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BACK TO BASICS: MAKING SENSE OF DRUGS THAT REDUCE BLOOD CLOTTING

How blood clots

Normal blood clotting

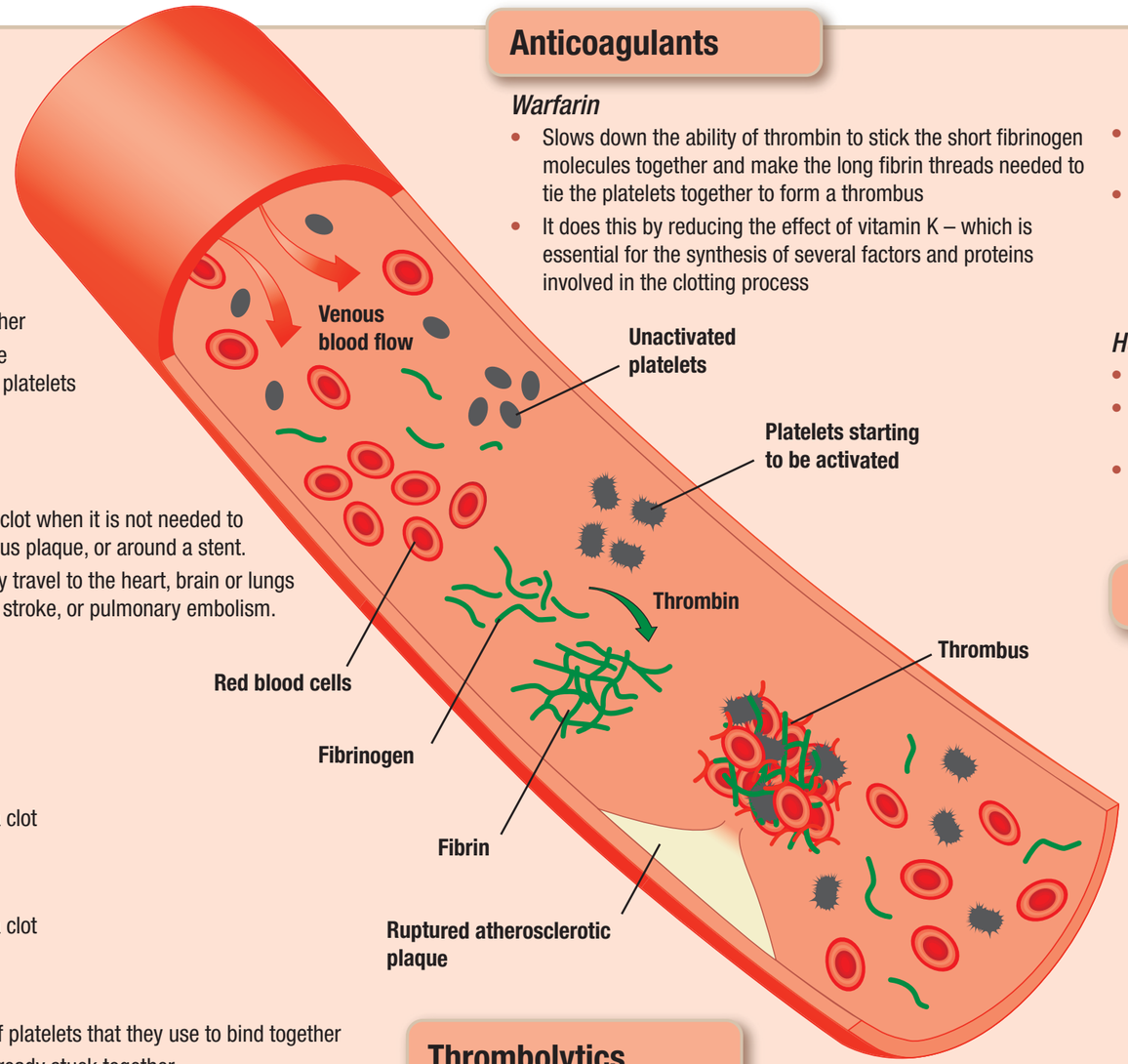
Blood clotting (haemostasis) is necessary to prevent blood loss after injury. Blood vessel injury triggers the following steps:

- The vessel constricts to reduce blood loss
- Circulating platelets stick to the vessel wall at the site of the injury
- Platelets are activated by thrombin and clump together
- Reactions involving coagulation proteins result in the production of long fibrin threads, which connect the platelets to form a stable plug, or clot
- Fibrinolysis dissolves fibrin, and the clot breaks up

Abnormal blood clotting

Excessive coagulation leads to the formation of a blood clot when it is not needed to prevent blood loss – such as where there is atheromatous plaque, or around a stent.

The formation of a clot can obstruct blood flow, or it may travel to the heart, brain or lungs and obstruct blood flow there, leading to a heart attack, stroke, or pulmonary embolism.



Antiplatelet drugs

Aspirin

- Blocks the ability of platelets to become activated
- This makes them less sticky and less able to form a clot

Thienopyridines

- Block the ability of platelets to become activated
- This makes them less sticky and less able to form a clot
- Examples include: ticlopidine, clopidogrel, prasugrel

GPIIb/IIIa inhibitors

- Block the main receptor (GPIIb/IIIa) on the surface of platelets that they use to bind together
- This breaks the links between platelets that have already stuck together
- Examples include: abciximab, tirofiban, eptifibatide

Phosphodiesterase inhibitors

- Increase the levels of chemicals inside platelets that stop them becoming activated
- This makes them less sticky and less able to form a clot
- Examples include: dipyridamole

Anticoagulants

Warfarin

- Slows down the ability of thrombin to stick the short fibrinogen molecules together and make the long fibrin threads needed to tie the platelets together to form a thrombus
- It does this by reducing the effect of vitamin K – which is essential for the synthesis of several factors and proteins involved in the clotting process
- Reduces the production of the fibrin threads that stick platelets together
- The downside of warfarin is that it needs regular monitoring to get the degree of anticoagulation just right, and it interacts with several other drugs and foods, which affects its anticoagulant effect

Heparin and low molecular weight heparins

- Bind to antithrombin to block several clotting enzymes
- This stops the formation of the fibrin threads that stick platelets together
- Examples of low molecular weight heparins include: enoxaparin, dalteparin, nadroparin and tinzaparin

Single coagulation factor inhibitors

Direct thrombin inhibitors

- Prevent the thrombin sticking the fibrinogen molecules together to make the longer fibrin threads
- This delay in making fibrin threads means that the platelets are naturally dispersed by tissue plasminogen before fibrin can tie them together to form a thrombus
- Examples include: dabigatran

Indirect factor Xa inhibitors

- Reduce levels of factor Xa, and so reduce levels of thrombin
- This reduces the production of fibrin threads that stick platelets together
- Examples include: fondaparinux

Thrombolytics

Tissue plasminogen activators (TPA)

- Stimulate tissue plasminogen, the blood's natural clot buster, on the blood clot
- Activated tissue plasminogen produces plasmin that breaks up the fibrin threads that hold the thrombus together – 'busting the clot'
- Examples include: alteplase, tenecteplase, reteplase

Other thrombolytics

- Stimulate production of plasminogen, to increase plasmin, but not just on the clot
- Examples include: streptokinase, urokinase