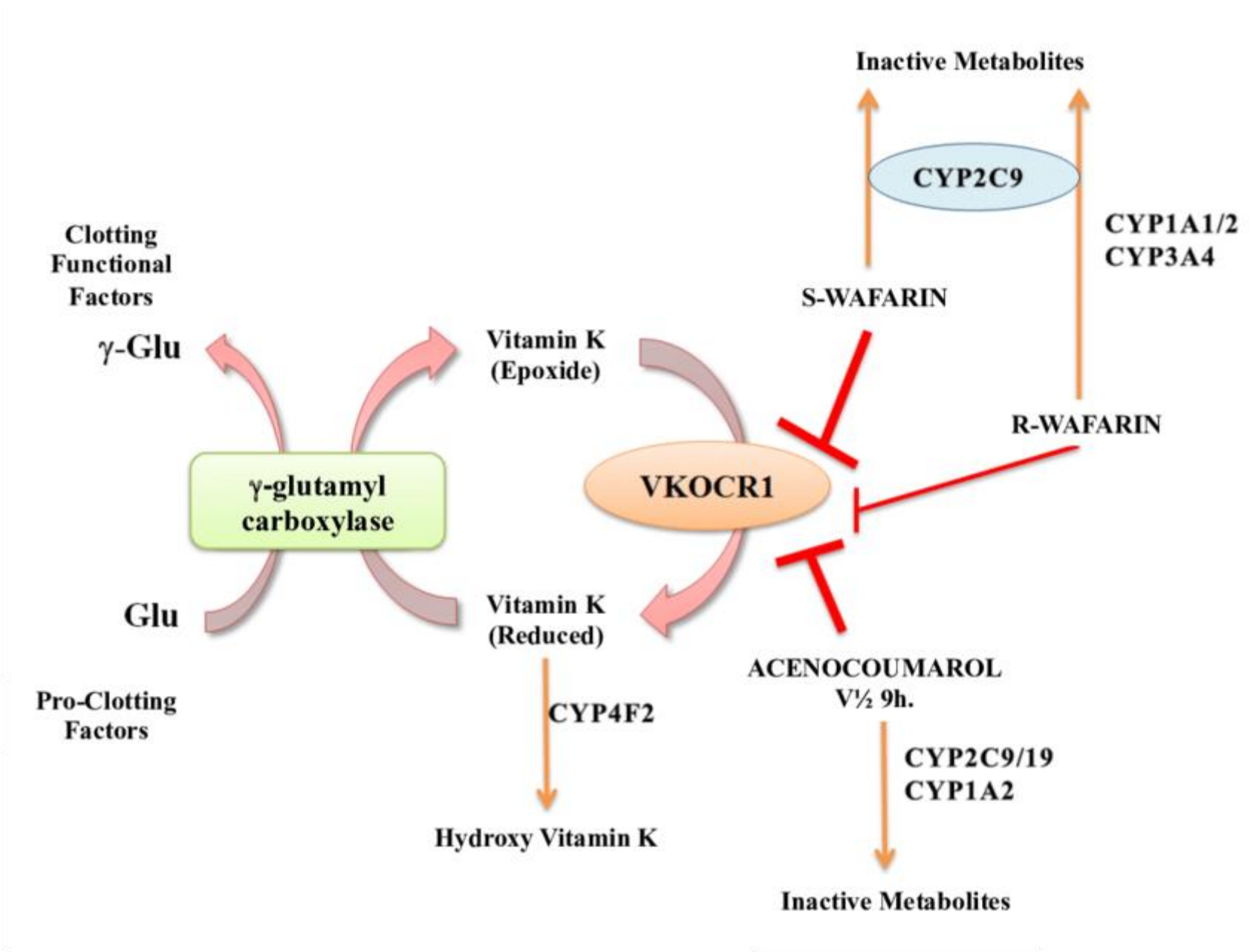
- Bivalirudin is a direct thrombin inhibitor.
- It is a synthetic congener of the naturally occurring anticoagulant hirudin.
- Used IV.
- Elimination half-life is ~ 25 min.
- Cleared by hepatic and renal elimination and proteolytic cleavage.
- It inhibits both circulating and clot-bound thrombin, reversibly.
- Thus, it has less bleeding risk than other r-hirudins.

# Bivalirudin

- It also inhibits thrombin-mediated platelet activation and aggregation.
- Used in percutaneous coronary intervention (PCI) and for HIT.
- Monitored by “**thrombin inhibitor assay**” which is better than aPTT because it is NOT affected by antiphospholipid antibodies.
- It is contraindicated in severe renal impairment.

# Warfarin

- **Vitamin K in its reduced form is a required cofactor for vitamin K-dependent carboxylation of factors II, VII, IX, and X, as well as the endogenous anticoagulant proteins C and S; which is required for their biologic activity.**
- **Warfarin inhibits the reduction of vitamin K epoxide, reducing the formation of complete functioning clotting factors.**
- **It has NO effect on preformed clotting factors, thus, full antithrombotic effect is NOT achieved for at least 6 days after warfarin therapy initiation.**





# Warfarin

- **The time required for warfarin to achieve its pharmacologic effect is dependent on coagulation protein elimination half-lives (6 hours for factor VII and 72 hours for prothrombin).**

# Half-Lives (hours)

## Clotting Factor

<b>II</b>	<b>72</b>
<b>VII</b>	<b>6</b>
<b>IX</b>	<b>24</b>
<b>X</b>	<b>40</b>
<b>Protein C</b>	<b>8</b>
<b>Protein S</b>	<b>30</b>

# Warfarin

- **Because of its narrow therapeutic index, predisposition to drug and food interactions, and exacerbation of bleeding, warfarin requires continuous patient monitoring and education to achieve optimal outcomes.**

# Warfarin

## **Adverse Effects:**

- 1. Bleeding (mild to life threatening).**
  - Vitamin K is the antidote, can be given parenterally or orally; the oral route is preferred in the absence of serious bleeding.**
  - In case of bleeding, warfarin should be temporarily stopped or the dose reduced.**
- 2. “Purple toe syndrome” is thought to be the result of cholesterol microembolization into the arterial circulation of the toes.**

# Warfarin

- 3. Warfarin-induced skin necrosis (due to thrombosis) in the first week of therapy (starts as a painful maculopapular rash and ecchymosis or purpura that progresses to necrotic gangrene).**
  - Areas of the body rich in subcutaneous fat are most commonly affected (breasts, thighs, buttocks, and abdomen).**

# Warfarin Drug–drug Interactions

<b>Pharmacodynamic Interaction</b>	<b>Mechanism</b>
<b>ASA/NSAIDs</b>	<b>Antiplatelet, GI injury</b>
<b>Clopidogrel/Ticlopidine</b>	<b>Antiplatelet</b>
<b>Tramadol</b>	<b>INR elevation (mech. Unknown)</b>
<b>Levothyroxine</b>	<b>Increased catabolism of clotting factors</b>
<b>Vitamin K containing food/Supplements</b>	<b>INR reduction (reverse warfarin mechanism of action)</b>

**INR Elevation****Amiodarone****Fluoroquinolones****Trimethoprim/sulfamethoxazole****Metronidazole****Azole antifungals****Statins****Isoniazid****NSAIDs****Sertraline****Gemfibrozil****Ethanol****Macrolides****Cimetidine****Omeprazole****Fluorouracil****INR Reduction****Rifampin****Barbiturates****Carbamazepine****Phenytoin****St John's wort****Cigarette smoking****Charcoal broiled food****Cholestyramine (Bile acid binding resins)****Oral contraceptives (Estrogens)**

**Open this site or link to see tables for more comprehensive description of drug and food interactions with warfarin, if you like.**

<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/486574>



# Pharmacogenomics

- **CYP2C9 is the hepatic microsomal enzyme responsible for metabolism of the more potent S-enantiomer of warfarin.**
- **Polymorphisms in CYP2C9 and the gene coding for VKOR (Vitamin K epoxide reductase) explain a substantial proportion of warfarin dose variability between patients.**
- **Poor metabolizer subtypes have been associated with increased risk of bleeding.**
- **Warfarin resistance can be due to mutations in the receptor gene.**
- **For individualized warfarin dosing consult ([www.warfarindosing.org](http://www.warfarindosing.org)).**

# Direct Oral Anticoagulants

## (DOACs):

- **Rivaroxaban, apixaban, and edoxaban** are potent and selective inhibitors of both free and clot-bound factor **Xa**.
- They do not require antithrombin to exert their anticoagulant effect.
- **Dabigatran** (prodrug) is a selective, reversible, **direct factor IIa inhibitor**.
- These drugs are partially eliminated by the kidney to various extent, and should be used with caution in patients with renal dysfunction.

# Direct Oral Anticoagulants

- Terminal half-lives ~10 hours for the Factor Xa inhibitors, and 16 hours for dabigatran.
- Rivaroxaban and apixaban are substrates of cytochrome CYP3A4, and P-glycoprotein.

## Indications:

1. The Xa inhibitors rivaroxaban and apixaban can prevent venous thromboembolism (VTE) following hip or knee replacement surgery.
2. Dabigatran, rivaroxaban and apixaban can be used for extended VTE treatment after the first 6 months of anticoagulant therapy.

# Direct Oral Anticoagulants

## Adverse Effects:

1. **Gastrointestinal complaints.**
2. **Bleeding** which ranges from minor – severe & fatal.
  - **Discontinuation of therapy and supportive management.**
  - **Activated charcoal may provide some benefits if drug intake occurred within 2 hours of presentation, and dabigatran is hemodialyzable.**

# Direct Oral Anticoagulants

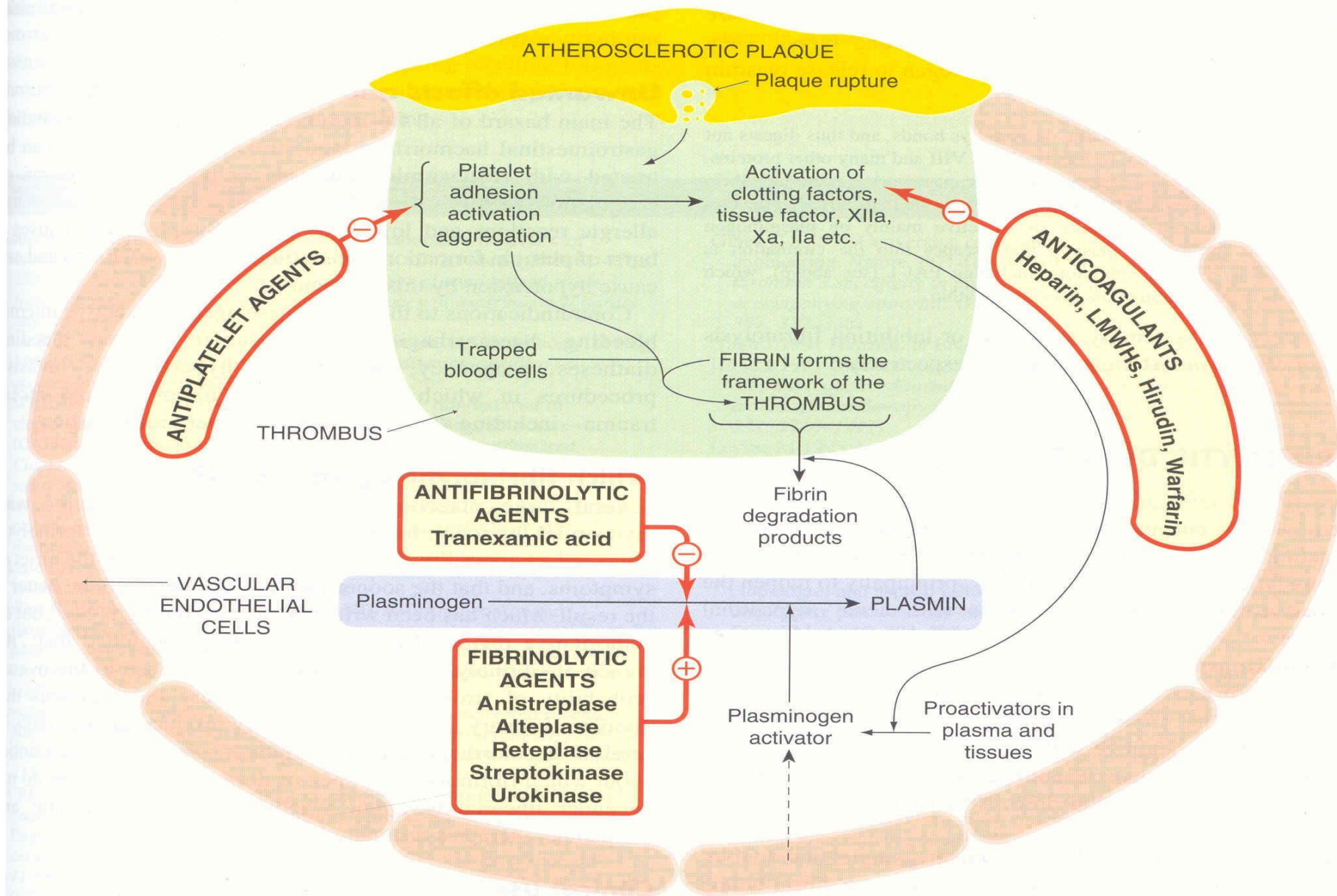
- **Idarucizumab** rapidly reverses the dabigatran anticoagulant effect following IV administration.
- It binds to dabigatran and its acylglucuronide with higher affinity than that of dabigatran to thrombin.
- It is used in life-threatening bleeding and when there is need for urgent surgical intervention.

# Direct Oral Anticoagulants

## Drug–drug and Drug–food Interactions:

- DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with P-gp inhibitors or inducers.
- Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP3A4.
- Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.

# Thrombolytic Agents



**Fibrinolytic system.** The schematic shows interactions with coagulation and platelet pathways and sites of action of drugs that modify these systems. (LMWHs, low-molecular-weight heparins.)



# Thrombolytic Agents

- The fibrinolytic system dissolves intravascular clots by the action of plasmin, a protease.
- Re-establish tissue perfusion.
- **Not alternative to anticoagulants.**
- Thrombolytic agents are plasminogen activators, including the “tissue plasminogen activator” (tPA).

# Thrombolytic Agents

- **First Generation TAs:**

1. Streptokinase

2. Urokinase

- **Second & Third Generation TAs:**

1. tPAs: Alteplase, Reteplase, Tenecteplase.

# Streptokinase

- Produced by Lancefield group C  $\beta$ -hemolytic streptococci.
- It is indirectly acting.
- **Nonenzymatic protein, binds to plasminogen and induces a conformational change that exposes the active site which converts plasminogen to plasmin.**
- **Antibodies from previous streptococcal infection may neutralize activity, thus, it requires a loading dose (LD).**
- **Adverse Effects:**  
Bleeding – systemic lytic state, Allergy, Anaphylaxis, Drug fever.

# Tissue Plasminogen Activator (tPA)

- It binds to fibrin with high affinity and activates plasminogen bound to the clot. i.e fibrin-selective activation.
- May activate circulating plasminogen at large doses or with long duration of therapy.
- Re-occlusion may be lessened by administration of heparin and antiplatelet drugs.
- Given by intravenous infusion.

**Adverse effects:** bleeding, allergy.

# Thrombolytic Agents

## Therapeutic uses:

1. Acute myocardial infarction: within 6 hours of onset, **infused over 1-3 hours.**
2. Central DVT.
3. Sever PE, or multiple PE.

**Infused over 12-72 hours**

4. Acute ischemic stroke (**??**): within 3 hours of onset.

**Contraindications:** Similar to anticoagulants.

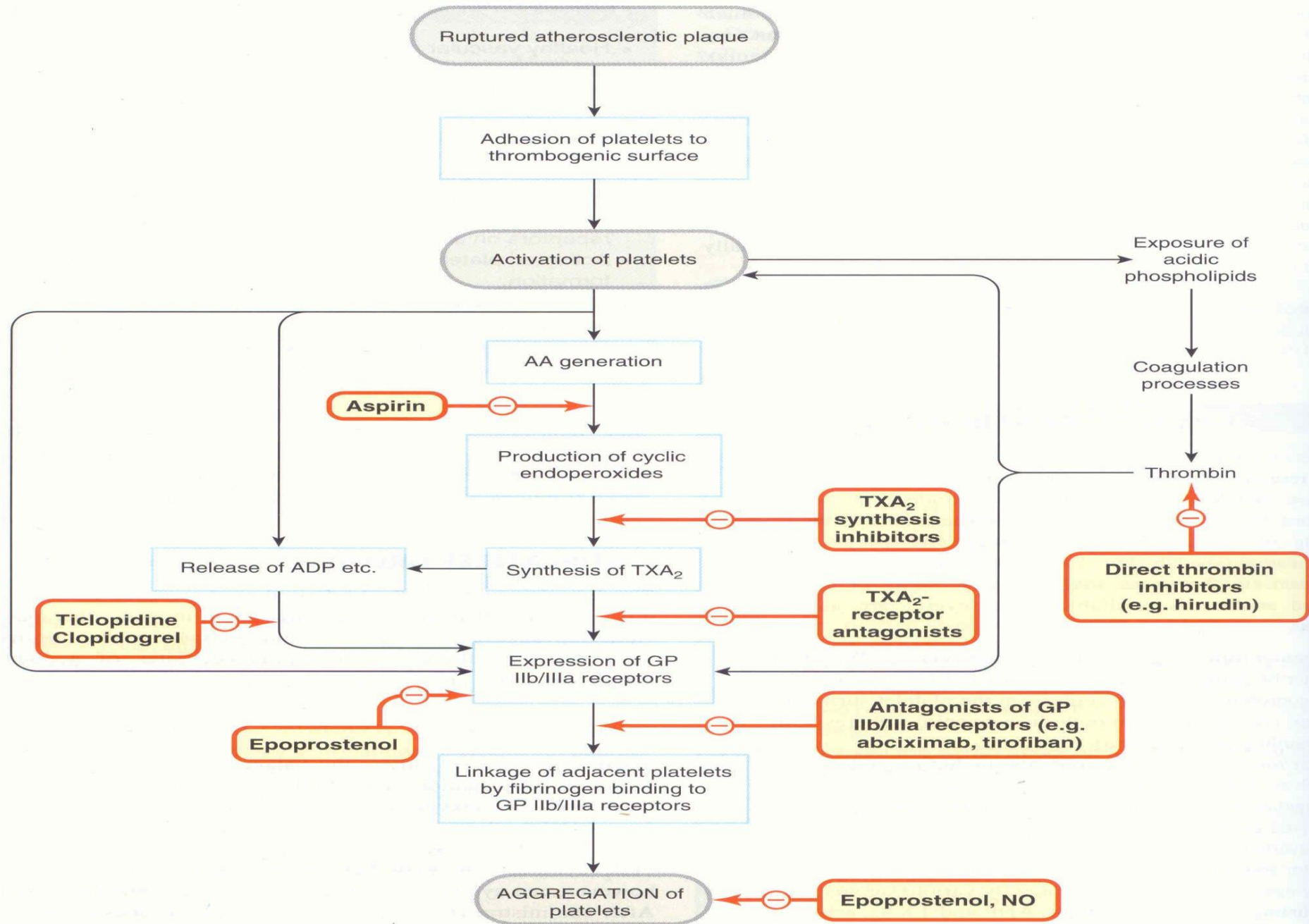
# Thrombolytic Agents - Antidotes

## Aminocaproic acid, Tranexamic acid:

- Bind to plasminogen and plasmin, thus preventing their action on fibrin.
- Contraindicated in disseminated Intravascular coagulation (DIC), and bleeding from kidney or ureters.

**Adverse effects: Thrombosis, Myopathy, Hypotension, Nausea.**

# Antiplatelet Drugs



**Platelet activation.** Events involved in platelet adhesion and aggregation are shown, with the sites of action of drugs and endogenous mediators. (AA, arachidonic acid; ADP, adenosine bisphosphate; GP, glycoprotein; NO, nitric oxide; TXA<sub>2</sub>, thromboxane A<sub>2</sub>.)



# Antiplatelet Drugs

- Platelets provide the initial hemostatic plug at the site of vascular injury and participate in atherosclerosis.

## Used for:

1. Prophylaxis of arterial thrombosis.
  2. Prophylaxis and management of Myocardial infarction & Ischemic stroke, Within 2 hours of onset.
- Administered as adjuncts to thrombolytic therapy along with heparin to maintain perfusion and limit size of infarction.

# Antiplatelet Drugs

## Classification:

1. Cyclooxygenase inhibitors: Aspirin.
2. PGI<sub>3</sub> generators: Eicosapentaenoic acid.
3. ADP receptor blockers: Clopidogrel and Ticlopidine.
4. GPIIb/IIIa receptor blockers: Abciximab, Eptifibatide, Tirofiban.
5. Others: Dipyrimadole and Cilostazol.

# Aspirin

- Irreversible inhibitor (acetylation of active site) of cyclooxygenase of platelets, thus, blocking the production of thromboxane  $A_2$ .
- The effect lasts for the life time of the platelet (7-10 days), why?
- Used at low doses (< 325 mg). Higher doses are not beneficial, because of inhibition of  $PGI_2$  production.

# Eicosapentaenoic Acid

- Unsaturated fatty acid present in cold water fish.
- Generates  $\text{PGI}_3$  and  $\text{TXA}_3$ .
- $\text{PGI}_3$  is an effective anti-aggregating agent like  $\text{PGI}_2$ , while  $\text{TXA}_3$  is much less active than  $\text{TXA}_2$ .

# Clopidogrel, Prasugrel & Ticlopidine

- Prevent formation of platelet plug & clot retraction.
- These drugs irreversibly block the ADP P2Y<sub>12</sub> receptor on platelets.
- This inhibits ADP-induced expression of platelet membrane GPIIb/IIIa receptor and fibrinogen binding to activated platelets.
- Needs 4 days to work, full effect 10 days.
- Clopidogrel is a prodrug that requires activation via the cytochrome P450 enzyme isoform CYP2C19.

# Clopidogrel, Prasugrel & Ticlopidine

## Therapeutic Uses:

- 1. Patients who require aspirin but can not take it:  
(myocardial infarction, unstable angina pectoris, transient ischemic attacks, ischemic strokes).**
- 2. Patients with coronary stents, in combination with aspirin.**

# Clopidogrel, Prasugrel & Ticlopidine

## **Adverse Effects:**

- 1. Bleeding (5%)**
  - 2. Nausea, dyspepsia, diarrhea (20%)**
  - 3. Severe Neutropenia (1%)**
  - 4. Thrombotic thrombocytopenic purpura**
  - 5. Cholestatic hepatitis**
- Less with clopidogrel**

# GPIIb/IIIa Receptor Blockers

- The platelet GP IIb/IIIa receptor functions as a receptor mainly for fibrinogen and vitronectin but also for fibronectin and von Willebrand factor.
- Activation of this complex is the final common pathway for platelet aggregation.
- Used in acute coronary syndromes parenterally.



# GPIIb/IIIa Receptor Blockers

**Include:**

**Abciximab:** a humanized monoclonal antibody against the receptor.

**Eptifibatide:** a fibrinogen analog.

**Tirofiban:** similar to Eptifibatide but smaller molecule.

# GPIIb/IIIa Receptor Blockers

## Dipyridamole:

- It is a vasodilator that also inhibits platelet function by inhibiting adenosine uptake and cGMP phosphodiesterase activity.
- It has little or no beneficial effect if used alone.
- It may be used in combination with aspirin to prevent cerebrovascular ischemia, or with warfarin for primary prophylaxis of thromboemboli in patients with prosthetic heart valves.

## Cilostazol:

- It is a phosphodiesterase inhibitor that promotes vasodilation and inhibition of platelet aggregation.
- It is used primarily to treat intermittent claudication.