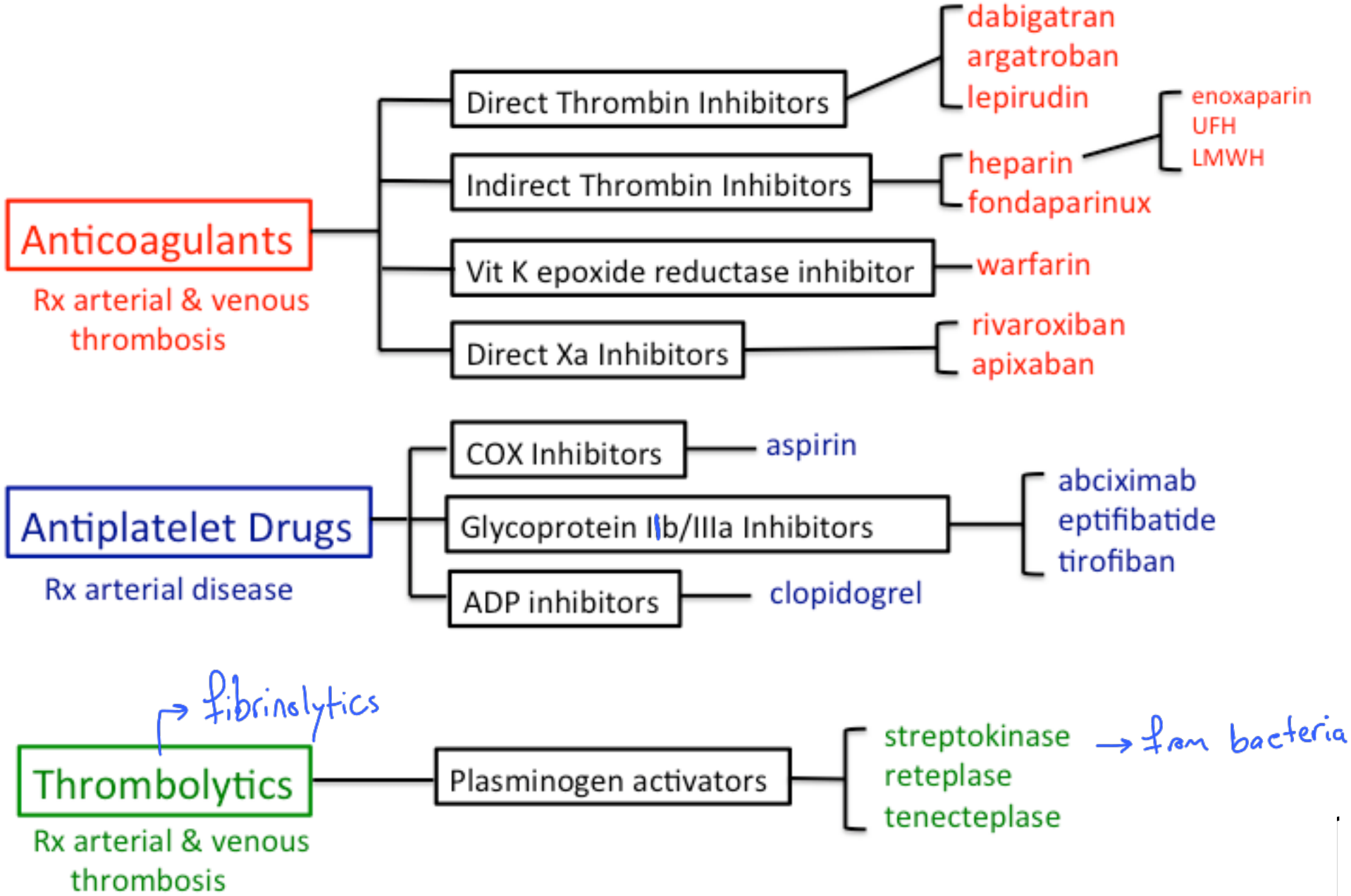
Anticoagulants, Thrombolytics, and Antiplatelet Drugs

Drugs Used to Treat Clotting Disorders



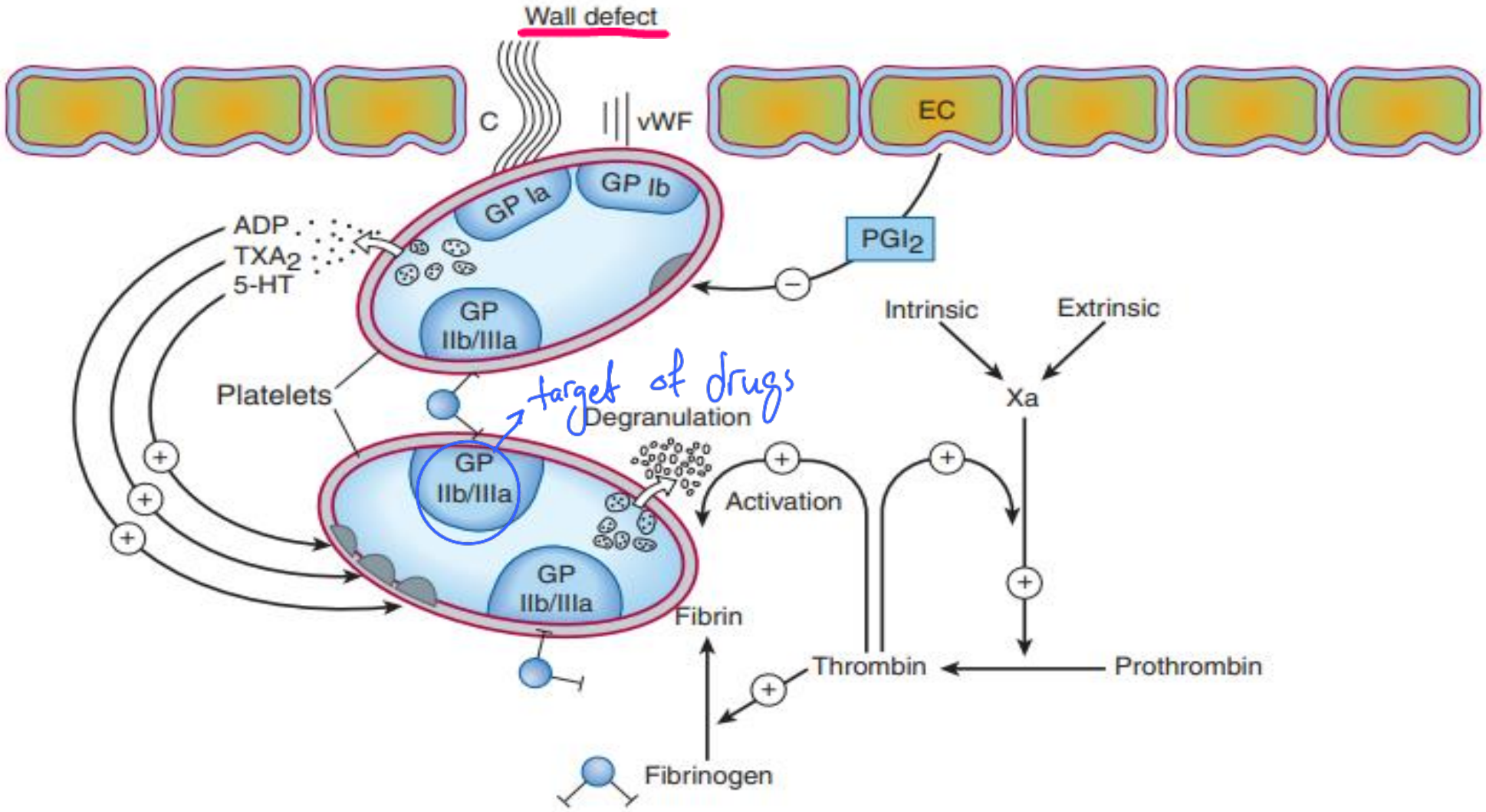


FIGURE 34–1 Thrombus formation at the site of the damaged vascular wall (EC, endothelial cell) and the role of platelets and clotting factors. Platelet membrane receptors include the glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor, binding von Willebrand factor (vWF); and GP IIb/IIIa, which binds fibrinogen and other macromolecules. Antiplatelet prostacyclin (PGI_2) is released from the endothelium. Aggregating substances released from the degranulating platelet include adenosine diphosphate (ADP), thromboxane A_2 (TXA_2), and serotonin (5-HT). Production of factor Xa is detailed in Figure 34–2. (Redrawn and reproduced, with permission, from Simoons ML, Decker JW: New directions in anticoagulant and antiplatelet treatment. [Editorial.] Br Heart J 1995;74:337.)

*we will not required to memorize numbers

Anticoagulant drugs

- **Indirect thrombin inhibitor**
  - UFH
  - LMWH
  - Fondaparinux
- **Direct thrombin /factor X inhibitor (DTI(**
  - Parenteral: Lepirudin / Bivalirudin
  - Oral: Rivaroxaban / Apixaban / Edoxaban / Dabigatran
- **Warfarin**
  - ↳ one of oldest drugs but it use has decrease because it is side effects.

Unfractionated Heparin UFH

Mechanism of Action:

- **The anticoagulant effect of UFH is mediated through binding to antithrombin.**

↳ Unfractioned Heparin.

- **UFH accelerates the anticoagulant action of antithrombin 100 -1,000 times.**

- **Antithrombin inhibits factor IIa, IXa, Xa, and XIIa activity.**

this important to differentiate between it & LMWH
↳ it will affect factor X & thrombin

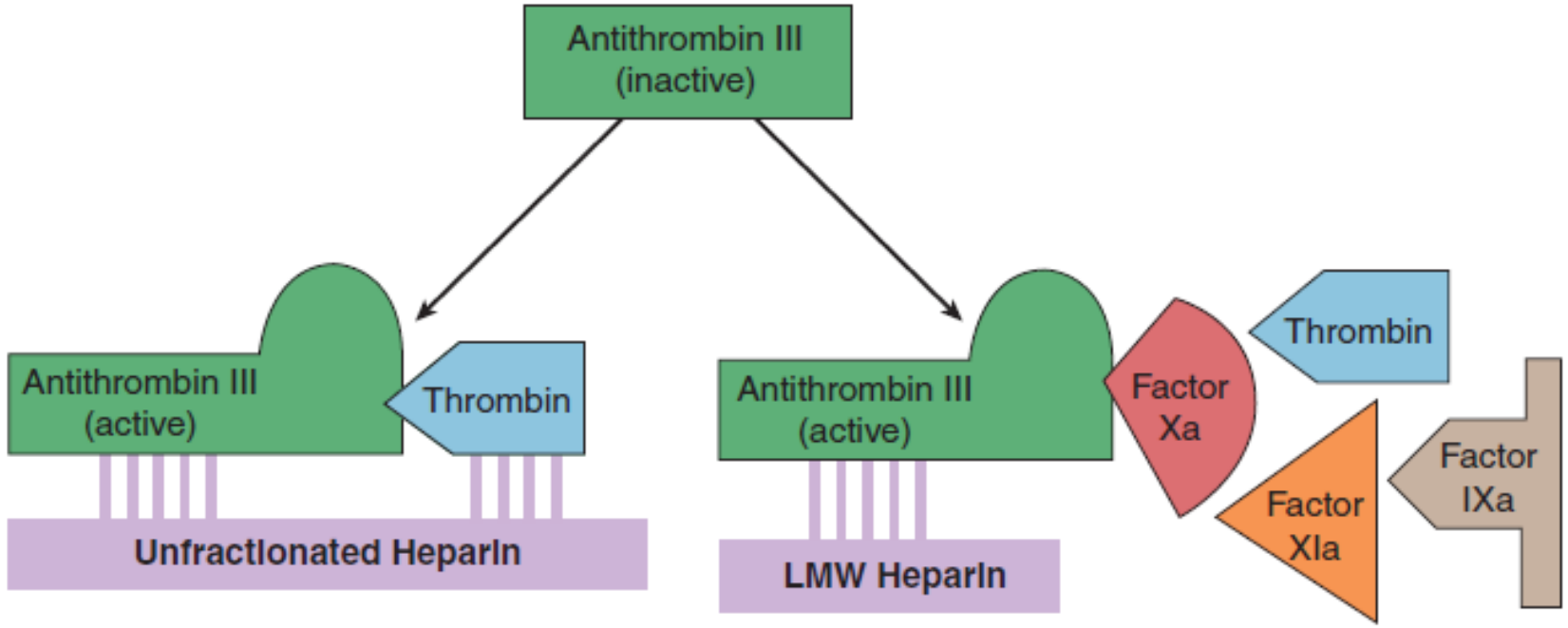


FIGURE 34–4 Cartoon illustrating differences between fondaparinux, low-molecular-weight heparins (LMWH), and high-molecular-weight heparin (HMWH, unfractionated heparin). Activated antithrombin III (AT III) degrades thrombin, factor X, and several other factors. Binding of these drugs to AT III can increase the catalytic action of AT III 1000-fold. The combination of AT III with unfractionated heparin increases degradation of both factor Xa and thrombin. Combination with fondaparinux or LMWH more selectively increases degradation of Xa.

Side effect of All anticoagulant ⟶ bleeding /important.

- It is preferred to administer UFH by **continuous intravenous infusion** .
  ↳ Preffered

- 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.**
  ↳ excretion is not dependent on their conc.

Adverse Effects:

1. **bleeding :**

- ***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 .
- Protamine sulfate neutralizes UFH in 5 minutes, and action persists for 2 hours

.2. Significant bone loss and osteoporosis when used for more than 6 months

So we should be carful in pragnancy because it is already loosing Ca^{2+}

3 .Heparin-induced thrombocytopenia (HIT :(

- HIT is caused by antibodies that bind to complexes of heparin and platelet factor 4 (PF.(4

- 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(

less chance
to develop HIT
but it is dangerous

Monitoring:

- 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: is common between UFH & LMWH

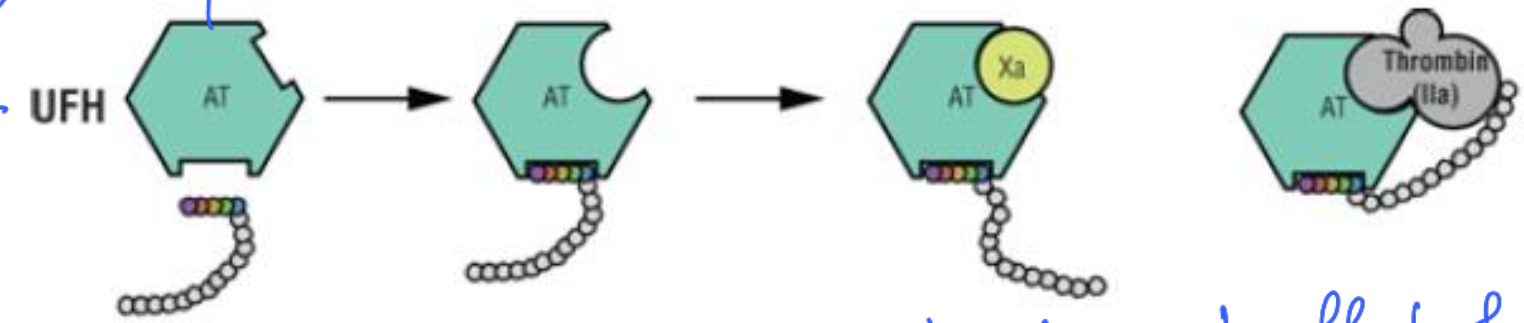
- Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.

use to treat gout.

* but I can use two drugs works on different targets.

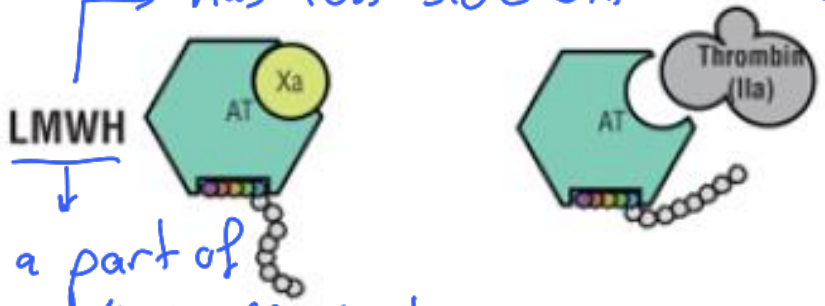
Pharmacologic activity of unfractionated heparin, low-molecular-weight heparins (LMWHs), and fondaparinux

large



it is related to Histamine because it is exist in basophils & mast cells

has less side effect of UFH



is a part of UFH (but effective)

part of LMWH → work on factor X

Low-Molecular-Weight Heparins (LMWHs(

)Enoxaparin, Dalteparin:(

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

Advantages include:

a) predictable anticoagulation dose response.→ So I can predict the bleeding time after administration of certin dose of LMWH.
b) improved subcutaneous bioavailability.
c) dose-independent elimination (first-order.(
d) longer half-life .
e) reduced need for routine laboratory monitoring.

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 .(**

→ one major difference between LMWH & UFH

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.

Monitoring

- Weight-based dosing of the LMW heparins results in predictable pharmacokinetics and plasma levels in patients with normal renal function. Therefore, LMW heparin levels are not generally measured except in the setting of renal insufficiency, obesity, and pregnancy. LMW heparin levels can be determined by anti-Xa units. Peak therapeutic levels should be0.5–1 unit/mL for twice-daily dosing, determined 4 hours afteradministration, and approximately 1.5 units/mL for once-daily dosing.

So if I give him a specific dose I will predict the bleeding time

*you will be asked about MOA.

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: Similar to UfH

- **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.**

↳ Complete Bioavailability

* we administrate the dose every half life.

Fondaparinux

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

* in situation when I change the drug to another drug So I need short lived drug
So when I stop the drug administration the drug stop it's action in the body.

UfH is short-lived drug.

Fondaparinux

Adverse Effects:

1. **Bleeding.**
2. **Rare cause of HIT.**

So become afraid from toxicity more because there is no Antidote.

- **No antidote to reverse its antithrombotic activity.**

Drug–drug Interactions:

Similar to UFH because it has the same MOA

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

Lepirudin

drug prototype

- **Hirudin** is derived from **Leech**. العلق
- **Lepirudin** is from recombinant DNA technology.
- **Irreversible inhibitor**, inactivates fibrin-bound **thrombin**.
- **Used IV or SC.** (mostly of other drugs is Reversible)
- **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.

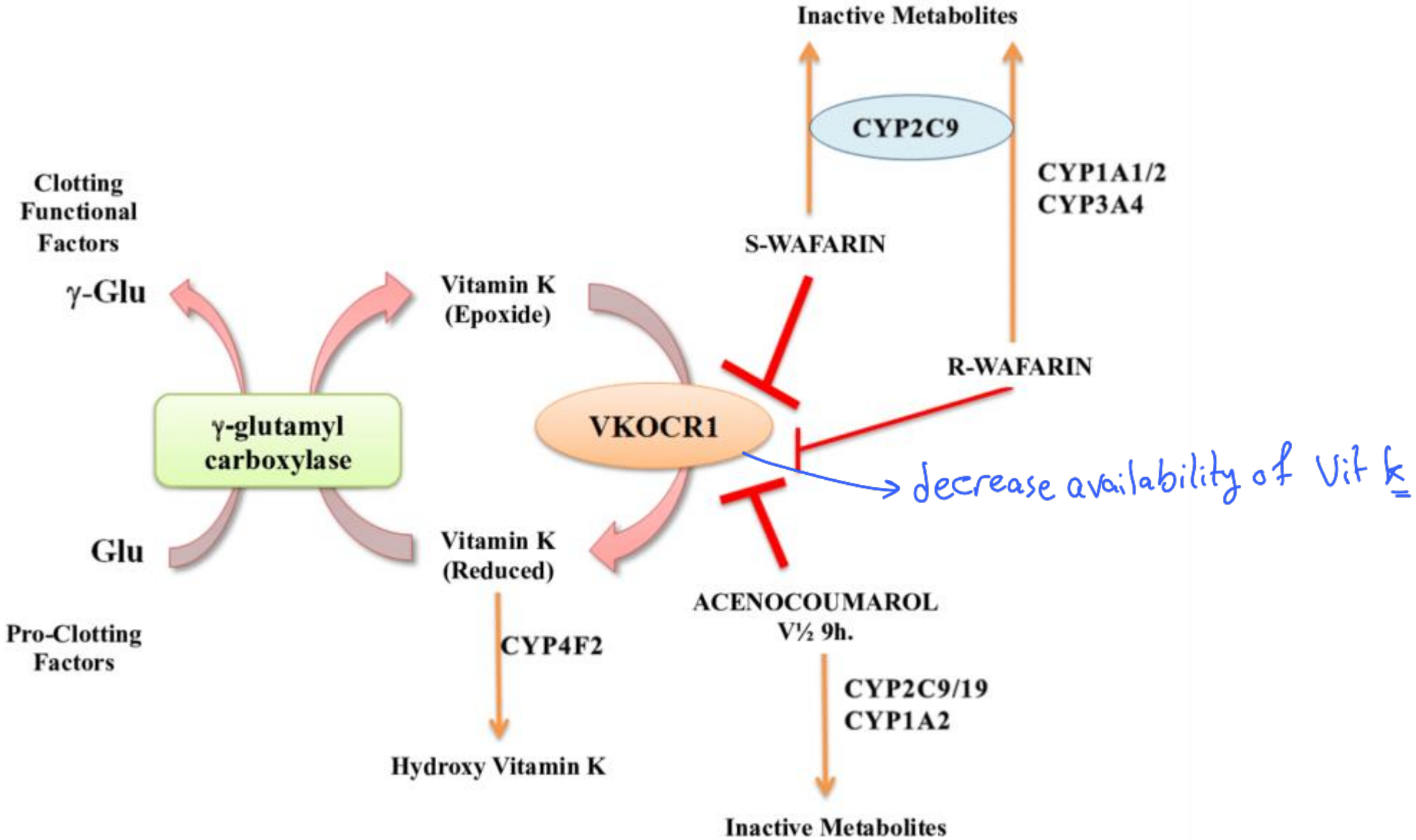
↳ the bleeding risk is less than irreversible.

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 is important.

- **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 .**


Inactive Metabolites
CYP2C9
CYP1A1/2
CYP3A4
Clotting
Functional
Factors
γ-Glu
S-WAFARIN
R-WAFARIN
Vitamin K
(Epoxide)
γ-glutamyl
carboxylase
VKOCR1
decrease availability of Vit K
Glu
Vitamin K
(Reduced)
ACENOCOUMAROL
V½ 9h.
Pro-Clotting
Factors
CYP4F2
CYP2C9/19
CYP1A2
Hydroxy Vitamin K
Inactive Metabolites

TD → Toxic effect conc.
ED → effictive effect conc.

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.**

why Warfarin is Major site of Drug-drug interaction?

because it is metabolized by Cytochrome P450 (it is enzyme that metabolized various drugs)

Warfarin

Adverse Effects:

1. **Bleeding (mild to life threatening .(**

- **Vitamin K is the antidote, can be given parenteraly 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 Drug–drug Interactions

Pharmacodynamic Interaction	Mechanism
ASA/NSAIDs	Antiplatelet, GI injury
Clopidogrel/Ticlopidine	Antiplatelet
Tramadol	INR elevation (mech. Unknown)
Levothyroxine (T4)	Increased catabolism of clotting factors
Vitamin K containing food/Supplements	INR reduction (reverse warfarin mechanism of action)

INR Elevation → increase bleedings.
Amiodarone → Anti-arrathymic
Fluoroquinolones
Trimethoprim/sulfamethoxazole
Metronidazole → Anti parasitic
* Azole antifungals
* Statins → Hyper lipidamia
Isoniazid → antifungal
* NSAIDs
Sertraline
Gemfibrozil
Ethanol
Macrolides
* Cimetidine
* Omeprazole
Fluorouracil

+ grapefruit juice

* metabolism of drug
  - Detoxification 70%
  - activation of prodrug
  - lead to toxic form of the drug

* it is Related to cytochrom P450

INR Reduction (inducer of the enzyme)
* Rifampin
Barbiturates
Carbamazepine
Phenytoin
St John's wort
* Cigarette smoking
Charcoal broiled food
* Cholestyramine (Bile acid binding resins)
* Oral contraceptives (Estrogens)

* the name with Star is for memorizing

Pharmacogenomics

- **Poor metabolizer subtypes have been associated with increased risk of bleeding.** So slower metabolism → increase Risk of bleeding.

Direct Oral Anticoagulants

factor X inhibitors

)DOACs:(

- **Rivaroxaban, apixaban are potent and selective inhibitors of both free and clot-bound factor Xa.** → important
- **They do not require antithrombin to exert their anticoagulant effect.** → binding factor X, some binds clot bound factor X or free one.
- **Dabigatran (prodrug) is a selective, reversible, direct factor IIa inhibitor .** → important. Atrial fibrilation → dysrythem of Atria of the heart → stasis of blood in Heart → Coagulation → should take oral Anticoagulants
- **These drugs are partially eliminated by the kidney to various extent, and should be used with caution in patients with renal dysfunction.**

*So if kidney enzymes such as createrine raise above 3.5 Some of drugs doses must to decrease and some drug must be changed to warfarin (even we don't like warfarin).

Direct Oral Anticoagulants

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.
3. Arterial fibriation

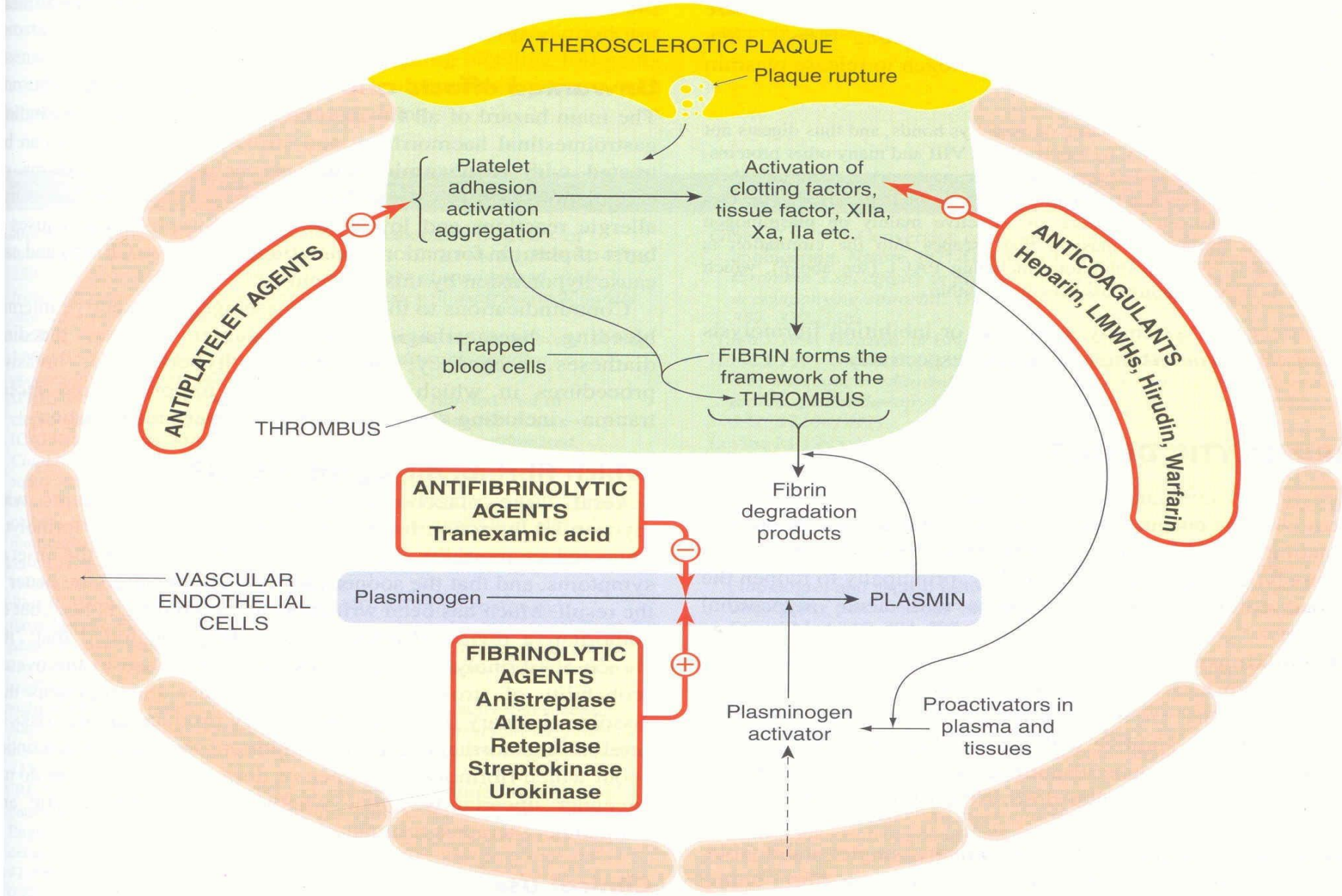
Direct Oral Anticoagulants

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 hemodializable .**

Thrombolytic Agents



Fibrinolytic system. The schematic shows interactions with coagulation and platelet pathways and sites of action of drugs that modify these systems. (LMHs, 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).(**

↳ in Strok situation

Thrombolytic Agents

- **First Generation TAs:**

  .1Streptokinase

- **Second & Third Generation TAs:**

  .1tPAs: Alteplase, Reteplase, Tenecteplase.

Streptokinase

- **Produced by Lancefield group C β-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 .

↳ because it is from baeteria

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.**

↳ less than streptokinase.

Thrombolytic Agents

Therapeutic uses:

.1Acute myocardial infarction: within 6 hours of onset, infused over 1-3 hours.

.2Central DVT.

.3Sever PE, or multiple PE.

Infused over 12-72 hours

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

Contraindications: Similar to anticoagulants.

Thrombolytic Agents - Antidotes

this drug is not required.

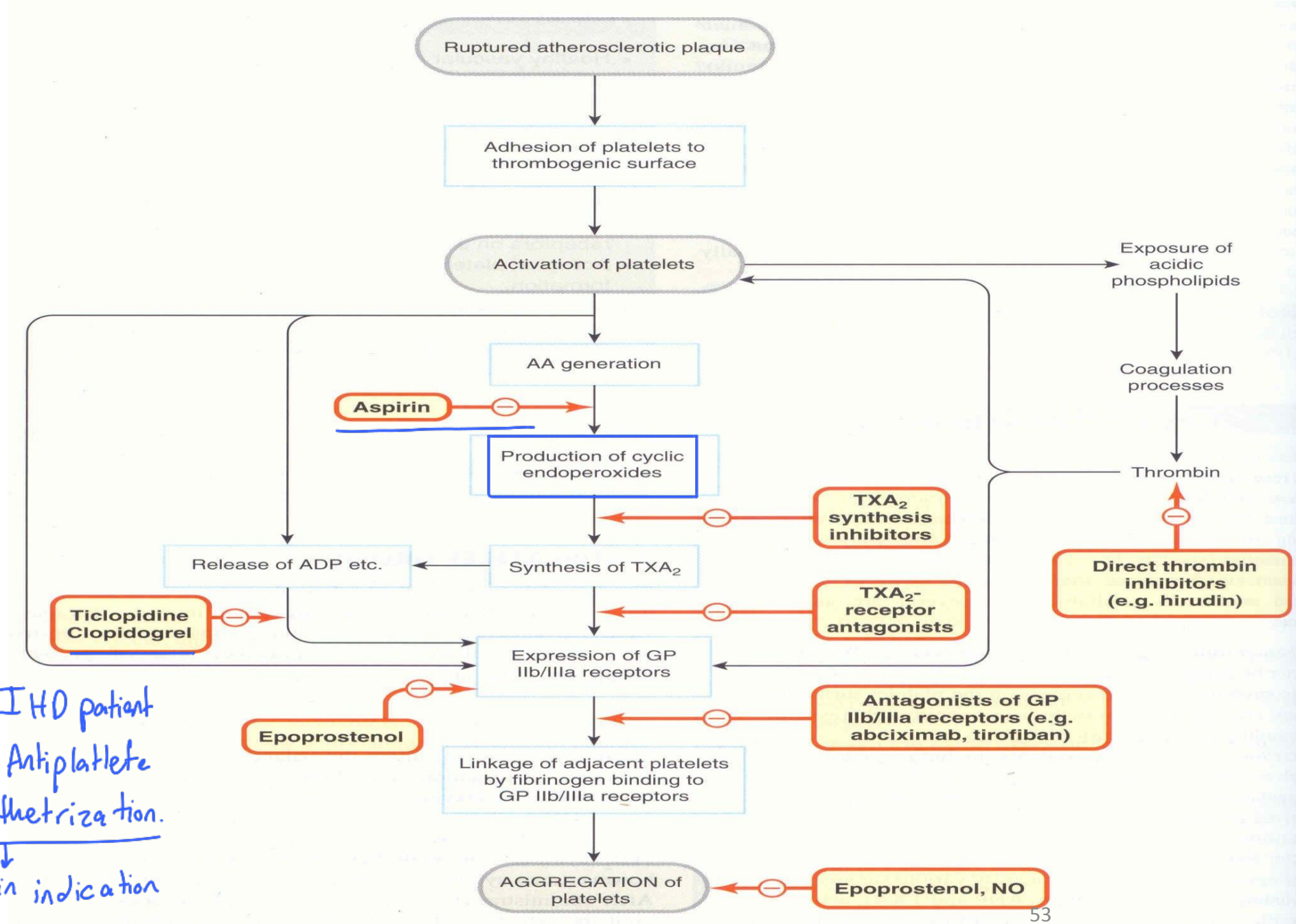
important.

Aminocaproic acid, Tranexamic acid:

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

Adverse effects: Thrombosis, Myopathy, Hypotension, Nausea.

Antiplatelet Drugs



* usually in IHD patient they take Antiplatlete after catheterization.
↓
main indication

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_2, thromboxane A_2.)

Antiplatelet Drugs

Used for:

1. **Prophylaxis of arterial thrombosis.**
2. **Prophylaxis and management of Myocardial infarction & Ischemic stroke, Within 2 hours of onset.**

Aspirin is irreversable inhibitor.

- **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.**

because platletes is not nucleated so it will not be able to synthesis new receptor or enzyme that targeted by aspirin.

* people aged more than 50 years might advised to take aspirin in low doses because they are at high risk of thrombosis.

Clopidogrel

- These drugs irreversibly block the ADP P2Y12 receptor on platelets.
- This inhibits ADP-induced expression of platelet membrane GPIIb/IIIa receptor and fibrinogen binding to activated platelets.

Clopidogrel, Prasugrel & Ticlopidine

Therapeutic Uses:

.1Patients who require aspirin but can not take it:

)myocardial infarction, unstable angina pectoris, transient ischemic attacks, ischemic strokes.(

.2Patients with coronary stents, in combination with aspirin.

at least these drugs must be administrated one year after Coronary stents

Clopidogrel, Prasugrel & Ticlopidine

Adverse Effects:

.1Bleeding ((5%

.2Nausea, dyspepsia, diarrhea ((20%

.3Severe Neutropenia ((1%

.4Thrombotic thrombocytopenic purpura

.5Cholestatic 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:

important

Abciximab: a humanized monoclonal antibody against the receptor.

it is givin IV because it is Antibody

it is used for IHD but it was ineffective because it does vasodilation in the normal area not the target one so it called coronary steal phenomena So nowadays it is used as platlete inhibitor only

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.

but this slide is not required for exam sakes