

# Antiplatelets, Anticoagulants and Fibrinolytic Agents

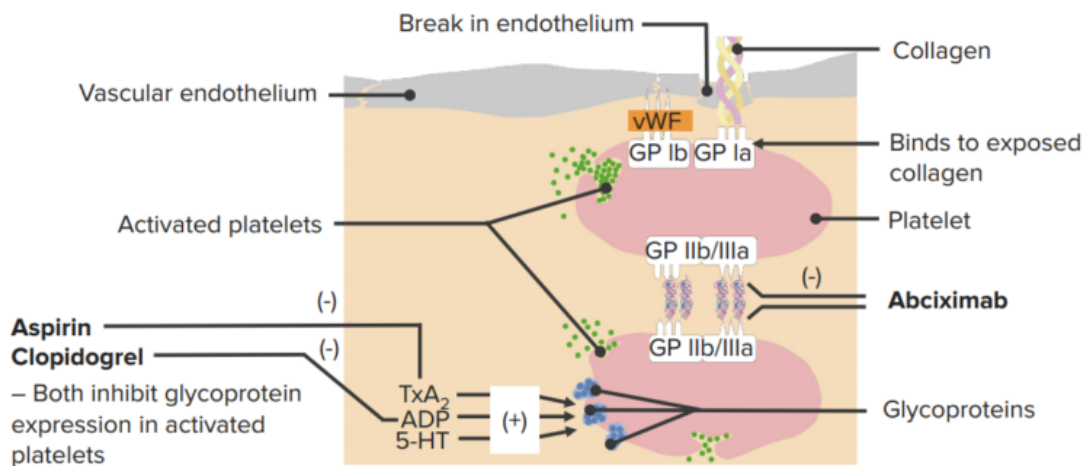
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**In this article, we are going to review the most commonly used antiplatelet, anticoagulant, and fibrinolytic therapies available to the clinician. Understanding the pharmacology of these three common classes of drugs make it possible for the clinician and surgeon to provide excellent hemostasis control.**



## Oral Antiplatelet Agents

As the name implies, these drugs alter the function of the platelets **rendering them incapable of adhering to each other and forming a blood clot.** The most commonly used drugs belonging to this family include aspirin, ticlopidine, clopidogrel, dipyridamole, and cilostazol.



Mechanism of antiplatelet interaction. Image by Lecturio

## Aspirin

The recommended dose of aspirin as an antiplatelet agent is 50 to 325 mg orally daily. Aspirin is known to have rapid absorption, usually within one hour. Unfortunately, the absorption of aspirin is affected by food. Its metabolism takes place in the liver.

The mechanism of action of aspirin involves the irreversible inhibition of cyclo-oxygenase I which is responsible for the production of prostaglandin G<sub>2</sub> and H<sub>2</sub>, and the subsequent production of thromboxane A<sub>2</sub>. Therefore, people taking aspirin are known to have a decreased level of thromboxane A<sub>2</sub>. Aspirin effects cannot be reversed until new platelets are formed, typically 7 to 10 days. Aspirin acts to inhibit aggregation of the platelet. It also possesses the potential to bring the anti-analgesic and antipyretic action.

Aspirin is the **first-line antiplatelet agent for the treatment and prevention of cerebrovascular disease**. Aspirin is also used as an adjunctive antiplatelet agent in endovascular procedures. However, its action is affected by food intake.

Mechanism	Acetylates and irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) to prevent conversion of arachidonic acid to thromboxane A <sub>2</sub> (TxA <sub>2</sub> ); ↑ bleeding time; no effect on PT, PTT
Clinical use	Antipyretic, analgesic, anti-inflammatory, antiplatelet drug
Toxicity	Gastric ulceration, bleeding, hyperventilation, Reye's syndrome, tinnitus (CN VIII)

## Ticlopidine and Clopidogrel

Ticlopidine is superior to aspirin in that its absorption is not affected by food.

It is an antiplatelet drug that works by inhibiting adenosine diphosphate (ADP) receptors that are required for platelet aggregation and plug formation.

Like aspirin, ticlopidine is **metabolized mainly by the liver**. The recommended dose is 250 mg orally twice per day. It can reduce the risk of thrombotic stroke. Ticlopidine is associated with severe neutropenia and thrombotic thrombocytopenic purpura, hence it is rarely used nowadays.

Clopidogrel is a **prodrug** that is converted to an active metabolite by the liver. Clopidogrel absorption is affected by proton pump inhibitors. Moreover, people taking clopidogrel who

have the genetic polymorphism CYP 2C19 are known to have reduced efficacy of the drug. Clopidogrel recommended dose is 75 mg orally, however, it can be titrated up to a maximum dose of 600 mg per day.

The clopidogrel mechanism of action involves the inhibition of adenosine diphosphate-related platelet aggregation. Clopidogrel is used in patients with cerebrovascular ischemic disease and is usually combined with aspirin in patients undergoing endovascular interventions.

Its effects peak in two days and last up to five days in circulation.

Some common side effects include upper respiratory tract infection, pain in the chest, [headache](#), easy bruisability, itching, and heartburns.

Mechanism	Inhibit platelet aggregation by irreversibly blocking ADP receptors; inhibit fibrinogen binding by preventing glycoprotein IIb/IIIa expression
Clinical use	Acute coronary syndrome, coronary stenting, ↓ incidence or recurrence of thrombotic stroke
Toxicity	Neutropenia (ticlopidine)

## Dipyridamole

This antiplatelet agent is also metabolized by the liver. An extended-release formulation is available in the dose of 200 mg that can be given twice per day. The mechanism of action involves the inhibition of phosphodiesterase and adenosine release. It inhibits RBC uptake of adenosine to inhibit the reactivity of the platelet. This results in reduced platelet aggregation.

Dipyridamole is commonly used in the **prevention of stroke**. Prevention of recurrent [stroke](#) can be also achieved with this antiplatelet agent.

Adverse effects of the drug include chest pain, headache, lightheadedness, and diarrhea.

Dipyridamole toxicity can be reversed by the use of aminophylline which reverses its dilating effect on blood vessels.

## Cilostazol

This antiplatelet agent has two favorable side effects in addition to its platelet inhibitory effect. It **reduces triglycerides and increases high-density lipoproteins**. In addition to that, it is known to induce relaxation of the smooth muscle cells of the arteries and arterioles. It causes vasodilation, especially in femoral blood vessels. The recommended dose is 100 mg orally twice per day. Its side effects include headache, diarrhea, and infection. Cilostazol is not approved for the treatment of cerebrovascular disease in the United States.

## Anticoagulants

Anticoagulants are drugs that cause blood coagulation and prevent thrombus formation and expansion. The most commonly used anticoagulants in clinical practice are warfarin and heparin. Novel anticoagulants have emerged in recent years and they are **superior to conventional anticoagulants for two main reasons:**

- More consistent therapeutic effect
- Lower complications rate, hence requiring less aggressive monitoring

# Warfarin

Warfarin's mechanism of action involves the inhibition of vitamin K epoxide reductase, which is an enzyme that is required for the reduction of the oxidized form of vitamin K. Vitamin K is required for the activation of the clotting factors II, VII, IX, and X. Therefore, the reduction of vitamin K availability for these clotting factors would result in anticoagulation. Warfarin induces a decrease in the activity of Protein C that results in some of its side effects.

The initial effects of warfarin start after 24 hours of administration, however, the peak anticoagulant effect is reached 3 to 5 days post-initiation. Warfarin is used in patients at an increased risk of thromboembolism disease or those with deep venous thrombosis.

It is started at a dose of 5 mg OD which is monitored via INR since its main pathway of action is the extrinsic pathway that is assessed by prothrombin time.

The main advantage of the drug over other [anticoagulants](#) is that it is cheap, available in the oral forms and thus it can be taken at home, while heparin is limited to hospital use for its agents act mostly on parenteral routes.

However, heparin is still needed before the effect of warfarin peaks and once INR is therapeutic, heparin is stopped and the patient can continue on warfarin alone.

## Therapeutic Indications

- Very useful for the long durational treatment of deep-vein thrombosis orally
- Effective after [myocardial infarction](#) for 2-6 months
- Useful for atrial fibrillation

## Some rare adverse effects of warfarin include

- Warfarin-induced skin necrosis
- Embryopathies
- Hemorrhage
- Flatulence and diarrhea

**Note:** Warfarin is strictly avoided in pregnancy because of its contradictory effects on bones of infant causing bone defects and hemorrhagic disorders.

## Treatment of warfarin overdose involves

- Administration of vitamin K
- Fresh-frozen plasma
- Activated clotting factors IX and VII

Mechanism	Interferes with normal synthesis and $\gamma$ -carboxylation of vitamin K-dependent clotting factors II, VII, and X and protein C and S; metabolized by the cytochrome P-450 pathway, in laboratory assay, has an effect on the extrinsic pathway and $\uparrow$ PZ. Long half-life
Clinical use	Chronic anticoagulation, not used in pregnant women (because warfarin, unlike heparin, can cross the placenta); follow PT/INR values
Toxicity	Bleeding, teratogenic, skin/tissue necrosis, drug-drug interactions

# Heparins

Heparin is used in the **treatment and prevention of venous thromboembolism** and in certain patients with cerebrovascular disease. Heparin binds to antithrombin III,

enhancing its activity by inhibiting thrombin and factor Xa.

- Intravenous unfractionated heparin that is administered as an infusion of 80 units/kg bolus then 18 units/kg/hr. continuous infusion.
- Subcutaneous unfractionated heparin that is administered at a dose of 333 units/kg loading dose and a maintenance dose of 250 units/kg every 12 hr.
- Low molecular weight heparin such as enoxaparin (clexane) that is administered at a dose of 1 mg/kg BD or 1.5 mg/kg OD. Other low molecular weight heparins include Dalteparin, nadroparin, tinzaparin. Their effects are rare but difficult to reverse once they have occurred.

If heparin is given, constant monitoring with dosage adjustment is required by using the activated partial thromboplastin time which signifies the adequacy of the intrinsic pathway where heparin works. The target aPTT is 2 times the upper limit of normal/baseline.

Mechanism of action of heparin involves inactivation of factor Xa and inhibition of conversion of prothrombin into thrombin in low doses and inactivation of factors IX, X, XI, and XII, thrombin and in inhibition of the conversion of fibrinogen into fibrin. It also stops the activation of factor VIII.

Common side effects of heparin that should be monitored include

- Heparin-induced thrombocytopenia (HIT)
- Intracerebral hemorrhage
- Immune hypersensitivity reaction
- [Anaphylaxis](#)
- Osteoporosis in case of long-term, high-dose use > 6 months

If bleeding occurs after the administration of heparin, IV protamine sulfate is used to reverse the anticoagulant effects of heparin.

Mechanism	Cofactor for activation of antithrombin, ↓ thrombin, and Xa; short half-life
Clinical use	Immediate anticoagulation for pulmonary embolism, stroke, acute coronary syndrome, MI, DVT; used during pregnancy (does not cross the placenta); follow PTT
Toxicity	Bleeding thrombocytopenia (HIT), osteoporosis, drug-drug interactions; for rapid reversal of heparinization, use protamine sulfate (a positively charged molecule that acts by binding negatively charged heparin)
Notes	Newer lower-molecular-weight heparins (e.g., enoxaparin) act more on Xa, have better bioavailability and 2—4 times longer half-life; can be ministered subcutaneously and without laboratory monitoring; not easily reversible Heparin-induced thrombocytopenia (HIT)—heparin binds to platelets, causing autoantibody production that destroys platelets and over activates the remaining ones, resulting in a thrombocytopenic, hypercoagulable state.

## Heparin vs. Warfarin

	<b>Heparin</b>	<b>Warfarin</b>
<b>Structure</b>	Large anionic, acidic polymer	Small lipid-soluble molecule
<b>Route of administration</b>	Parenteral (IV, SC)	Oral
<b>Site of action</b>	Blood	Liver

<b>Onset of action</b>	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors
<b>Mechanism of action</b>	Activates antithrombin, which ↓ the action of IIA (thrombin) and Xa	Impairs the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X (vitamin K antagonist)
<b>Duration of action</b>	Acute (hours)	Chronic (days)
<b>Inhibits coagulation in vitro</b>	Yes	No
<b>Treatment of acute overdose</b>	Protamine sulfate	IV vitamin K and fresh frozen plasma
<b>Monitoring</b>	PTT (intrinsic pathway)	PT/INR (extrinsic pathways)
<b>Crosses placenta</b>	No	Yes (teratogenic)

## Fibrinolytic Agents

Fibrinolytic drugs are the thrombolytic drugs that can stimulate the dissolution of the blood clot. These agents are the **mainstay treatments for acute stroke**. They are also commonly used in neurointerventional procedures. The intravenous administration of alteplase is the current golden standard of care for acute ischemic stroke.

### Streptokinase

Streptokinase is not commonly used in the treatment of acute ischemic stroke given the high risk of intracranial hemorrhage. Streptokinase might be used in some **patients with acute coronary artery syndrome**.

### Recombinant tissue plasminogen activators

Recombinant tissue plasminogen activators (rtPAs) include:

- Alteplase
- Reteplase
- Tenecteplase
- Desmoteplase

They are responsible for the conversion of the proenzyme plasminogen into plasmin. It is indulged in the breakdown of blood clots. Alteplase is used in the treatment of acute ischemic stroke and is currently the only FDA approved agent for the **acute treatment of ischemic stroke**.

Lower doses of alteplase are used intra-arterially for thrombolysis in the endovascular treatment of acute stroke. The other rtPAs are still not approved for the treatment of acute ischemic stroke. They have a relatively long half-life and are known to be less neurotoxic than alteplase.

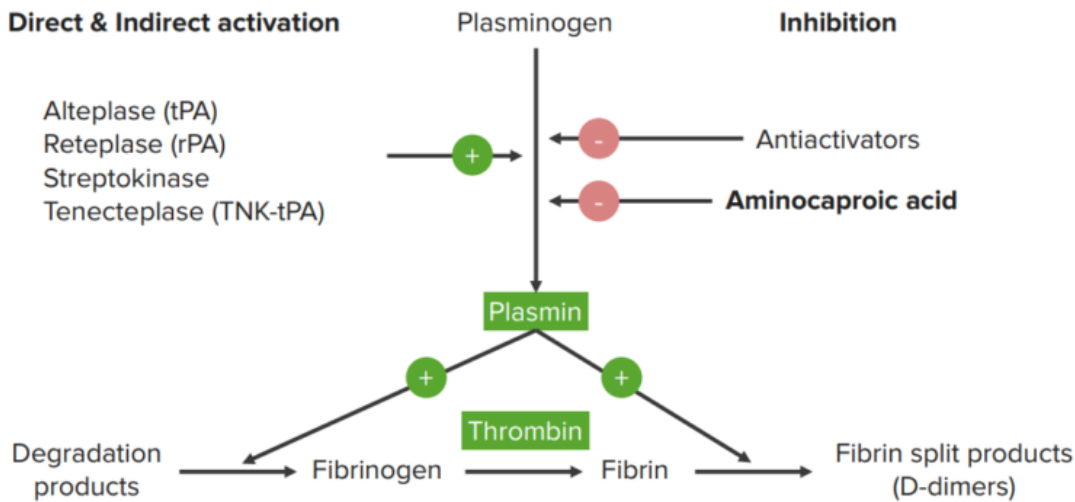


Image by Lecturio

**Hemorrhage is a possible side effect** in patients receiving tPAs. Intracranial hemorrhage was reported in up to 6.4% of the patients receiving tPA for the treatment of acute ischemic stroke. It may cause 1 in 6 patients, it may result in death and long-term disability.

Immune **hypersensitivity reactions** are also possible and occur in up to 0.02 % of the cases. Angioedema is very rare; however, it has been previously reported in some patients receiving alteplase. Currently, there are no potent antidote treatments against the fibrinolytic effects of rTPAs.

**Therefore, keystones in preventing complications are:**

- Careful patient's selection
- Examination of possible contraindications
- Meticulous dosing

## References

American Academy of Neurology:

[http://n.neurology.org/content/79/13\\_Supplement\\_1/S68](http://n.neurology.org/content/79/13_Supplement_1/S68)

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