DRUGS AFFECTING BLOOD

ANTICOAGULANTS, PLATELET INHIBITORS , THROMBOLYTICS AND TREATMENT OF BLEEDING

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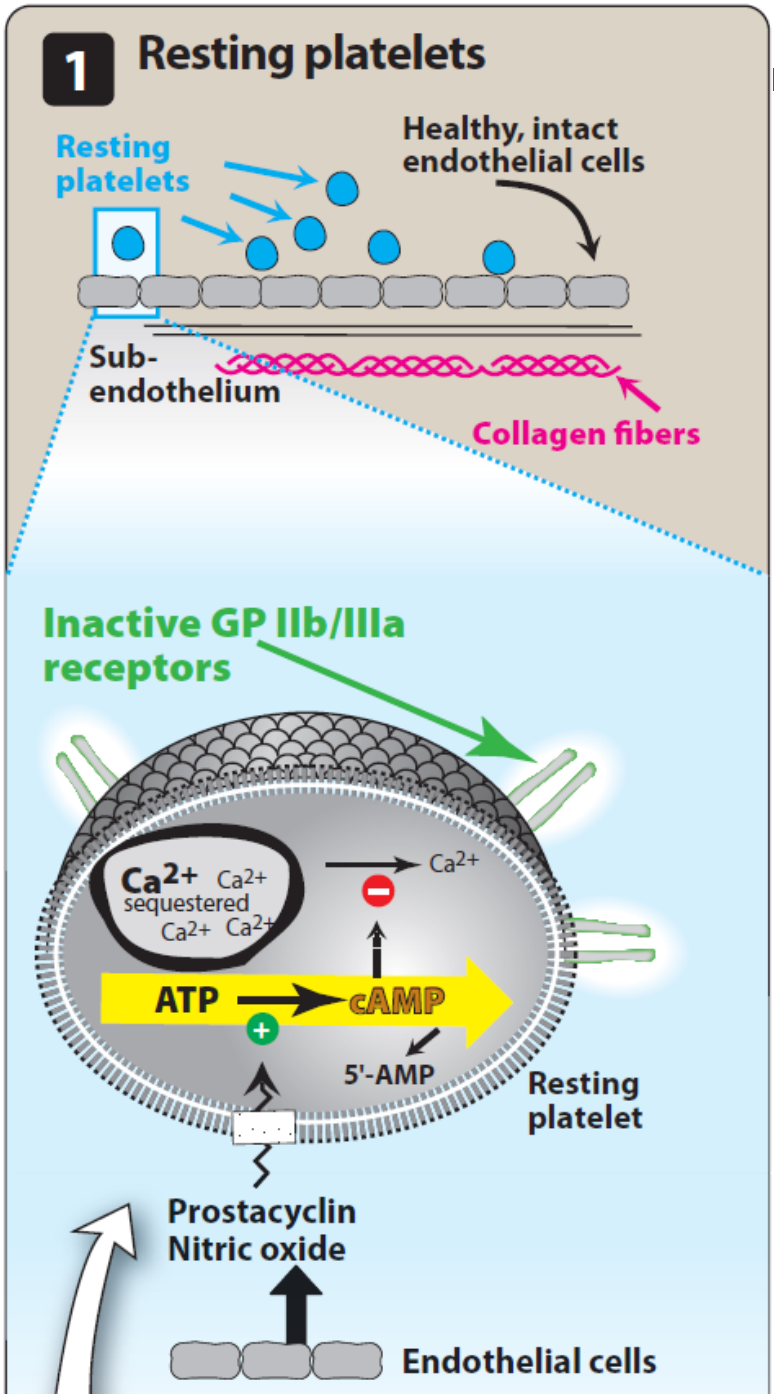
Figures and tables are originated from Lippincott's Pharmacology (6th Edition) and and Katzung&Trevor Basic and Clinical Pharmacology (13th Edition).

THROMBUS: A clot that adheres to a vessel wall

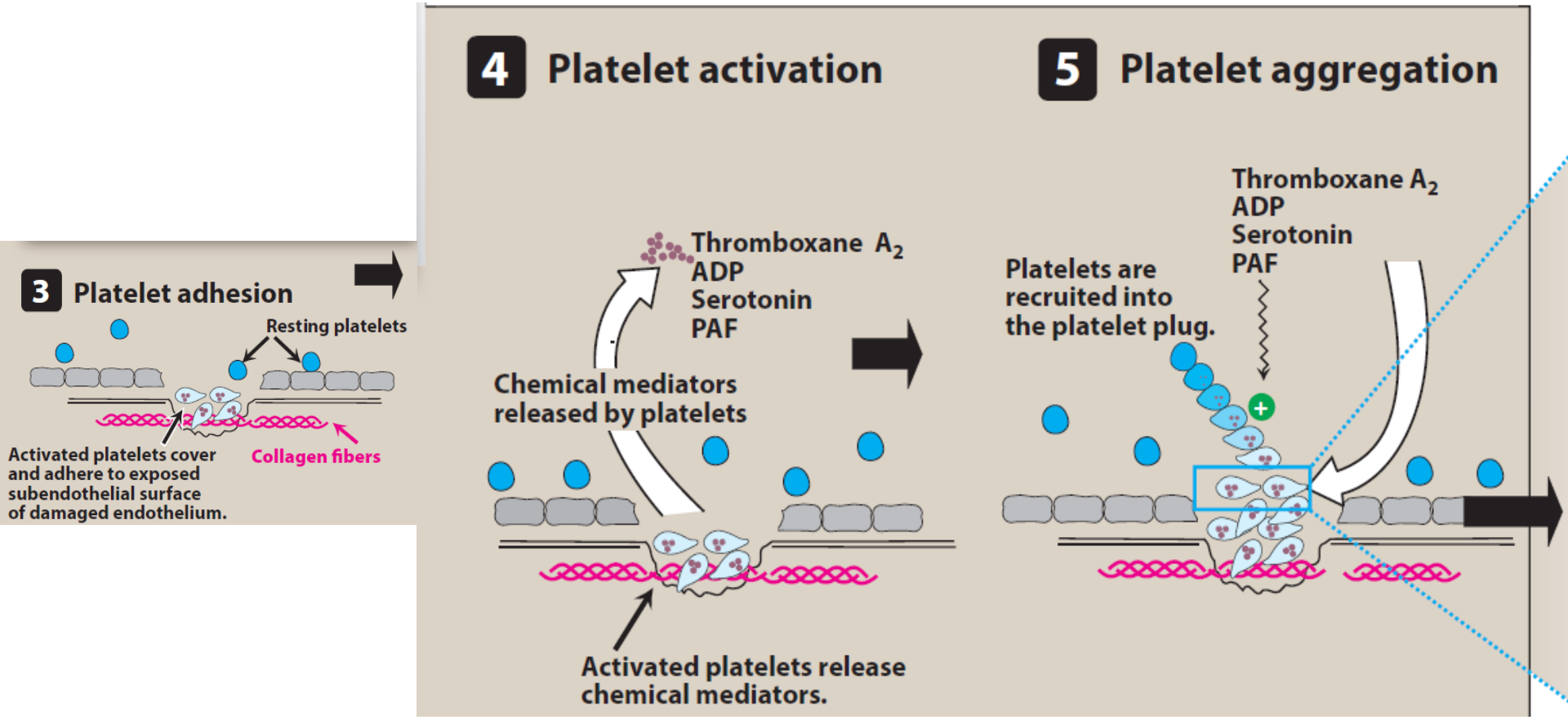
EMBOLUS: An intravascular clot that floats in the blood
A detached thrombus becomes an embolus.

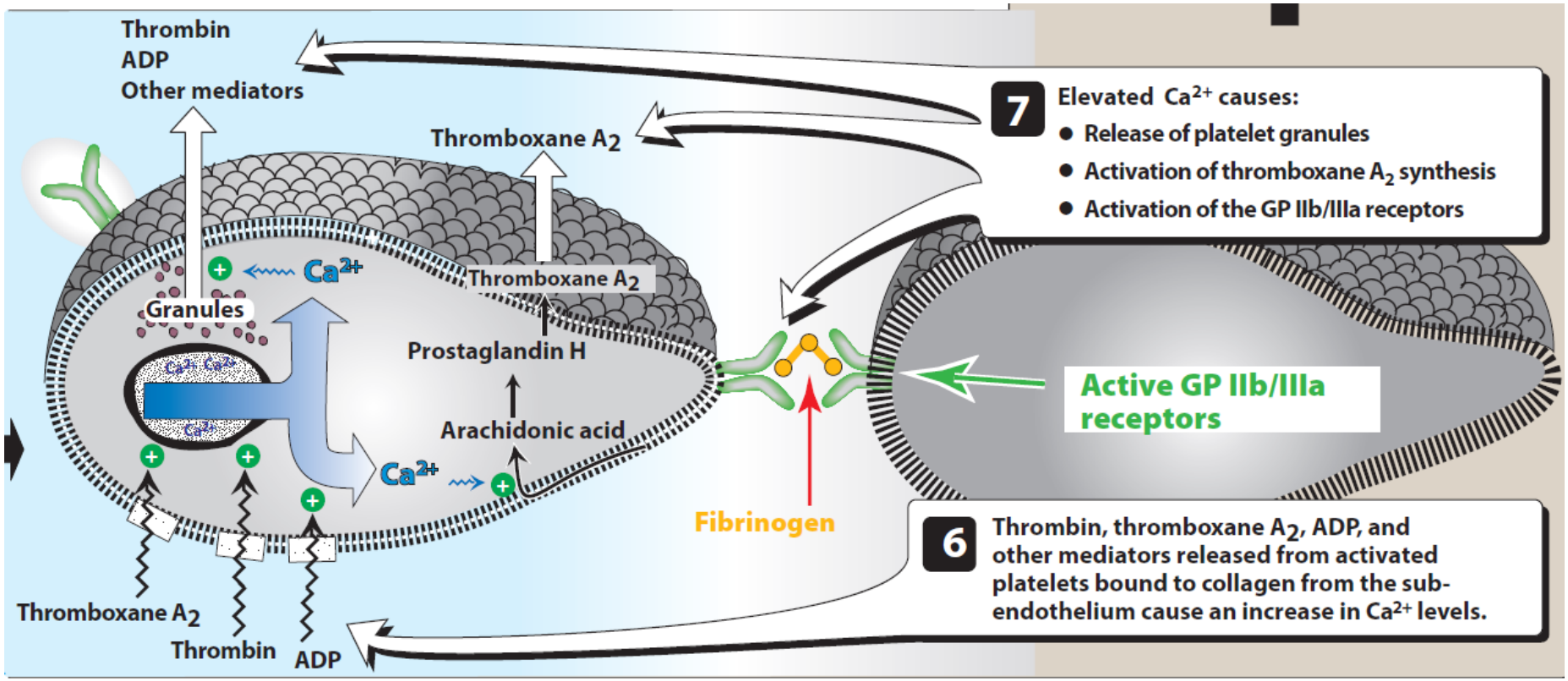
Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by atherosclerosis. Arterial thrombosis usually consists of a platelet-rich clot.

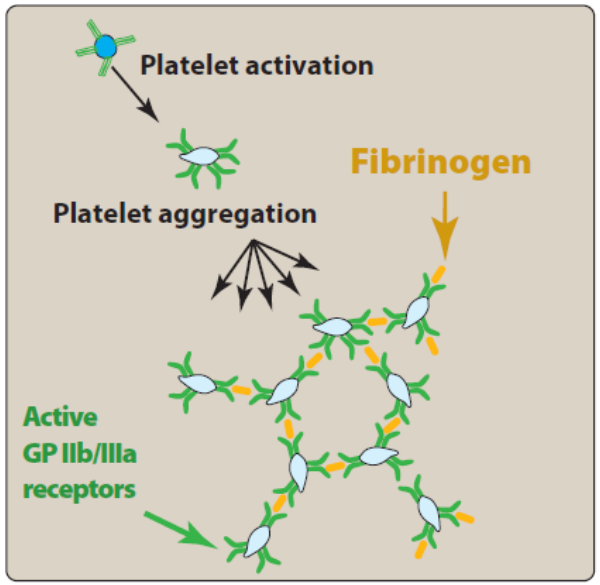
Venous thrombosis is triggered by inappropriate activation of the coagulation cascade.

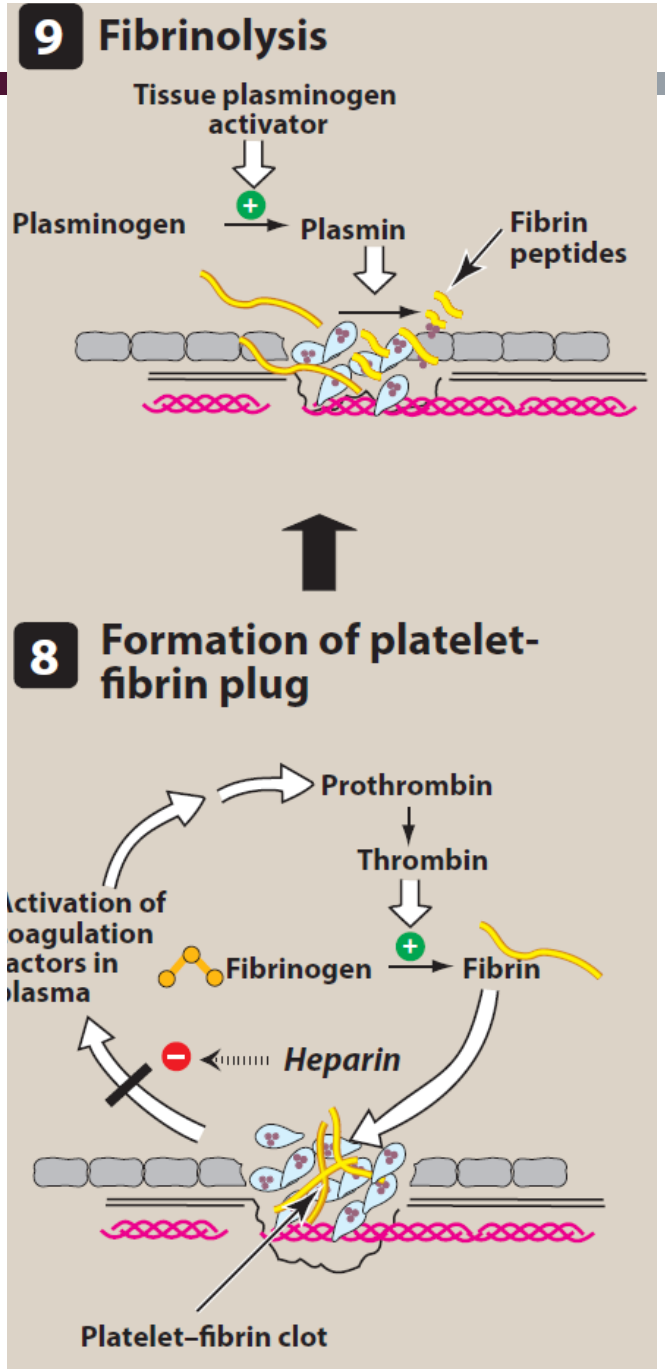


- Healthy, intact endothelium releases prostacyclin into plasma.
- Prostacyclin binds to platelet membrane receptors, causing synthesis of cAMP.
- cAMP stabilizes inactive GP IIb/IIIa receptors and inhibits release of granules containing platelet aggregation agents or Ca^{2+}.


3 Platelet adhesion
Resting platelets
Activated platelets cover and adhere to exposed subendothelial surface of damaged endothelium.
Collagen fibers
4 Platelet activation
Thromboxane A_2
ADP
Serotonin
PAF
Chemical mediators released by platelets
Activated platelets release chemical mediators.
5 Platelet aggregation
Thromboxane A_2
ADP
Serotonin
PAF
Platelets are recruited into the platelet plug.

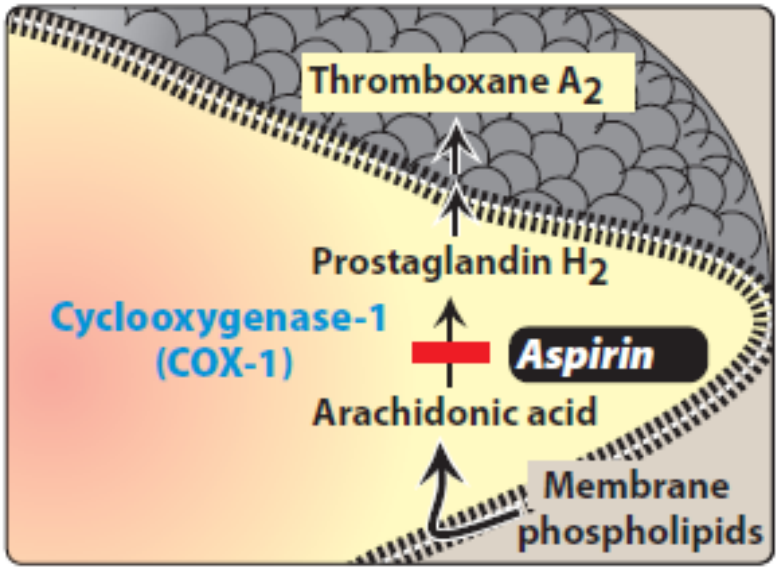

Thrombin
ADP
Other mediators
Thromboxane A2
7
Elevated Ca2+ causes:
Release of platelet granules
Activation of thromboxane A2 synthesis
Activation of the GP IIb/IIIa receptors
Ca2+
Granules
Thromboxane A2
Prostaglandin H
Arachidonic acid
Active GP IIb/IIIa receptors
Ca2+
Fibrinogen
6
Thrombin, thromboxane A2, ADP, and other mediators released from activated platelets bound to collagen from the sub-endothelium cause an increase in Ca2+ levels.
Thromboxane A2
Thrombin
ADP


Platelet activation
Fibrinogen
Platelet aggregation
Active
GP IIb/IIIa
receptors


9 Fibrinolysis
Tissue plasminogen activator
Plasminogen
Plasmin
Fibrin peptides
8 Formation of platelet-fibrin plug
Prothrombin
Thrombin
Activation of coagulation factors in plasma
Fibrinogen
Fibrin
Heparin
Platelet–fibrin clot

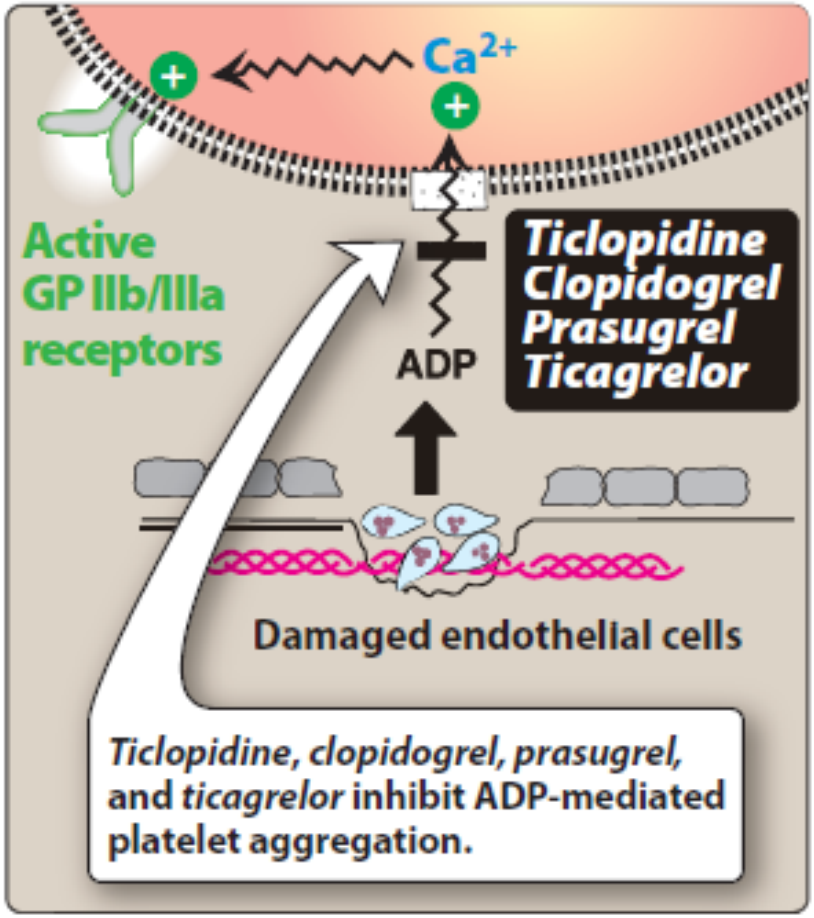
Platelet Inhibitors

Aspirin



75-300 mg/day.
Life-time of thrombocyte is around 8-10 days.
Life-time of aspirin is around 20 min.
Irreversible blockage.

Clopidogrel, Ticlodipine, Prasugrel, Ticagrelor



$P2Y_{12}$ receptor inhibitors.

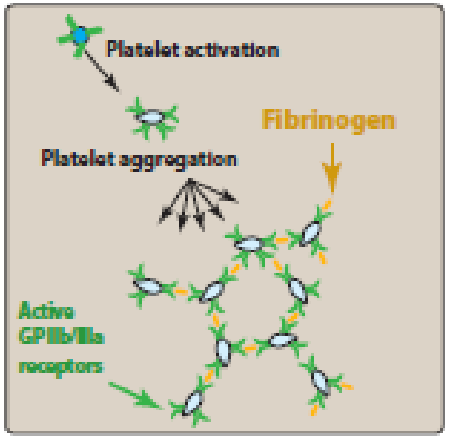
Irreversible blockage except ticagrelor.

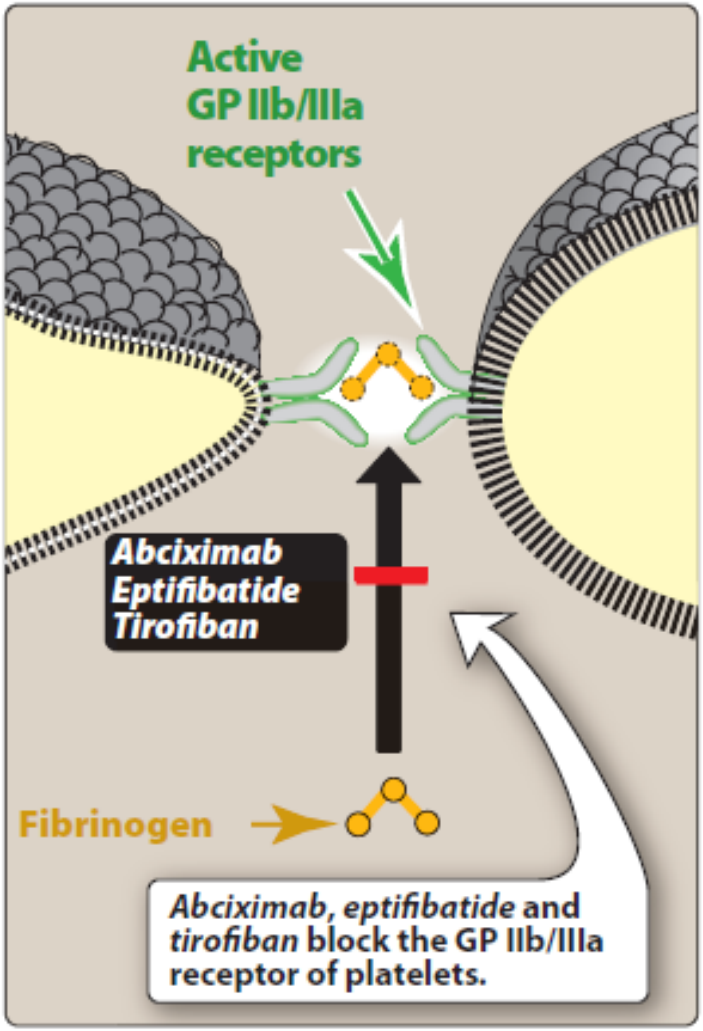
Clopidogrel is a prodrug.

Synergistic effect with aspirin.

Clopidogrel: An alternative to aspirin. Genetic polymorphism-active metabolite!!

Abciximab, Eptifibatide, Tirofiban





Abciximab: Chimeric monoclonal antibody that inhibits the GPIIb/IIIa receptor complex. Blocks the binding of fibrinogen and vWf and aggregation does not occur.

Eptifibatide: Cyclic peptide that binds to the GPIIb/IIIa at the site that interacts with the arginine-glycine-aspartic acid sequence of fibrinogen.

Tirofiban: Non-peptide structure that blocks the same site as eptifibatide.

Given intravenously along with aspirin/clopidogrel and low dose of heparin.

Anticoagulants

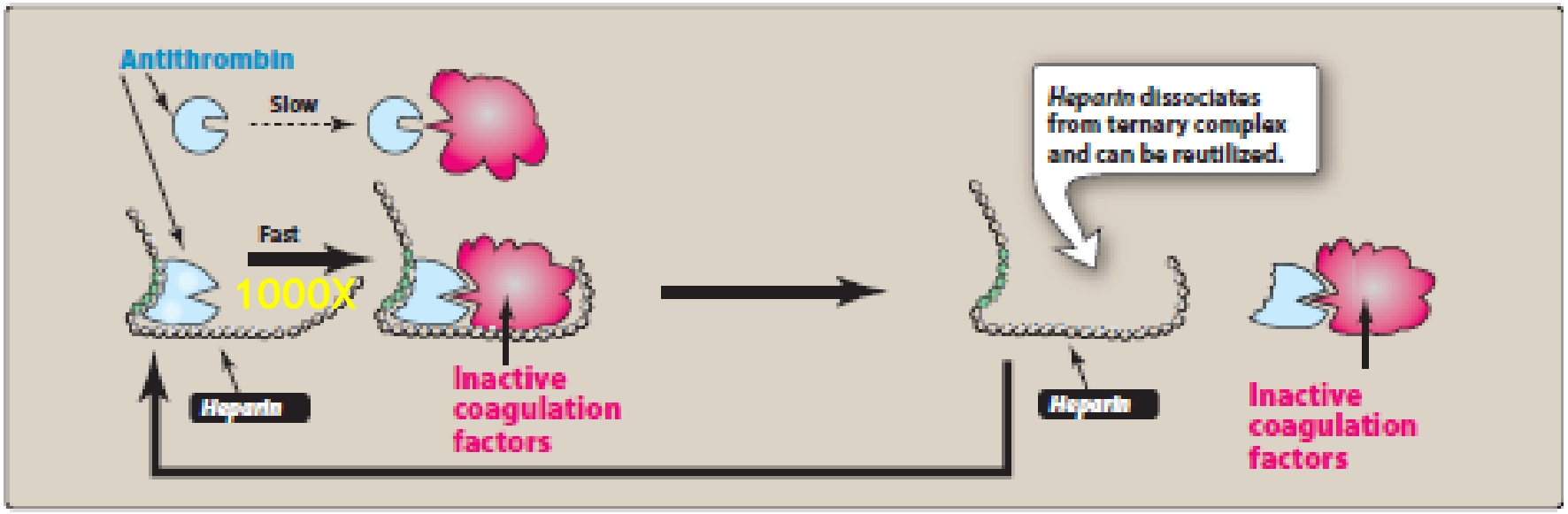
The anticoagulant drugs inhibit either the action of the coagulation factors (e.g. heparin) or interfere with the synthesis of the coagulation factors (e.g. warfarin).

Indirect thrombin inhibitors

1. Heparin *Enhance the binding to antithrombin III with the subsequent rapid inactivation of coagulation factors*
2. Low molecular weight heparins (LMWH)
3. Fondaparinux *Inhibition of factor Xa*

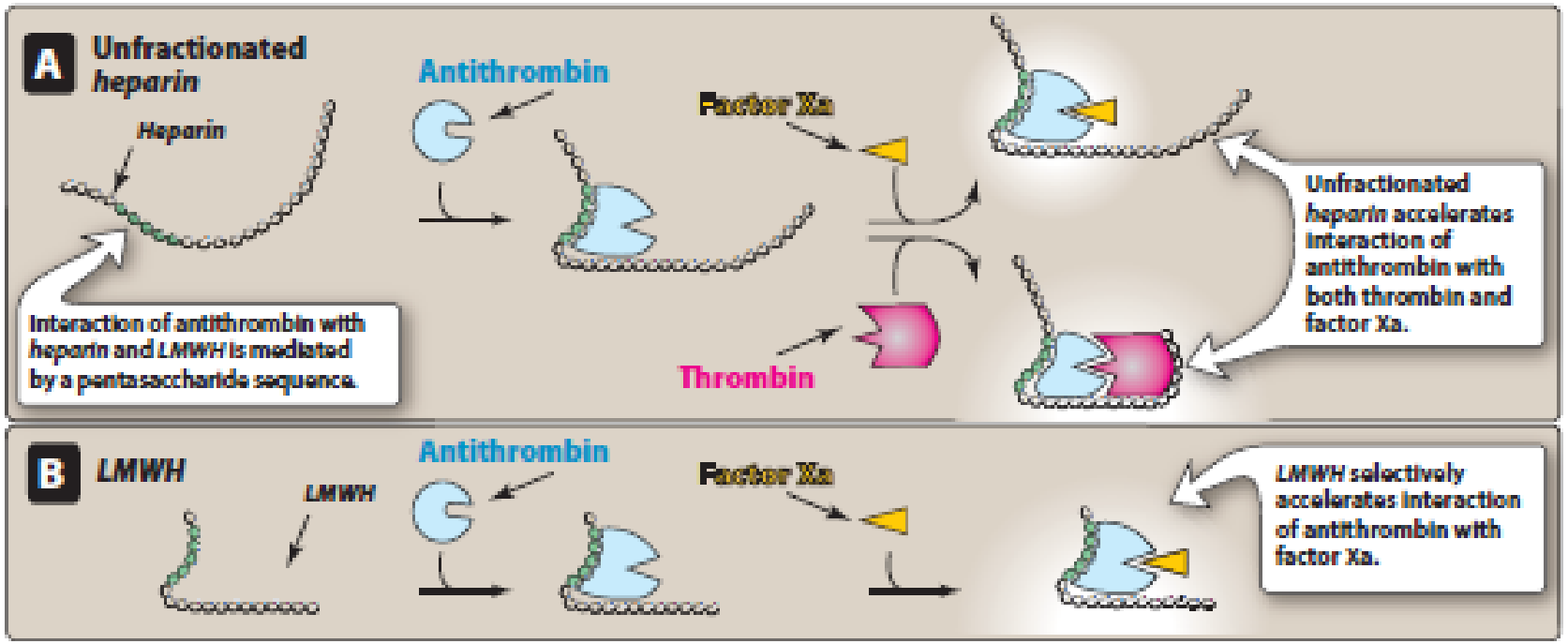
Heparin

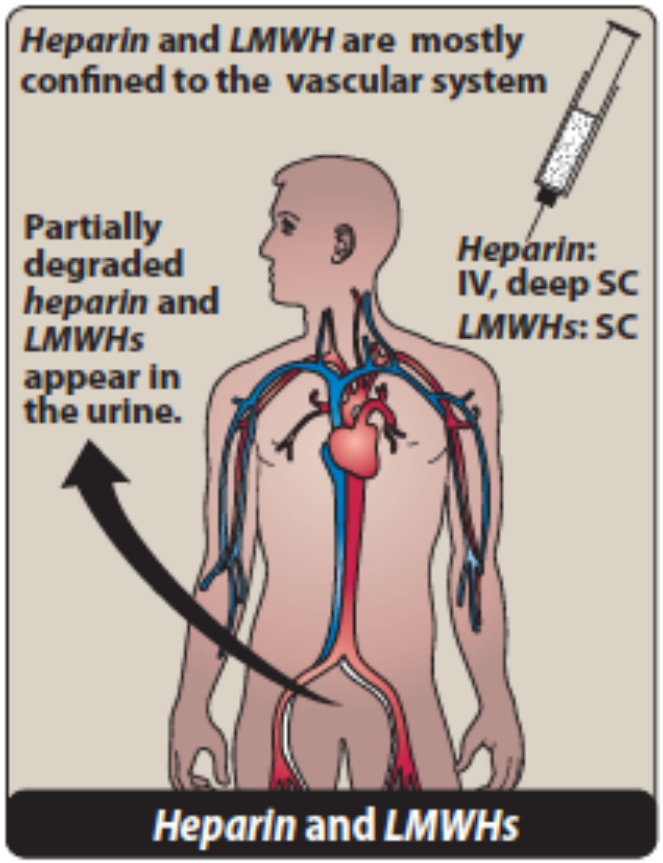
Antitrombin III: trombin (IIa), IXa and Xa



LMWH

Enoxaparine, dalteparin, tinzaparin

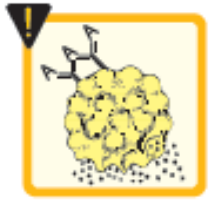




DRUG CHARACTERISTIC	*HEPARIN*	*LMWHs*
Intravenous half-life	2 hours	4 hours
Anticoagulant response	Variable	Predicable
Bioavailability:	20%	90%
Major adverse effect	Frequent bleeding	Less frequent bleeding
Setting for therapy	Hospital	Hospital and outpatient

Adverse effects

Bleeding



Hypersensitivity

Thrombo-cytopenia

Osteoporosis (long-term therapy)

Heparin and LMWHs are contraindicated in patients who have hypersensitivity to heparin, bleeding disorders, alcoholism or who have had recent surgery.

Excessive bleeding may be managed by treating with protamine sulfate. It is very important that the dosage of protamine sulfate is carefully titrated, because protamine sulfate is a weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential.

Fondaparinux

Pentasaccharide anticoagulant that is synthetically derived.
Selectively inhibits only factor Xa.
By selectively binding to antithrombin III, the agent potentiates (300-to 1000-fold) the innate neutralization of factor Xa by antithrombin III.
t1/2~17-21h, sc.
Requires less monitoring than heparin.
Bleeding is the major side effect.
Contraindicated in patients with severe renal impairment.
There is no avaible agent for the reversal of bleeding associated with fondaparinux.

Anticoagulants

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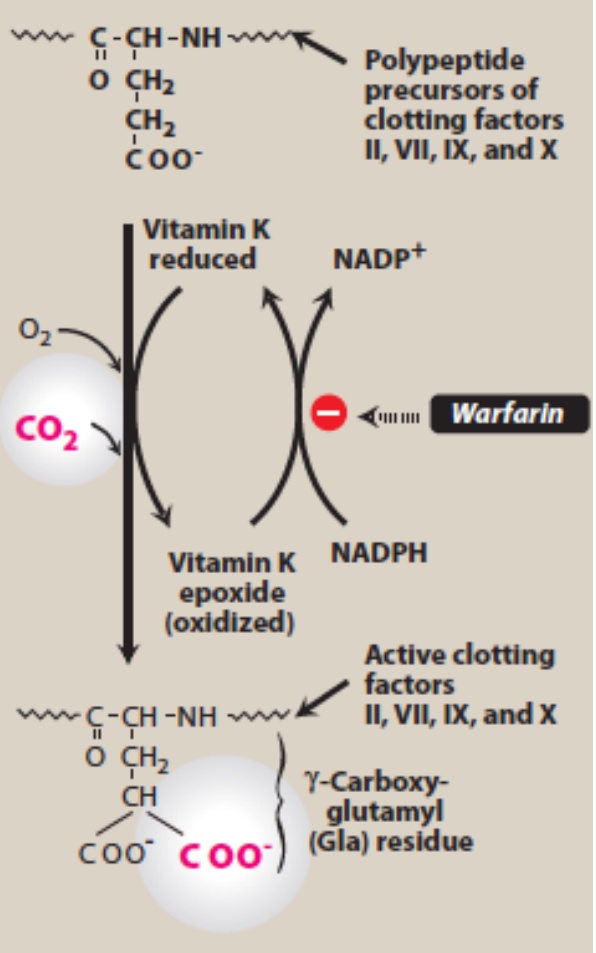


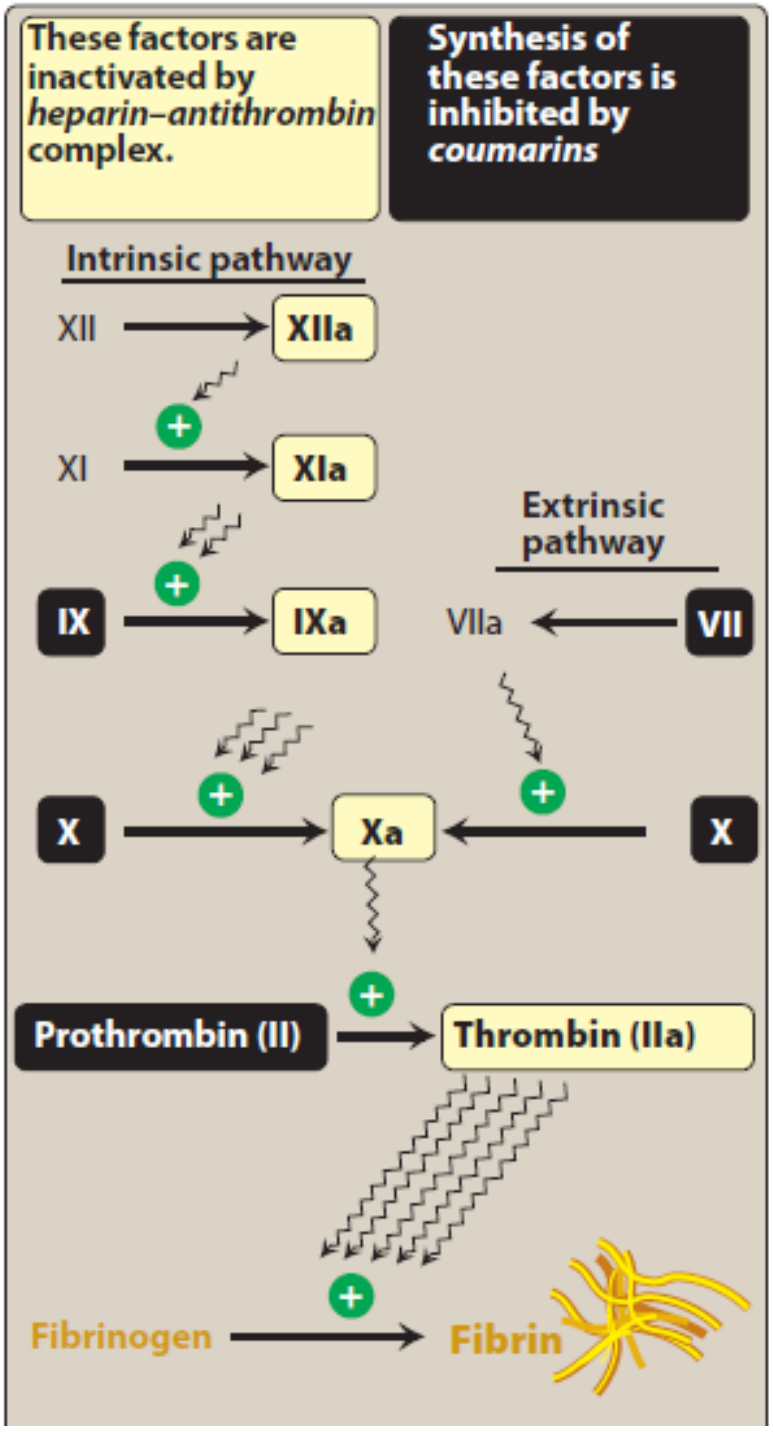
The INR is the standard by which the anticoagulant activity of warfarin therapy is monitored.

The goal of warfarin therapy is an INR of 2 to 3 for most indications, with an INR of 2.5 to 3.5 targeted for some mechanical valves and other indications.

Warfarin has a narrow therapeutic index. Frequent monitorizing may be required.

Unlike heparin, the anticoagulant effects of warfarin are not observed immediately after drug administration.

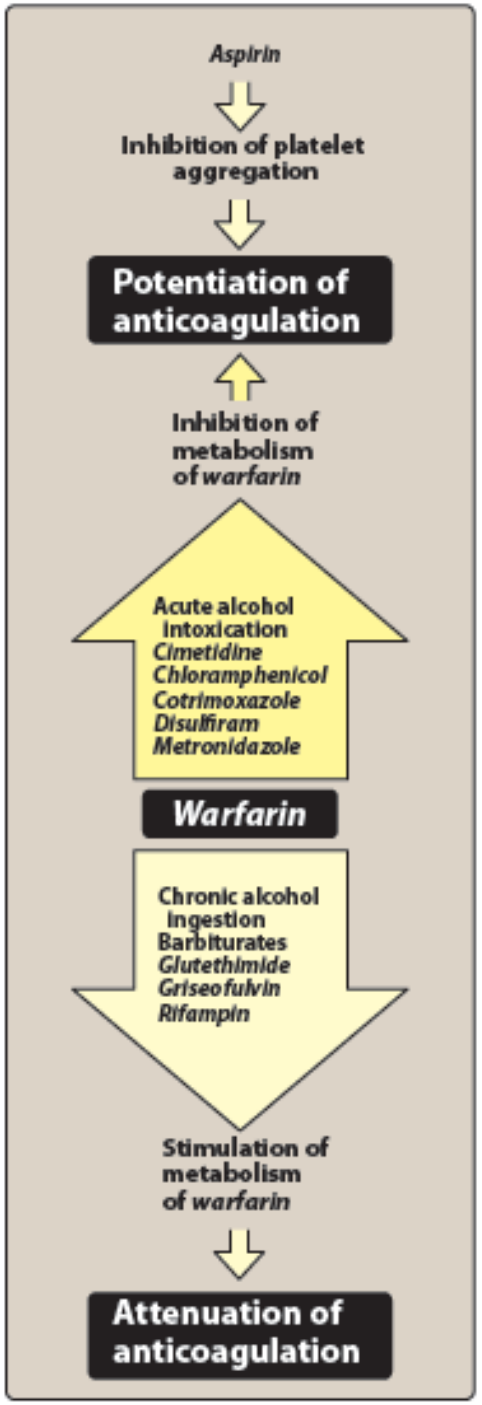
The anticoagulant effects of warfarin can be overcome by the administration of vitamin K.


These factors are inactivated by *heparin–antithrombin* complex.
Synthesis of these factors is inhibited by *coumarins*
Intrinsic pathway
XII
XIIa
XI
XIa
IX
IXa
Extrinsic pathway
VIIa
VII
X
Xa
X
Prothrombin (II)
Thrombin (IIa)
Fibrinogen
Fibrin

The principal adverse effect is hemorrhage.
The agent has a black box warning for bleeding risk.
It is important to frequently monitor the INR and adjust the dose of warfarin.

Warfarin is teratogenic and should never be used during pregnancy.
If anticoagulant therapy is needed during pregnancy, heparin or LMWH may be administered.

Drug interactions!!

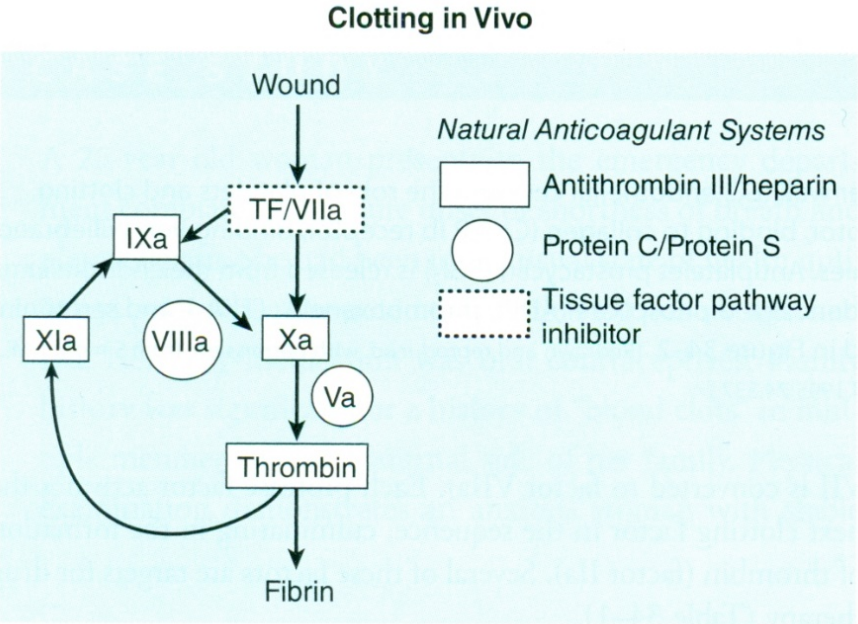


Oral Inhibitors of Factor Xa

Rivaroxaban and Apixaban

They bind to the active site of factor Xa, preventing its ability to convert prothrombin to thrombin.

They have constant doses.
No need for monitorization.
Their clinical effects start quickly.
Their half-lifes are shorter than warfarin.



Both drugs are primarily metabolized by CYP3A4.
Bleeding is the most serious adverse effect.
No antidote avaible to reverse bleeding caused by these agents.
Neither drug should be used in severe renal dysfunction.

Direct Thrombine Inhibitors

Bivaluridin and desirudin: Parenteral anticoagulants. Selective direct thrombin inhibitors that reversibly inhibit the catalytic site of both free and clot-bound thrombin. In patients with normal renal function, the half-life of bivaluridin is 25 minutes. Dosage adjustments are required in patients with renal impairment. Bleeding is the major side effects.

Argatroban: Synthetic parenteral anticoagulant. Direct thrombin inhibitor. Metabolized in the liver and has a half-life of about 50 minutes. Because argatroban is metabolized in the liver, it may be used in patients with renal dysfunction, but it should be used cautiously in patients with hepatic imparment. Bleeding!!

Dabigatran eteksilat mezilat: Prodrug of the active metabolite dabigatran, an oral direct thrombin inhibitor. CYP450 system does not play a role in the metabolism of dabigatran. It is eliminated renally. The major adverse effect is bleeding (especially age of >75). Dabigatran does not require INR monitorization.

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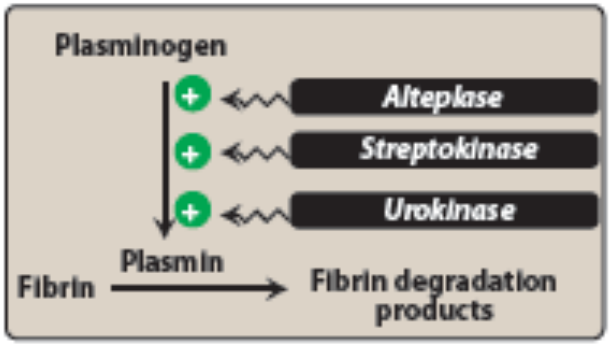
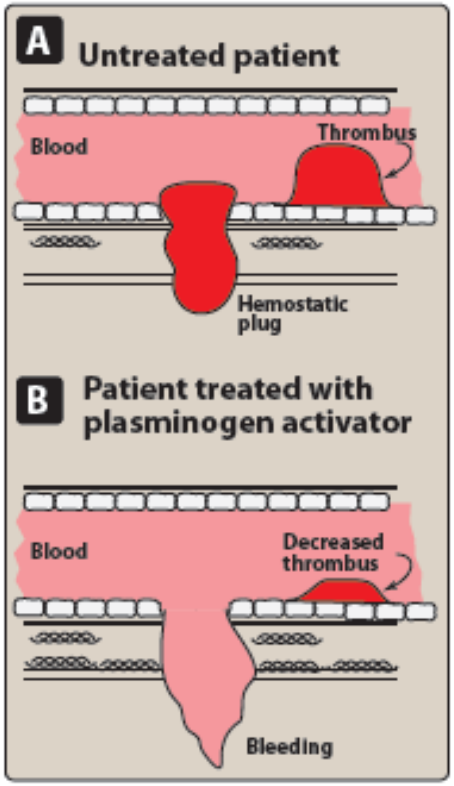
Thrombolytic drugs



Agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and thus dissolves clots.

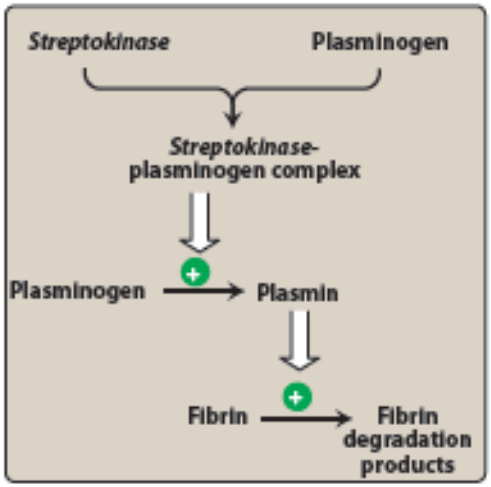
1. Streptokinase
2. Alteplase*
3. Reteplase* *(Recombinant form)*
4. Tenecteplase* *(Recombinant form)*
5. Urokinase

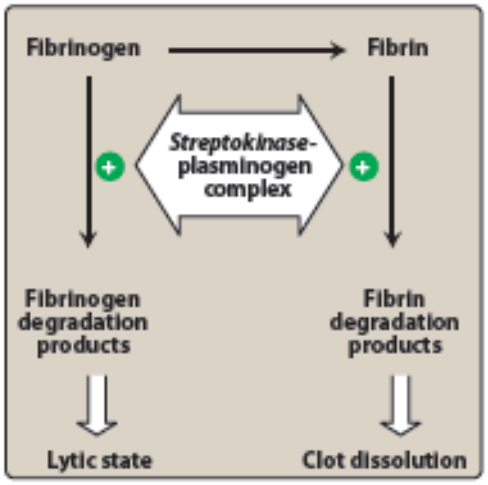
**2, 3, 4: fibrin-selective*

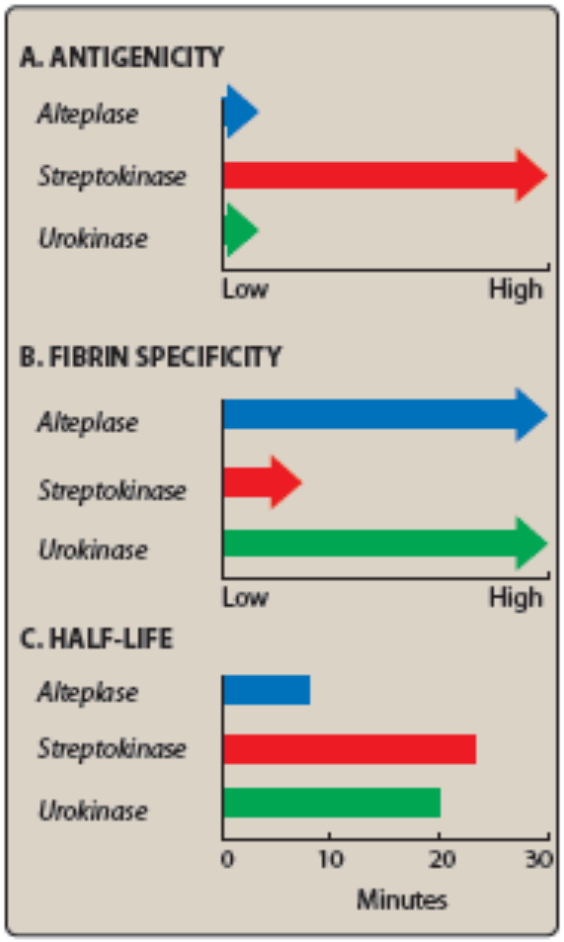


The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. **Hemorrhage** is a major side effect.
These drugs are contraindicated in pregnancy and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding and metastatic cancer.

Streptokinase







Alteplase: Formerly known as tissue plasminogen activator or tPA, it is obtained as a product of recombinant DNA technology.

It has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug.

Fibrin-selective at low doses. Very short half-life (5-30 min). May cause orolingual angioedema esp. combined with ACE inhibitors.

Reteplase: Genetically engineered, smaller derivative of recombinant tPA. Longer half-life compared to alteplase.

Tenecteplase: Another recombinant tPA with a longer half-life and greater binding affinity for fibrin than alteplase.

Drugs Used to Treat Bleeding

Medication	Antidote for Bleeding Caused by	Adverse Effects	Monitoring Parameters
Aminocaproic acid *Tranexamic acid*	Fibrinolytic state	Muscle necrosis Thrombosis CVA Seizure	CBC Muscle enzymes Blood pressure
Protamine sulfate	*Heparin*	Flushing Nausea/vomiting Dyspnea Bradyarrhythmia Hypotension Anaphylaxis	Coagulation monitoring Blood pressure Heart rate
Vitamin K1	*Warfarin*	Skin reaction Anaphylaxis	PT/INR

CBC=complete blood count, CVA = cerebrovascular accident, PT=prothrombin time, INR=international normalized ratio

Bleeding problems may have originated from pathologic conditions (hemophilia), as a result of fibrinolytic state or use of anticoagulants.

• **Aminocaproic acid or tranexamic acid:** Both agents are synthetic, orally active, excreted in urine and inhibit plasminogen activation. Tranexamic acid is 10X potent. Intravascular thrombosis is a potential side effect.

• **Protamine sulfate:** Antagonize the anticoagulant effect of heparin. Adverse effect of drug administration include hypersensitivity as well as dyspnea, flushing, bradycardia and hypotension when rapidly injected.

• **Vitamin K:** Inhibit the effect of warfarin. It may be administered via the oral, subcutaneous or intravenous route. The response to vitamin K is slow, requiring about 24 hours to reduce INR.