

Anticoagulants and Procoagulants: Drugs on Blood Coagulation

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Our body employs many mechanisms in order to maintain homeostasis. One particular term that is worth our attention when it comes to tackling homeostasis is hemostasis or the body's tendency to prevent the contents of our intravascular compartment (blood) to leak into different compartments within the body and into the external environment. This term also refers to the body's maintenance of the smooth flow of blood within the blood vessels. Hemostasis consists of intricate interdependent mechanisms. These have been the focus of many pharmacological studies that aim to address certain blood disorders. Read everything about it here.



Blood Coagulation

Normal mechanism

Blood coagulation *in vivo*

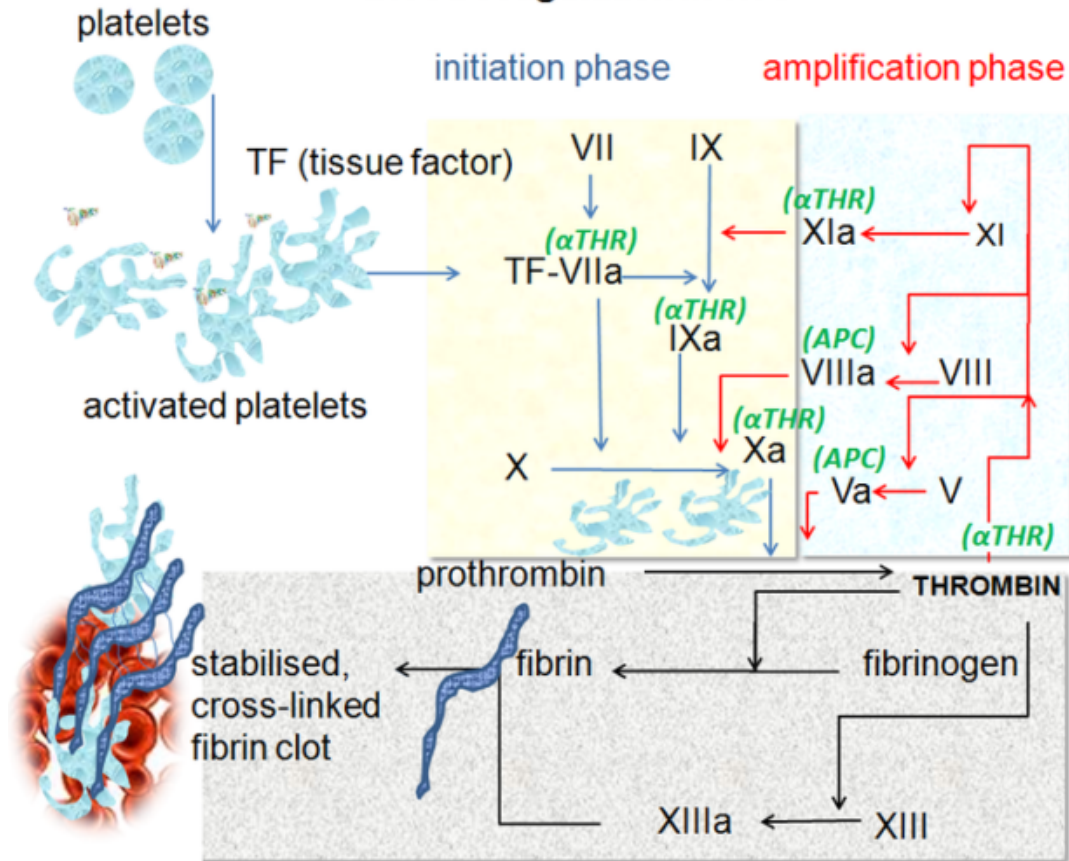


Image: Blood coagulation pathways in vivo. By Graham Beards, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Generally, hemostasis is composed of four main processes that eventually halt leakage of blood from blood vessels:

1. **Vascular constriction** (from spasms due to damage)
2. **Platelet plug formation**
3. **Blood clotting**
4. **Fibrous restructuring** of blood clots

Under normal circumstances, the endothelium of the [blood vessels](#) is an anticoagulant in nature. However, a break in its integrity triggers its tendency to become procoagulant, leading to hemostatic mechanisms. Any break in the surface of the endothelium exposes **collagen** and **von Willebrand factor (VWF)**, which are substances that promote platelet adherence to the area.

Once platelets are aggregated in the site of injury, their products during initial activation, such as **thromboxane A2 (TXA2)**, **adenosine diphosphate (ADP)**, and **serotonin (5-HT)**, are released. The substances are responsible for vasoconstriction and further platelet recruitment and activation. Receptors on the platelets' surfaces, particularly the **α IIb β 3 integrin (IIb/IIIa) receptors**, also change in conformation during activation, making them more receptive to additional platelets and fibrinogen.

A formed clot or **thrombus** can take on one of two forms. **White thrombi** generally are made up of platelets and commonly are seen in blood vessels with high flow velocities, such as the arteries. On the other hand, **red thrombi** consist of more fibrin and trapped red blood cells than platelets and commonly are found in low-pressure vessels, such as the veins. These are usually the cause of deep vein thromboses.

After an initial blood clot is formed, further conversions are set off. First, the conversion of **prothrombin to thrombin** happens in the presence of activated platelets, **prothrombin activator**, and calcium ions at the injured site. Thrombin, in turn, cleaves **fibrinogen to form fibrin**.

Fibrinogen and fibrin are actually what make blood coagulable. Fibrinogen is produced by the **liver**. Its absence in other bodily fluids, such as lymph and interstitial fluid, confers their inherent uncoagulable states. The activated form, fibrin, serves in the formation of a meshwork that reinforces a formed blood clot.

The newly reinforced blood clot is now able to trap in more platelets and red blood cells. A few minutes after formation, the blood clot contracts, thanks to some factors released by the activated platelets. This extracts a factor-free fluid from the clot called **serum**. This also pulls the edges of the clot that are apposed to the vessel wall, thereby contracting the breakage on the site.

The Clotting Cascade

The three pathways that makeup the classical blood coagulation pathway

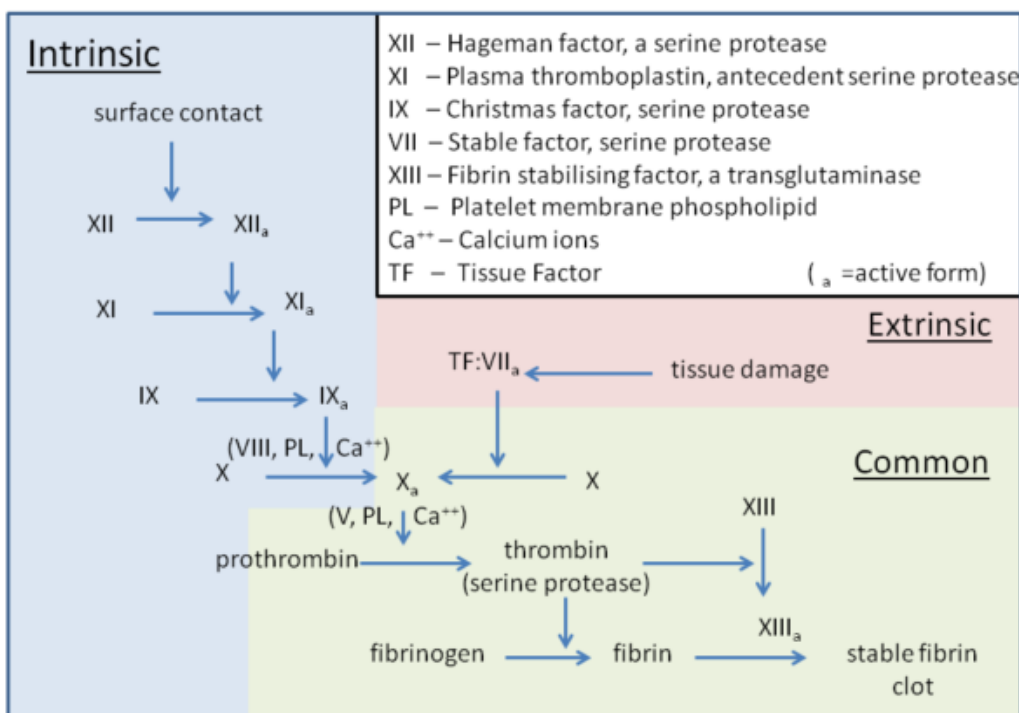


Image: The components and pathways that make up the classical blood coagulation cascade. By Graham Beards, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Once a platelet plug is formed, the same substances that are produced from the platelets continue to act and set off the **clotting cascade**, a series of reactions that lead to the coagulation of blood.

It all starts with the formation of thrombin with the help of the substance that limits the whole clotting cascade, prothrombin activator. This is produced in 2 different but interconnected ways that eventually lead to the activation of prothrombin. The pathways are basically a series of reactions converting different **zymogen factors** into potent clotting factors.

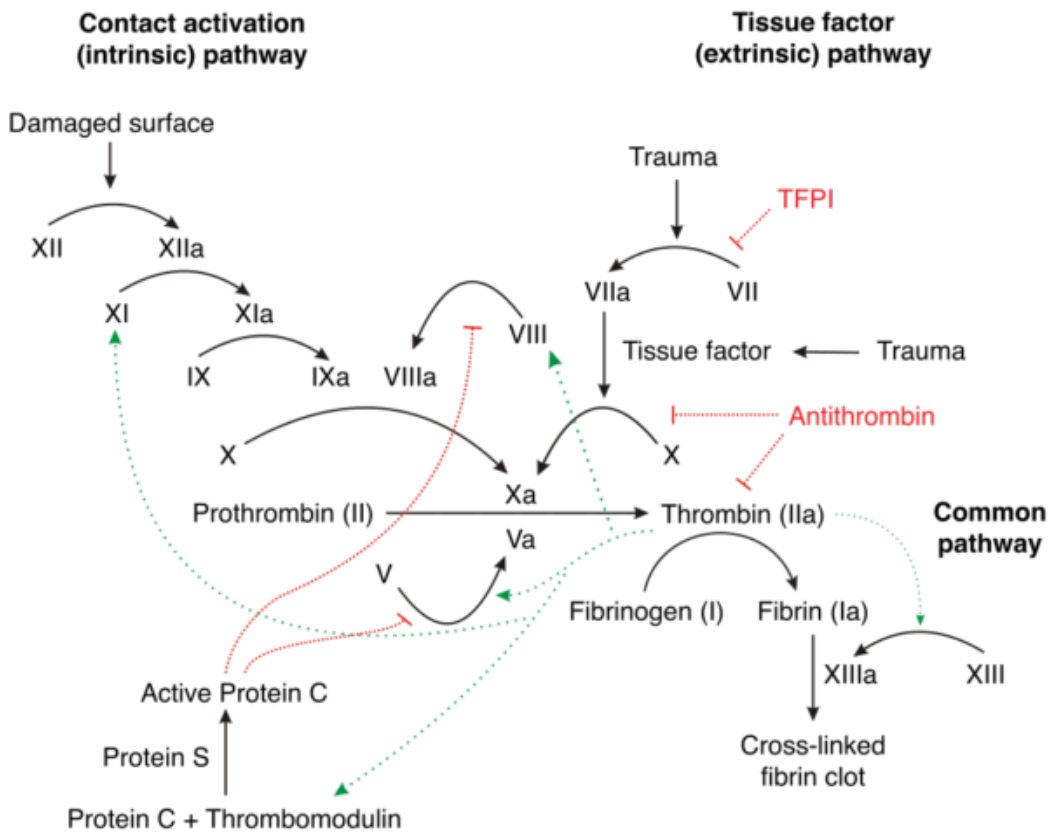


Image: More in-depth version of the coagulation cascade. By Joe D, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Extrinsic Pathway

Damaged endothelial and tissues release **tissue factor**, which is later used along with **factor VII** and calcium ions to activate **factor X**. The now-activated factor X (**factor Xa**) combines with phospholipids coming from the tissue factor and platelets, and with **factor V**, to form **prothrombin activator complex**, which is responsible for the cleavage of prothrombin to thrombin in the presence of calcium ions.

Intrinsic Pathway

The exposure of blood to collagen (or glass *in vitro*) triggers the activation of **factor XII** to **factor XIIa**. This also causes the platelets to express phospholipids that contain **platelet factor 3 (pf3)**. Factor XIIa along with **high-molecular-weight kininogen** and the enzyme **prekallikrein** activates **factor XI**. Factor XIa activates **factor IX**. In the presence of **factor VIIIa**, and phospholipids and **factor III** coming from the platelets, factor IXa cleaves **factor X**. Factor Xa binds with factor V and phospholipids to form the same prothrombin activator complex produced in the extrinsic pathway.

Fibrinolysis

Once the injury in the blood vessels is healed, there is no need for the presence of a blood clot. Therefore, the body initiates fibrinolysis by cleaving the zymogen **plasminogen** into a potent clot-remodeling and -degrading agent called **plasmin** with the help of **tissue plasminogen activator, or t-PA**. This mechanism is inherently inhibited under normal circumstances in the presence of a **plasminogen activator**

inhibitor or is released by the endothelium.

Conditions that Affect Coagulation

Excessive Bleeding Conditions

Excessive bleeding is caused by a lack of any of the clotting factors and substances involved in hemostasis. Such conditions are categorized into 3 groups:

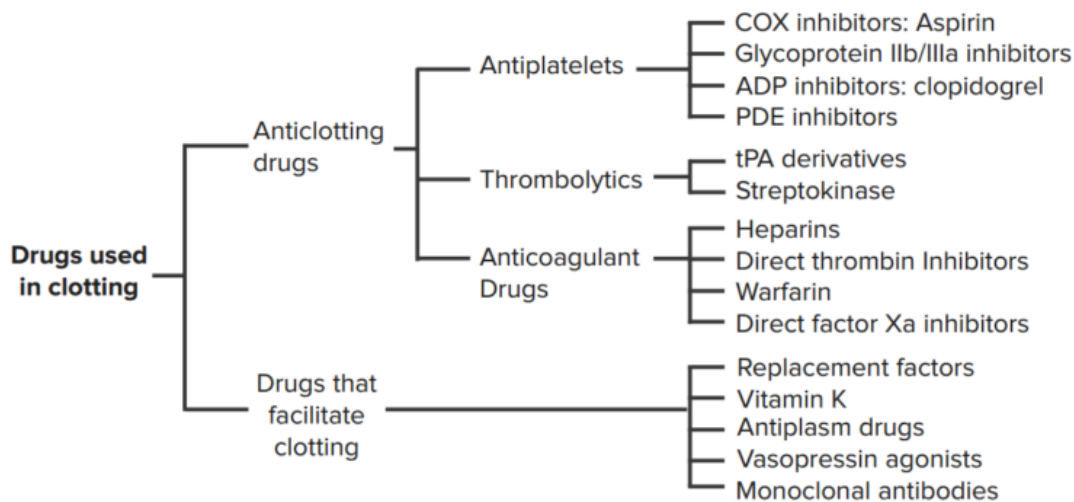
1. **Vitamin K deficiency:** liver disease, in neonates with absent vitamin K-producing intestinal flora, fat malabsorption
2. **Hemophilias:** classic hemophilia or hemophilia A (factor VIII deficiency), Christmas disease, or hemophilia B (factor IX deficiency)
3. **Thrombocytopenia**

Hypercoagulable conditions

As mentioned before, a problematic thrombus may form if coagulation is not regulated. A thrombus may cause more trouble if it lodges in a remote area in the form of an **embolus**. There are 2 known causes of thrombus formation:

1. **Roughened endothelium:** arteriosclerosis, infection, or trauma
2. **Stasis of blood:** immobility, varicosities

Pharmacology: Anticlotting Agents



Antiplatelets

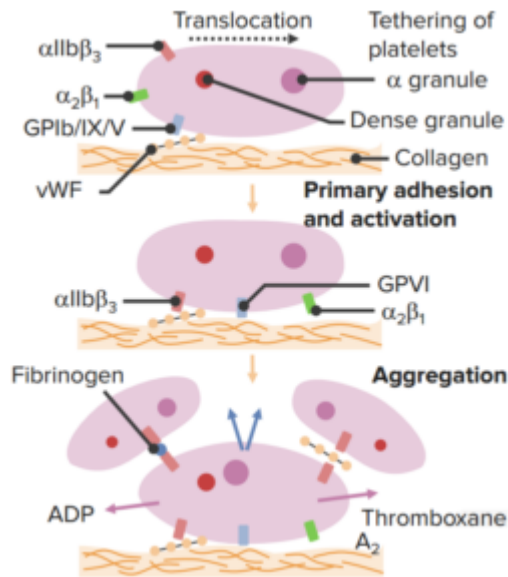


Image: Antiplatelets. By Lecturio

Antiplatelet drugs are targeted to manipulate the substances that are found outside platelets and interact with their membrane receptors, those that are found within platelets but interact with their membrane receptors, and those that are produced and remain inside platelets.

- **Adhesion:** GPIIb/IIIa (called αIIbβ₃ in Europe) allow “adherence” directly to collagen.
- **Aggregation:** GPIIb/IIIa (called αIIbβ₃ in Europe) cross-links to other platelets, as well as binds to VWF.
- **Release:** Thromboxane A₂ and ADP are released when platelets bind to damaged tissue.

Aspirin

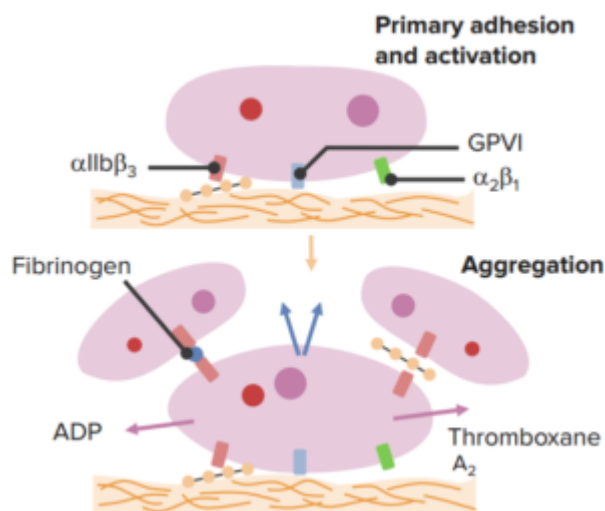


Image: Glycoprotein. By Lecturio

As mentioned, TXA₂ is produced from platelets and is helpful in causing platelet aggregation by changing the structure of platelets. Its inhibition by aspirin is made possible by the irreversible acetylation of **cyclooxygenase**, an enzyme needed by platelets and tissues to produce TXA₂. The effects of aspirin are eliminated once a new

set of platelets is produced in the body. This usually takes 3–7 days. The drug is known to reduce the occurrence of myocardial ischemia, stroke, and peripheral arterial ischemia.

Glycoprotein IIb/IIIa Inhibitors

Abciximab, eptifibatid, and tirofiban are drugs that inhibit the clumping of platelets by acting on the IIb/IIIa receptors on the surface of platelets. This, in turn, inhibits the binding of these receptors to fibrinogen, fibronectin, and VWF, all of which facilitate platelet adhesion and aggregation. The drugs are used to treat acute coronary syndromes and are given to patients after angioplasty to prevent restenosis.

ADP inhibitors

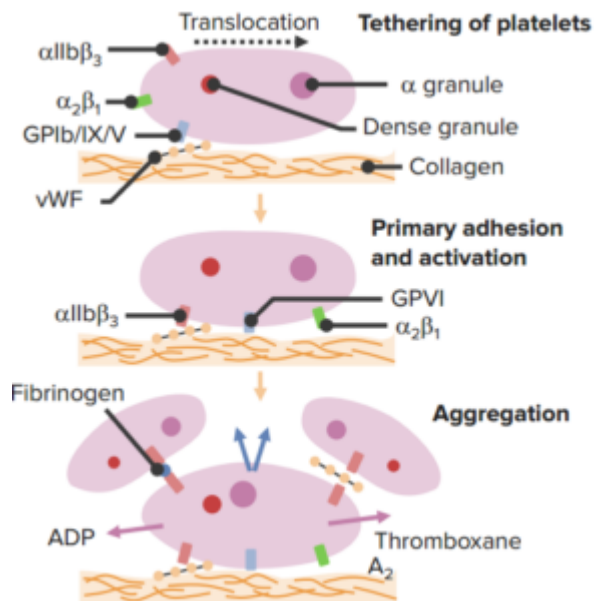


Image: Adp-inhibitors. By Lecturio

Because ADP is needed for platelet aggregation as well, one way to inhibit aggregation is to keep the substance unbound to platelets. **Clopidogrel, prasugrel, and ticlopidine** achieve this by irreversibly binding to ADP receptors on platelets after their conversion in the liver. **Ticagrelor**, a relatively new drug, does not require hepatic conversion in order to be inactive. Unlike the previously mentioned ADP inhibitors, it works by reversibly inactivating the IIb/IIIa receptors. ADP inhibitors are given to prevent transient ischemic attacks, stroke, and restenosis of stents.

Phosphodiesterase/Adenosine Uptake Inhibitors

Cyclic guanosine monophosphate (cGMP) and adenosine are naturally occurring platelet inhibitors. Of course, increased amounts in the bloodstream would result in clotting delays. This is possible in the presence of dipyridamole and cilostazol, which block the action of phosphodiesterase (also known as PDE), an enzyme that metabolizes cGMP, leading to decreased amounts. The drugs also inhibit the uptake of adenosine, keeping them available to platelets. They are given in combination with other drugs as maintenance with heart valve replacement and stroke prevention. Cilostazol, in particular, is given for intermittent claudication.

Antiplatelets: Uses

Aspirin	Reduces subsequent myocardial infarction, stroke, and peripheral arterial ischemia
Eptifibatide, tirofiban	Prevents restenosis after angioplasty; used in acute coronary syndrome
Clopidogrel	Prevents transient ischemic attacks and strokes; reduces restenosis of stents
Dipyridamole	Adjunct to warfarin in patients with heart valve replacement Adjunct to aspirin in patients for secondary prevention of stroke
Cilostazol	Treats intermittent claudication

Antiplatelets: Toxicity

Aspirin	Bleeding (0.3 %)
Ticlopidine	Bleeding (0.5 %), severe neutropenia (1 %), thrombotic thrombocytopenic purpura (rare)
Eptifibatide, tirofiban	Bleeding, thrombocytopenia (chronic use)
Clopidogrel	Bleeding (< 1 %)
Dipyridamole	Bleeding (1–2 %)
Cilostazol	Contraindicated in heart failure

Pharmacology: **Anticoagulants**

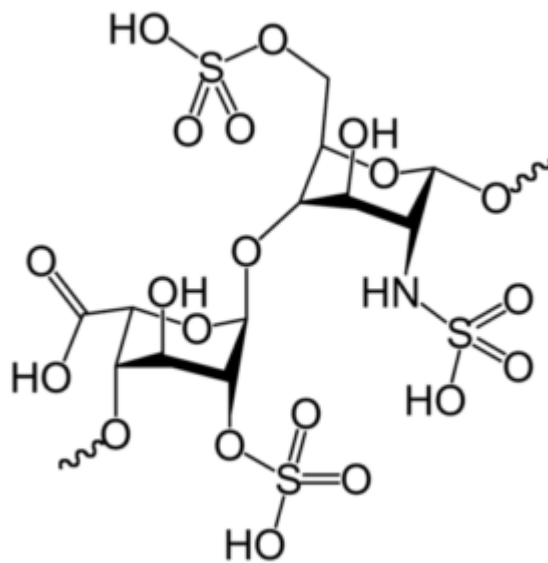


Image: Heparin. By Pngbot, License: Public domain

Heparins

Under normal circumstances, antithrombin, an endogenous anticoagulant, inhibits coagulation by forming complexes with clotting factors IIa, IXa, and Xa. However, in the presence of heparin, this reaction is a thousand-fold faster due to the exposure of more active sites of antithrombin after binding with heparin. Working as a cofactor, heparin is released from the complex unchanged, ready to bind with more antithrombin.

Unfractionated heparins are neutralized by protamine and are known to cause heparin-induced thrombocytopenia and thrombosis (HITT), as well as [osteoporosis](#). For this reason, newer, low-molecular-weight heparins (enoxaparin, dalteparin, and tinzaparin) have been developed.

Direct Thrombin Inhibitors

Bivalirudin, argatroban, and dabigatran bind to active sites of thrombin, thereby inhibiting its action. These drugs are favorable choices for patients who have had HIT.

Warfarin

This and other coumarin derivatives inhibit coagulation by keeping prothrombin and clotting factors VII, IX, and X inactive. They do so by prohibiting vitamin K epoxide reductase and the vitamin K-dependent carboxylation of glutamate residues in said substrates for coagulation. The drugs usually have an 8- to 12-hour delay in onset of action. However, their effects depend on the rate of replacement of the inactive substrates. This may take as long as 60 hours.

Direct Factor Xa Inhibitors

Rivaroxaban, apixaban, and edoxaban act on the point where the extrinsic and intrinsic pathways converge. The drugs are used for stroke prevention in nonvalvular atrial fibrillation, deep vein thrombophlebitis prevention in postoperative hip and knee surgery, and soon for aspirin replacement.

Pharmacology: Thrombolytics

Streptokinase, urokinase, alteplase, reteplase, and tenecteplase lyse thrombi by facilitating the rapid formation of plasmin from plasminogen. The drugs generally have a systemic effect, lysing all thrombi that may come in their way. Because of this mechanism, patients receiving thrombolytics are at high risk for intracranial hemorrhage and bleeding. The use of these drugs requires meticulous evaluation. Before percutaneous coronary interventions were used for [myocardial infarction](#), thrombolytics were the first-line management for cardiac perfusion problems.

Pharmacology: Procoagulants

Vitamin K

Vitamin K is a fat-soluble substance in green leafy vegetables that **assists in the post-ribosomal activation of prothrombin** and factors VII, IX, and X. The vitamin also may be synthesized in the intestines by normal flora available in parenteral and oral forms. Vitamin K is given to reverse the effects of warfarin and to address vitamin K deficiency in certain cases.

Replacement factors

In cases of deficiency in clotting factors, such as hemophilia, the more logical treatment is the use of replacement factors. This may be in the form of plasma-derived factor concentrates that may have been heat- or detergent-treated to prevent transmission of blood-borne diseases, such as hepatitis and [human immunodeficiency virus](#). Recombinant and lyophilized replacement factors also are available. Mixtures of clotting factors and monoclonal antibodies (**idarucizumab**) have been introduced in the latest treatment plans.

Vasopressin agonists

Desmopressin acetate, an antidiuretic hormone analog, can work as a procoagulant by increasing factor VIII activity. It can be used as prophylaxis during minor surgeries or tooth extractions. It also can work in combination with factor replacement for hemophilia A.

Antiplasmin Agents

Aminocaproic acid and **tranexamic acid** exert their antithrombotic effect by keeping the active form of plasminogen, plasmin, from forming. The drugs also increase the formation of VWF and factor VIII. Antiplasmin agents are used as adjuncts to hemophilia therapy, as well as to treat and prevent postoperative bleeding.

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