



Artery Academy

Done by Mariam

Drugs Used in Coagulation Disorders

Pharmacology 1

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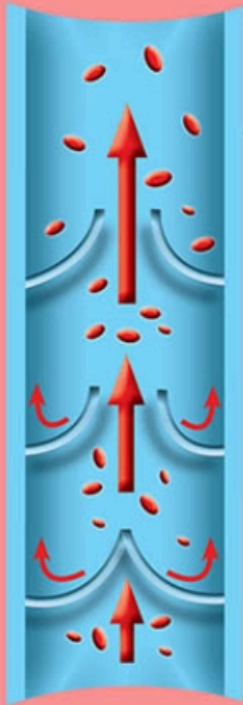
Thrombosis

- Blood hemostasis refers to the finely regulated dynamic process of maintaining fluidity of the blood, repairing vascular injury, and limiting blood loss while avoiding vessel occlusion (thrombosis) and inadequate perfusion of vital organs.
- Either extreme—excessive bleeding or thrombosis—represents a breakdown of the hemostatic mechanism.
- Thrombosis, the formation of an unwanted clot within a blood vessel.
- It is important to distinguish between thrombi and emboli: حطيتكم صورة توضّح الفرق
 - A clot that adheres to a vessel wall is called a “thrombus,”
 - An intravascular clot that floats in the blood is termed an “embolus.” خثرة متحركة
- Thus, a detached thrombus becomes an embolus.
- Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients.
- Thrombotic disorders include acute myocardial infarction, deep vein thrombosis (DVT), pulmonary embolism, and acute ischemic stroke.

أول شيء نحكي عنه هو **blood homeostasis** بمعنى إنه: هسا الدم عبارة عن **liquid** ليبيه هاد ما بزيد عن الوضع الطبيعي وبصيرله **hemorrhage** أو بقل عن الوضع الطبيعي وبصيرله **coagulation** ! لأنه بحالة توازن ما بين وبين
ف هون ال **blood homeostasis** رح يعمل على
1) maintaining fluidity of the blood
2) repairing vascular injury
3) limiting blood loss وجود
4) inadequate perfusion of vital organs .
ف في حال صار عنا **bleeding** أو **thrombosis** هون بكون صار اختلال بهاد التوازن ، يعني
خلل بال **homeostatic mechanism** .

هسا خلونا نرجع للسلامة نعرف شو يعني **thrombosis** ؟ وشو الفرق بينها وبين **emboli**
علمًا إنه التنين يُعتبروا **dangerous** لأنهم بمنعوا وصول الأوكسجين وال **nutrients**
للأنسجة

DEEP VEIN THROMBOSIS



Normal vein

Blood moving toward the heart



Thrombosis

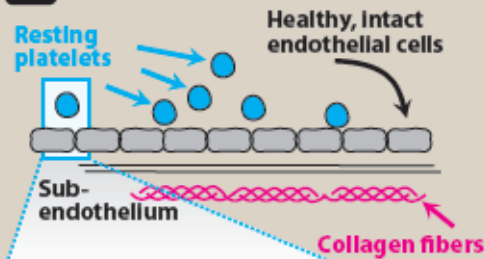
Damaged open and warped valves
Blood flowing in both direction
Blood accumulating in vein



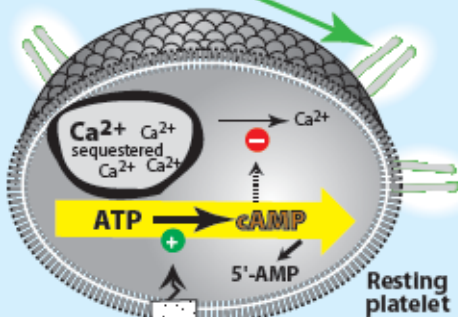
Embolus

When blood moving slowly, a clot or thrombus can form. A part of the clot can break off and travel in the bloodstream (embolus)

1 Resting platelets



Inactive GP IIb/IIIa receptors



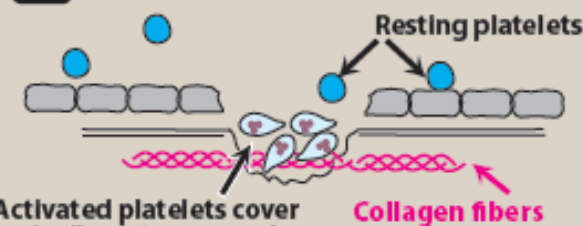
Prostacyclin
Nitric oxide

Endothelial cells

- 2 Healthy, intact endothelium releases prostacyclin into plasma.
- Prostacyclin binds to platelet membrane receptors, causing synthesis of cAMP.
- cAMP stabilizes inactive GP IIb/IIIa receptors and inhibits release of granules containing platelet aggregation agents or Ca^{2+} .

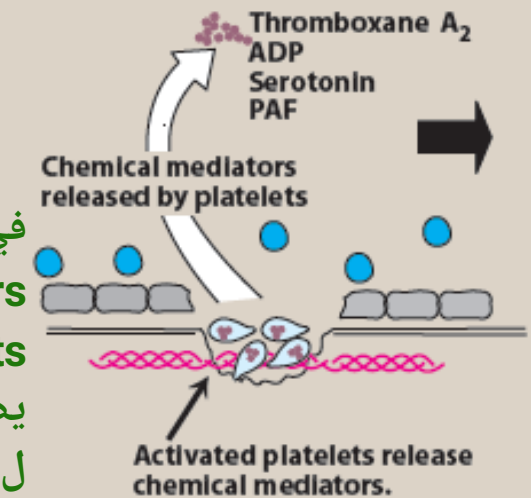
الفكرة إنه ال platelets هي already موجودة بجسمنا لكن ال endothelium ح تعمل إفراز ل prostacyclin في البلازما ، وهاي ال prostacyclin ح ترتبط بال platelet membrane receptors وتساهم بتكوين ال cAMP بالتالي هاي ال cAMP ح تعمل stabilizes inactive ال GP IIb/IIIa receptors ف بتمنع تكوين granules (إلي بتحتوي على agent بتساهم إنه يصير platelets aggregation أو ايونات الكالسيوم

3 Platelet adhesion

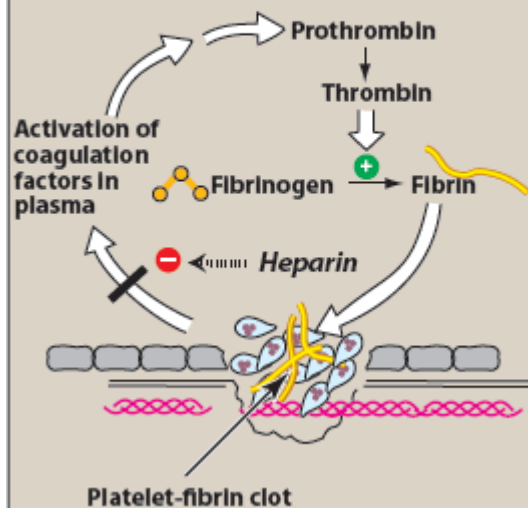


في حال صار عند الشخص injury ، هاي ال receptors ح يصير لها activation ، ف ال activated platelets هون أول شي ح يصير لها تغيير بشكلها وبعدين ح تعمل release ل chemical mediators ، هلا هاي ال chemical mediators عبارة عن: thromboxane A₂, Serotonin, platelets Activating factor, adenosine diphosphate

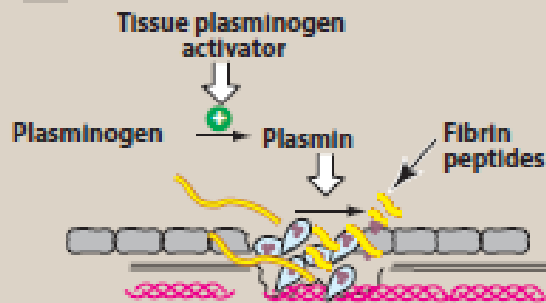
4 Platelet activation



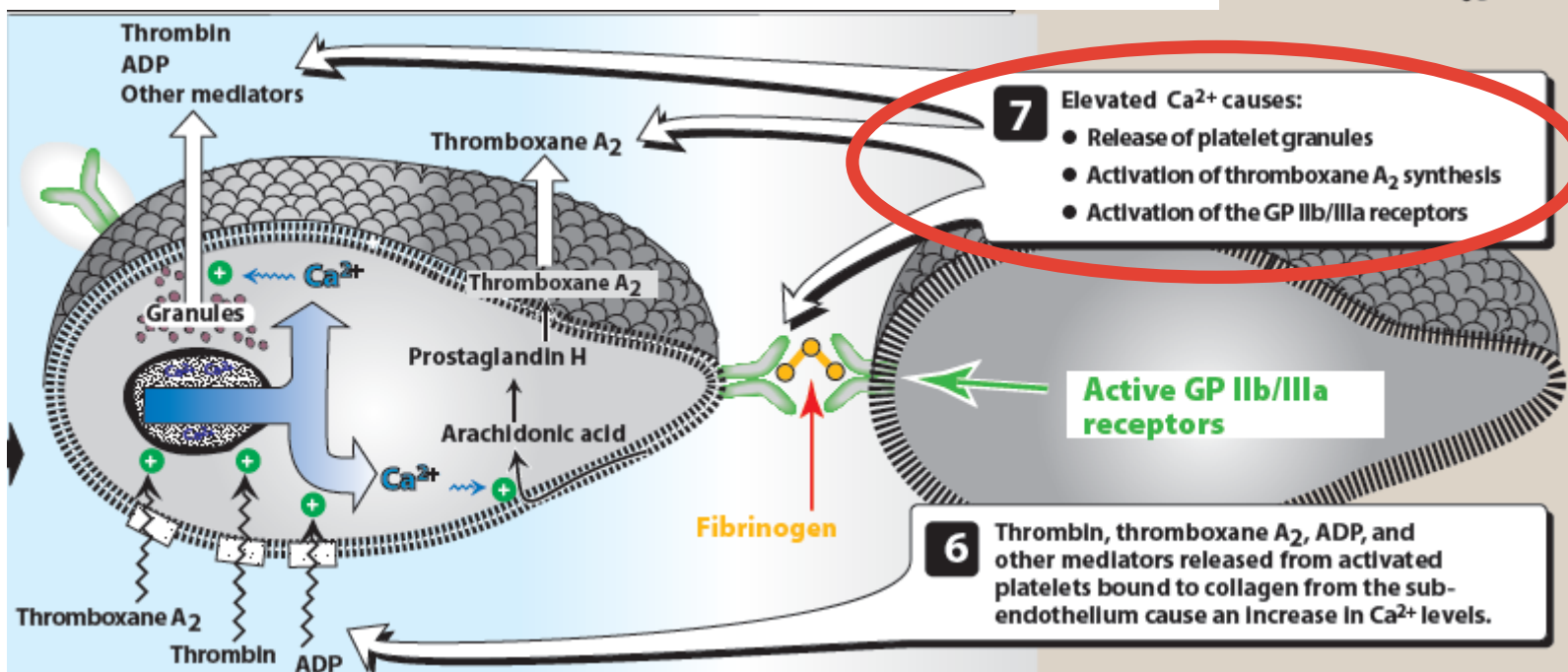
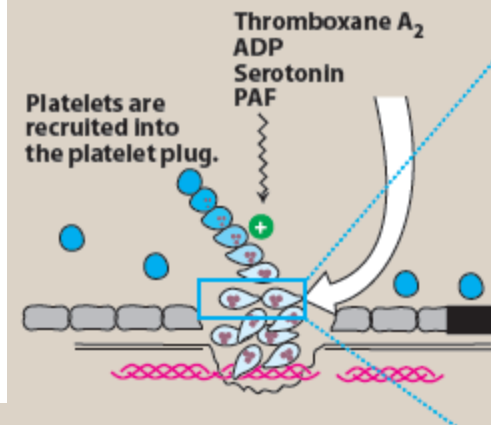
8 Formation of platelet-fibrin plug



9 Fibrinolysis

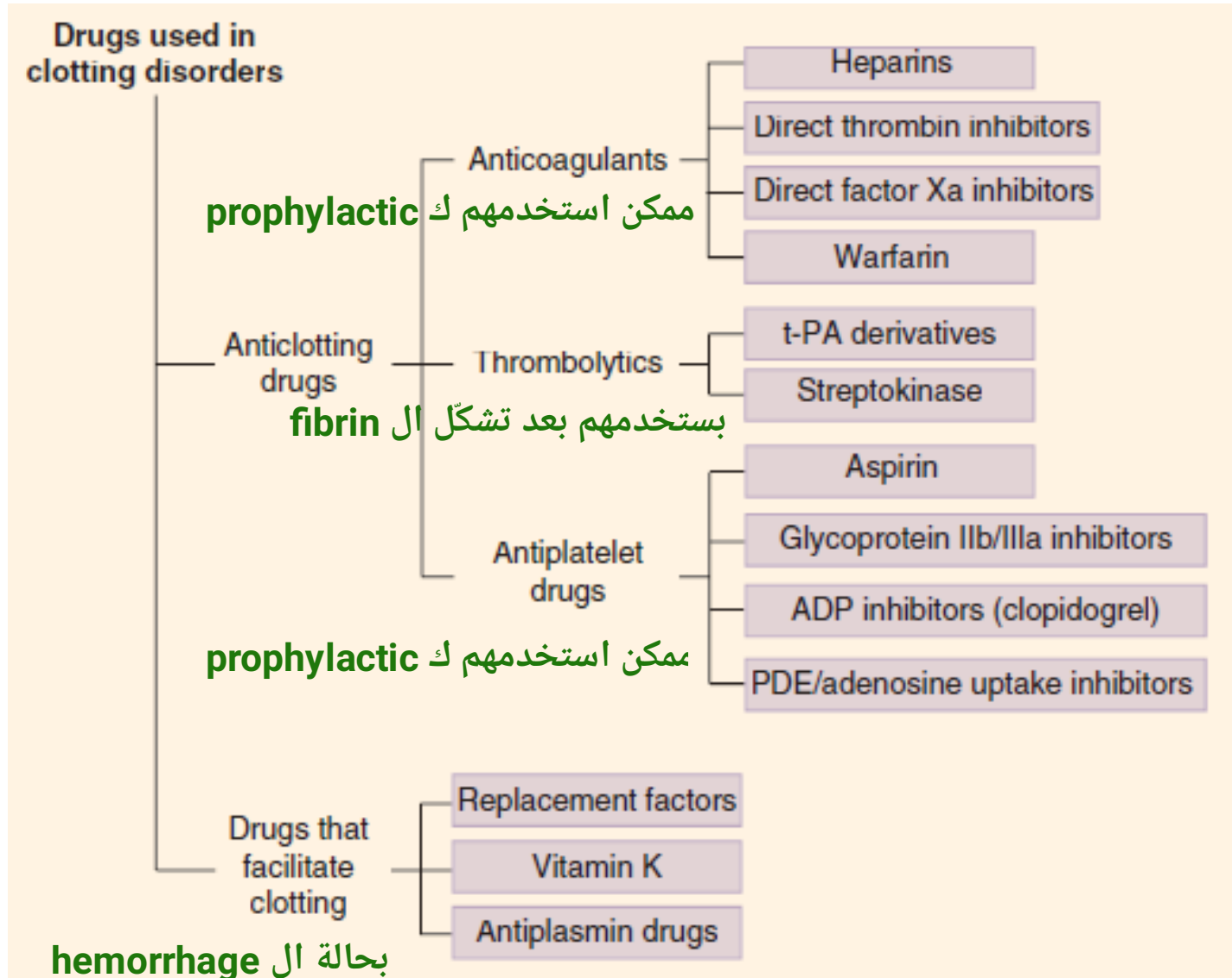


5 Platelet aggregation



المخطط
هون
واضح
بس
ضروري
اعرفوا
نتائج
ارتفاع
ايونات
الكالسيوم

ال classification هاد مش صعب لأنه ح نرجع نعيده بالتفصيل بالسلايدات الجاية
بس ضروري نكون عارفين كل class شو بحتوي ادوية



Thrombolytic Drugs

مثل كأنهم بعملوا activation لتحويل ال

plasmin ل plasminogen

بحللوها

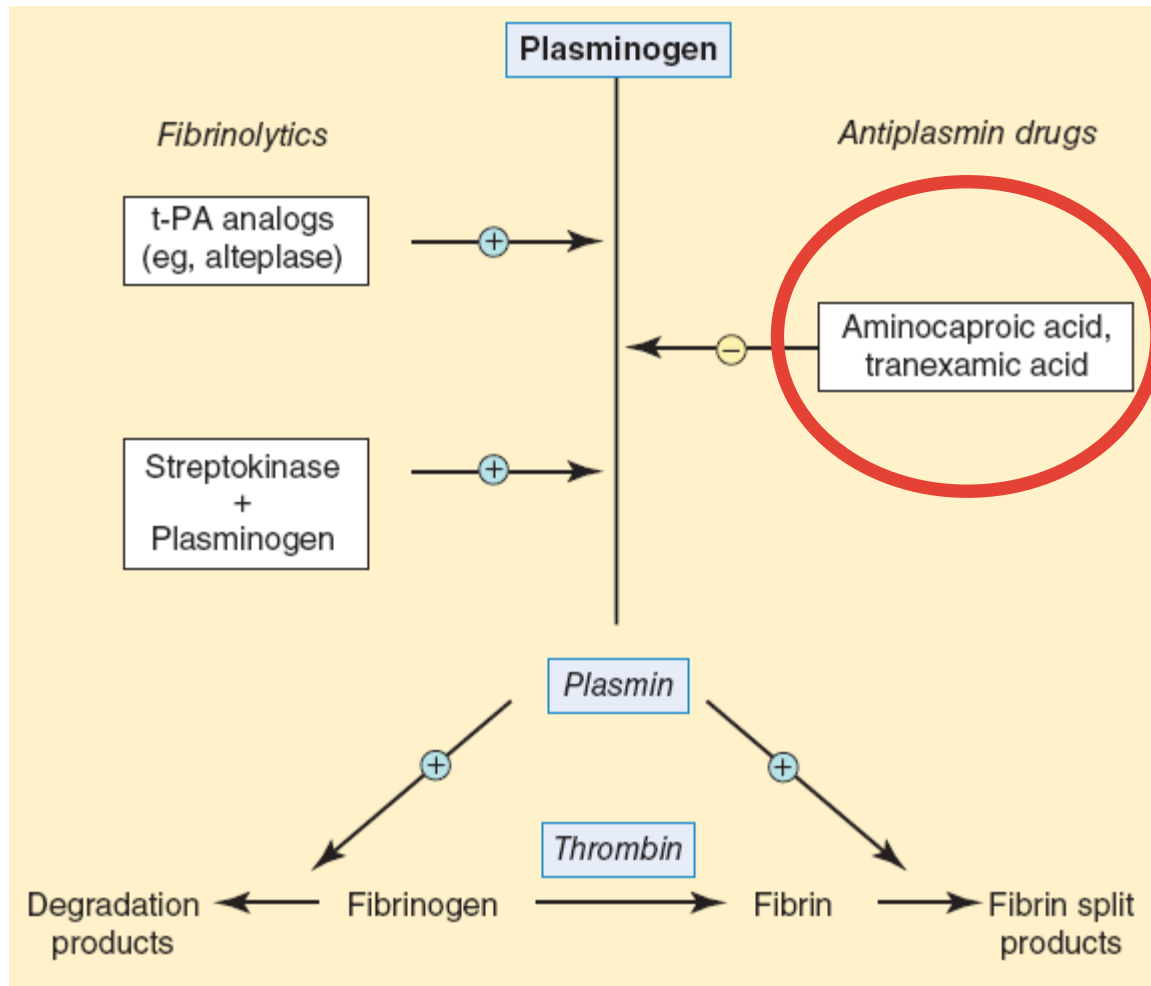
- Thrombolytic (fibrinolytic) drugs rapidly lyse thrombi by catalyzing the formation of the serine protease **plasmin** from its precursor, **plasminogen**.
- The thrombolytic drugs used most commonly are either forms of the endogenous **tissue plasminogen activator (t-PA; eg, alteplase, tenecteplase, and reteplase)** or a protein synthesized by streptococci (**streptokinase**).
في فسمين أو تصنيفين للأدوية بال Thrombolytic
- All are given intravenously. **IV**

Mechanism of Action

- Plasmin is an endogenous fibrinolytic enzyme that degrades clots by splitting fibrin into fragments. The thrombolytic drugs catalyze the conversion of the inactive precursor, **plasminogen**, to **plasmin**.

شو هو ال plasmin ؟ هو عبارة عن endogenous fibrinolytic enzymes بحلل التجلطات
أو ال clot يعني عن طريق splitting أو تقسيم ال fibrin ل fragments

Thrombolytic Drugs



Thrombolytic Drugs

متى يستخدمه؟

Clinical Uses

- The major application of the thrombolytic agents is as an alternative to percutaneous coronary angioplasty in the emergency treatment of coronary artery thrombosis. Under ideal conditions (ie, treatment within 6 h), these agents can promptly recanalize the occluded coronary vessel.
- Administration of fibrinolytic drugs by the intravenous route is also indicated in cases of severe pulmonary embolism and severe deep venous thrombosis.

لأنه في حال كان الشخص عنده emoli ف هو مُعرّض جدًا يصير معه thrombosis

Thrombolytic Drugs

Toxicity

أكثر مشكلة بنخاف منها بكل هاي الأدوية هو أنه يصير **Bleeding**!

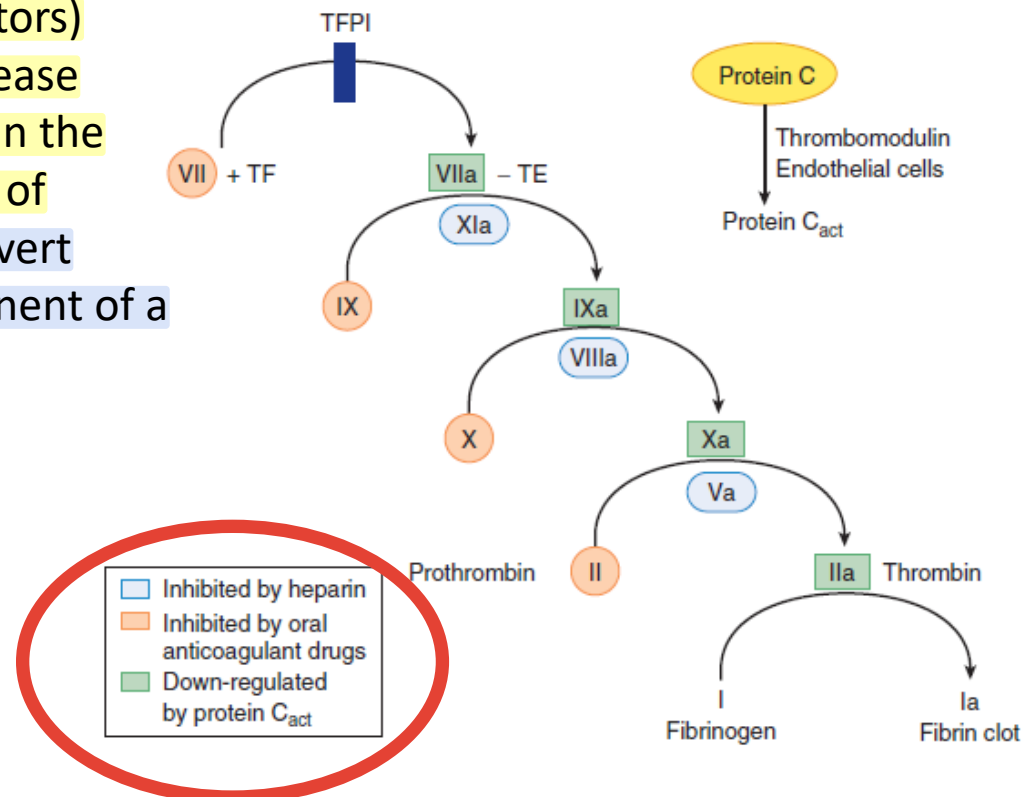
- **Bleeding** is the most important hazard and has about the same frequency with all the thrombolytic drugs.
- **Cerebral hemorrhage** is the most serious manifestation. **يمكن كمان يعمل نزيف دماغي**.
- **Streptokinase**, a **bacterial protein**, can evoke the production of antibodies that cause it to **lose its effectiveness or induce severe allergic reactions** on subsequent therapy. Patients who have had streptococcal infections may have preformed antibodies to the drug.
- Because they are **human proteins**, the recombinant forms of t-PA are not subject to this problem. However, **they are much more expensive than streptokinase and not much more effective.**

بتحريك إنه ال **streptokinase** هو جاي من **bacterial protein** لهيك رح يعمل بالجسم **antibodies** بتقلل من فعاليته أو بتعمل **allergic reactions** لهيك ما بنعطيه ك علاج مرة ثانية على عكس باقي ال **agents** إلي بتكون جاي من **human protein** ف ما بتكون عندها نفس مشكلة ال **streptokinase** بس هم أغلى وبنفس الوقت مش بنفس الفعالية

Blood Coagulation Cascade

Number	Roman Numeral
1	I
2	II
3	III
4	IV
5	V
6	VI
7	VII
8	VIII
9	IX
10	X

- The main initiator of blood coagulation in vivo is the tissue factor (TF)-factor VIIa pathway.
- Tissue factor** is a transmembrane protein ubiquitously expressed outside the vasculature, but not normally expressed in an active form within vessels.
- Several circulating proteins (clotting factors) interact in a cascading series. Each protease factor activates the next clotting factor in the sequence, culminating in the formation of **thrombin (factor IIa)**, which in turn convert fibrinogen to fibrin, an essential component of a functional clot.
- Several of these factors are targets for drug therapy.



Thrombin

ال thrombin هي إلي حفزت تحويل ال fibrinogen ل fibrin ف بالتالي يمنع ال bleeding

- Thrombin has a **central role** in blood hemostasis and has many functions.
- In clotting, thrombin:
 1. proteolytically cleaves small peptides from fibrinogen, allowing fibrinogen to polymerize and form a fibrin clot.
 2. Thrombin also activates many upstream clotting factors, leading to more thrombin generation.
 3. It activates factor XIII, a transaminase that cross-links the fibrin polymer and stabilizes the clot.
 4. Thrombin also exerts **anti** coagulant effects by activating the protein C pathway, which attenuates the clotting response.
- It should therefore be apparent that **the response to vascular injury is a complex and precisely modulated process that ensures that under normal circumstances, repair of vascular injury occurs without thrombosis and downstream ischemia; that is, the response is proportionate and reversible.**

رح يعمل ال thrombin على:

(١) إنه **proteolytically cleaves small peptides** "تقطع" من ال **fibrinogen** ف بالتالي رح يسمح لل **fibrinogen** إنها تعمل **polymerize** وتشكل **fibrin clot**

(٢) بعمل على تحفيز ال **upstream clotting factors** إلي حكيانهم من ١ ل ١٠ ف هالشي ح يعمل **more thrombin generation**

(٣) رح يحفز ال **factor** رقم ١٣ إلي هو **transaminase** بربط ال **fibrin polymer** وبعمل **. stabilizes the clot**

(٤) إله دور **anti coagulant** عن طريق تنشيط **protein C pathway** إلي بدوره رح يخفف من ال **.clotting response**

Endogenous Anticoagulants

- **Antithrombin** is an endogenous anticoagulant and a member of the serine protease inhibitor family; it inactivates the serine proteases IIa, IXa, Xa, XIa, and XIIa.
- The endogenous anticoagulants **protein C** and **protein S** ^{بتخفف} attenuate the blood clotting cascade by proteolysis of the two cofactors Va and VIIIa.

يُعتبر endogenous anticoagulant إلى بعمل
Inactivation لل serine proteases رقم ٢ و ٩ و ١٠ و ١١ و ١٢

يعني بالنهاية شي بعمل clot وشي بعمل lysis
لهي ال clot ف هيك بنحقق توازن

بال Thrombolytic كان already ال fibrin موجود وبدي اعمله lysis ، بينما هون رح نمنع
أصلاً تكوّن ال fibrin

Anticoagulants

- Anticoagulants inhibit the formation of fibrin clots.
- The anticoagulant drugs inhibit either the action of the coagulation factors (such as heparin and heparin-related agents) or interfere with the synthesis of the coagulation factors (such as warfarin).
- Three major types of anticoagulants are available:
 1. Heparin and related products, which must be used parenterally.
 2. Direct thrombin and factor X inhibitors, which are used parenterally or orally.
 3. The orally active coumarin derivatives (eg, warfarin).

رح نكمل شرحه بالبارت الثاني