

Anticoagulants, Antiplatelet and antihyperlipidemic Drugs

Blood must remain fluid within the vasculature and yet clot quickly when exposed to subendothelial surfaces at sites of vascular injury. Under normal circumstances, a delicate balance between coagulation and fibrinolysis prevents both thrombosis and haemorrhage. Alteration of this balance in favour of coagulation results in thrombosis. Thrombi, composed of platelet aggregates, fibrin, and trapped red blood cells, can form in arteries or veins. Antithrombotic drugs used to treat thrombosis include antiplatelet drugs, which inhibit platelet activation or aggregation; anticoagulants, which attenuate fibrin formation; and fibrinolytic agents, which degrade fibrin. All antithrombotic drugs increase the risk of bleeding.

THROMBUS VERSUS EMBOLUS

A clot that adheres to a vessel wall is called a "thrombus," whereas an intravascular clot that floats in the blood is termed an "embolus." 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. Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by atherosclerosis. Arterial thrombosis usually consists of a platelet-rich clot. In contrast, venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.

PLATELET RESPONSE TO VASCULAR INJURY

Physical trauma to the vascular system, such as a puncture or a cut, initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade. These interactions lead to haemostasis or the cessation of blood loss from a damaged blood vessel. Platelets are central in this process. Initially, there is vasospasm of the damaged blood vessel to prevent further blood loss. The next step involves the formation of a platelet–fibrin plug at the site of the puncture. The creation of an unwanted thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system, rather than external physical trauma.

Chemical mediators synthesized by endothelial cells:

Chemical mediators, such as prostacyclin and nitric oxide, are synthesised by intact endothelial cells and act as inhibitors of platelet aggregation. Damaged endothelial cells synthesise less prostacyclin than healthy cells, resulting in lower prostacyclin levels. Since there is less this will lead to platelet aggregation.

Roles of thrombin, thromboxanes, and collagen: The platelet membrane also contains receptors that can bind thrombin, thromboxanes, and exposed collagen. In the intact, normal vessel, circulating levels of thrombin and thromboxane are low, and the intact endothelium covers the collagen in the subendothelial layers. The corresponding platelet receptors are, thus, unoccupied, and as a result, platelet activation and aggregation are not initiated. However, when occupied, each of these receptor types triggers a series of reactions leading to the release into the circulation

of intracellular granules by the platelets. This ultimately stimulates platelet aggregation.

Platelet adhesion

When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the subendothelium. This triggers a complex series of chemical reactions, resulting in platelet activation.

Platelet activation

Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue. This causes the release of platelet granules containing chemical mediators, such as adenosine diphosphate (ADP), thromboxane A₂, platelet activation factor, and thrombin. These signalling molecules bind to receptors in the outer membrane of resting platelets circulating nearby, which ultimately resulted in elevating the levels of calcium and a decreased concentration of cAMP (cyclic adenosine monophosphate) within the platelet that lead to enhance the platelet aggregation.

Platelet aggregation

The increase in cytosolic calcium accompanying activation is due to a release of sequestered stores within the platelet. This leads to 1) the release of platelet granules containing mediators, such as ADP and serotonin that activate other platelets; 2) activation of thromboxane A₂ synthesis; and 3) activation of glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen and, ultimately, regulate platelet-platelet interaction and thrombus formation. Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation. This leads to an avalanche of platelet aggregation, because each activated platelet can recruit other platelets.

Formation of a clot

Local stimulation of the coagulation cascade by tissue factors released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (factor IIa). In turn, thrombin, a serine protease, catalyses the hydrolysis of fibrinogen to fibrin, which is incorporated into the clot. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a haemostatic platelet-fibrin plug.

Fibrinolysis

During clot formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators in the tissue. Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal.

PLATELET AGGREGATION INHIBITORS

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation. The platelet aggregation inhibitors inhibit cyclooxygenase-1 (COX-1) or block GP IIb/IIIa or ADP receptors, thereby interfering with the signals that promote platelet aggregation.

Aspirin

Mechanism of action: Aspirin irreversibly inhibits thromboxane A₂ synthesis by acetylation of a serine residue on the active site of COX-1, thereby irreversibly inactivating the enzyme. This shifts the balance of chemical mediators to favour the antiaggregatory effects of prostacyclin, thereby preventing platelet aggregation.

The inhibitory effect is rapid, and aspirin-induced suppression of thromboxane A₂ and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days. Repeated administration of aspirin has a cumulative effect on the function of platelets.

Therapeutic use:

- Used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI.
- Complete inactivation of platelets occurs with 75 mg of aspirin given daily. The recommended dose of aspirin ranges from 50 to 325 mg daily.
- The half-life of aspirin ranges from 15 to 20 minutes and for salicylic acid (its metabolite) is 3 to 12 hours.

Adverse effects:

- Bleeding time is prolonged by aspirin treatment, causing complications that include an increased incidence of haemorrhagic stroke and gastrointestinal (GI) bleeding, especially at higher doses of the drug.
- Nonsteroidal anti-inflammatory drugs, such as ibuprofen, inhibit COX-1 by transiently competing at the catalytic site. Ibuprofen, if taken within the 2 hours prior to aspirin, can obstruct the access of aspirin to the serine residue and, thereby, antagonise platelet inhibition by aspirin. Therefore, immediate release aspirin should be taken at least 60 minutes before or at least 8 hours after ibuprofen.
- Although celecoxib (a selective COX-2 inhibitor) does not interfere with the antiaggregating activity of aspirin, there is some evidence that it may contribute to cardiovascular events by shifting the balance of chemical mediators in favour of thromboxane A₂.

Ticlopidine, clopidogrel, prasugrel, and ticagrelor

Ticlopidine, clopidogrel, prasugrel, and ticagrelor are P₂Y₁₂ ADP receptor inhibitors that also block platelet aggregation but by a mechanism different from that of aspirin.

Mechanism of action: These drugs inhibit the binding of ADP to its receptors on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other. Ticagrelor binds to the P₂Y₁₂ ADP receptor in a reversible manner. The other agents bind irreversibly. The maximum inhibition of platelet aggregation is achieved in 1 to 3 hours with ticagrelor, 2 to 4 hours with prasugrel, 3 to 4 days with ticlopidine, and 3 to 5 days with clopidogrel. When treatment is suspended, the platelet system requires time to recover.

Therapeutic use:

- Clopidogrel is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and in those with established peripheral arterial disease. It is also approved for prophylaxis of thrombotic events in acute coronary syndromes (unstable angina or non-ST-elevation MI).
- Additionally, clopidogrel is used to prevent thrombotic events associated with percutaneous coronary intervention (PCI) with or without coronary stenting.
- Ticlopidine is similar in structure to clopidogrel. It is indicated for the prevention of transient ischemic attacks (TIA) and strokes in patients with a prior cerebral thrombotic event. However, due to life-threatening hematologic adverse reactions, ticlopidine is generally reserved for patients who are intolerant to other therapies.
- Prasugrel is approved to decrease thrombotic cardiovascular events in patients with acute coronary syndromes (like unstable angina, non-ST-elevation MI, and ST-elevation MI managed with PCI).
- Ticagrelor is approved for the prevention of arterial thromboembolism in patients with unstable angina and acute MI, including those undergoing PCI.

Adverse effects:

- These agents can cause prolonged bleeding for which there is no antidote.
- Ticlopidine is associated with severe hematologic reactions that limit its use, such as aplastic anaemia.
- Clopidogrel causes fewer adverse reactions, and the incidence of neutropenia is lower.
- Prasugrel is contraindicated in patients with history of TIA or stroke. Prasugrel and ticagrelor carry black box warnings for bleeding.

BLOOD COAGULATION

The coagulation process that generates thrombin consists of two interrelated pathways, the extrinsic and the intrinsic systems. The extrinsic system is initiated by the activation of clotting factor VII by tissue factor (also known as thromboplastin). Tissue factor is a membrane protein that is normally separated from the blood by the endothelial cells that line the vasculature. However, in response to vascular injury, tissue factor becomes exposed to blood. There it can bind and activate factor VII, initiating the extrinsic pathway. The intrinsic system is triggered by the activation of clotting factor XII (Figure 1). This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.

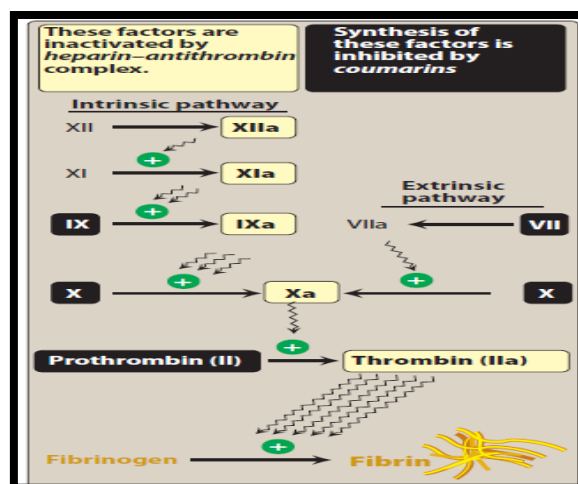


Figure 1: Formation of a fibrin clot.

Inhibitors of coagulation

It is important that coagulation is restricted to the local site of vascular injury. Endogenously, there are several inhibitors of coagulation factors, including protein C, protein S, antithrombin III, and tissue factor pathway inhibitor. The mechanism of action of several anticoagulant agents, including heparin and heparin-related products, involves activation of these endogenous inhibitors (primarily antithrombin III).

ANTICOAGULANTS

The anticoagulant drugs inhibit either the action of the coagulation factors (for example, heparin) or interfere with the synthesis of the coagulation factors (for example, vitamin K antagonists such as warfarin).

Heparin

Heparin is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi. Heparin occurs naturally as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown. It is extracted for commercial use from porcine intestinal mucosa.

Mechanism of action: Heparin acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors. Antithrombin III is an α globulin that inhibits serine proteases of thrombin (factor IIa) and factor Xa (Figure 1). In the absence of heparin, antithrombin III interacts very slowly with thrombin and factor Xa. When heparin molecules bind to antithrombin III, a conformational change occurs that catalyses the inhibition of thrombin about 1000-fold (Figure 2). A unique pentasaccharide sequence contained in heparin and permits their binding to antithrombin III.

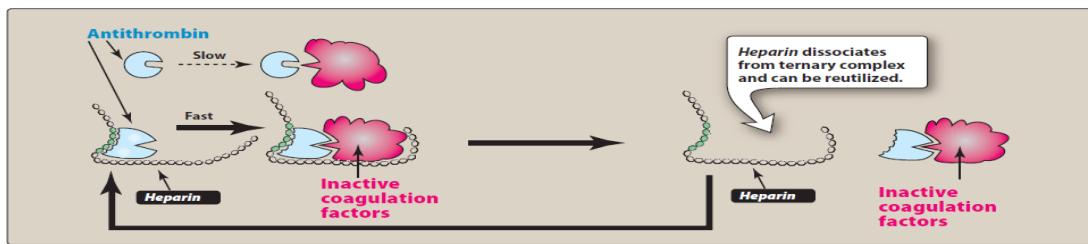


Figure 2: Heparin accelerates inactivation of coagulation factors by antithrombin.

Therapeutic use:

- Heparin limits the expansion of thrombi by preventing fibrin formation. These agents are used for the treatment of acute venous thromboembolism (DVT or PE).
- Heparin is also used for prophylaxis of postoperative venous thrombosis in patients undergoing surgery (for example, hip replacement) and those with acute MI. These drugs are the anticoagulants of choice for treating pregnant women, because they do not cross the placenta, due to their large size and negative charge.

Pharmacokinetics:

- Heparin must be administered subcutaneously or intravenously, because the drug does not readily cross membranes.
- Heparin is often initiated as an intravenous bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of heparin, titrating the dose so that the activated partial thromboplastin time (aPTT) is 1.5- to 2.5-fold that of the normal control. [Note: The aPTT is the standard test used to monitor the extent of anticoagulation with heparin.]
- The anticoagulant effect with heparin occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection). In the blood, heparin binds to many proteins that neutralise its activity, causing unpredictable pharmacokinetics.
- Heparin binding to plasma proteins is variable in patients with thromboembolic diseases.

Adverse effects:

- The chief complication of heparin therapy is bleeding. Careful monitoring of the patient and laboratory parameters is required to minimise bleeding.
- Excessive bleeding may be managed by discontinuing the drug or by treating with protamine sulfate. When infused slowly, the latter combines ionically with heparin to form a stable, 1:1 inactive complex. It is very important that the dosage of protamine sulfate is carefully titrated (1 mg for every 100 units of heparin administered), because protamine sulfate is a weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential.
- Heparin preparations are obtained from porcine sources and, therefore, may be antigenic. Possible adverse reactions include chills, fever, urticaria, and anaphylactic shock.

- Heparin-induced thrombocytopenia (HIT) is a serious condition, in which circulating blood contains an abnormally low number of platelets.
- Heparin therapy should be discontinued when patients develop HIT or show severe thrombocytopenia.
- In cases of HIT, heparin can be replaced by another anticoagulant, such as argatroban.
- In addition, osteoporosis has been observed in patients on long-term heparin therapy.
- Heparin is contraindicated in patients who have hypersensitivity to heparin, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.

Warfarin

- The coumarin anticoagulants owe their action to the ability to antagonise the cofactor functions of vitamin K.
- The only therapeutically relevant coumarin anticoagulant is warfarin. Initially used as a rodenticide, warfarin is now widely used clinically as an oral anticoagulant.
- The INR is the standard by which the anticoagulant activity of warfarin therapy is monitored.
- The goal of warfarin therapy is an INR (international normalized ratio) 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. Therefore, it is important that the INR is maintained within the optimal range as much as possible, and frequent monitoring may be required.

Mechanism of action:

- Vitamin K is an important cofactor in producing the clotting factors (which are II, VII, IX, and X) (Figure 1) that are required in formation blood clot.
- Vitamin K is usually produced by the liver using vitamin K epoxide reductase, the enzyme that is inhibited by warfarin.
- Unlike heparin, the anticoagulant effects of warfarin are not observed immediately after drug administration. Instead, peak effects may be delayed for 72 to 96 hours, which is the time required to deplete the pool of circulating clotting factors.
- The anticoagulant effects of warfarin can be overcome by the administration of vitamin K.
- However, reversal following administration of vitamin K takes approximately 24 hours (the time necessary for degradation of already synthesised clotting factors).

Therapeutic use: Warfarin is used in the prevention and treatment of DVT and PE, stroke prevention, stroke prevention in the setting of atrial fibrillation and/or

prosthetic heart valves. It is also used for prevention of venous thromboembolism during orthopedic or gynecologic surgery.

Pharmacokinetics

- Warfarin is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation).
- Warfarin is highly bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk. However, drugs that have a greater affinity for the albumin-binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity.
- The mean half-life of warfarin is approximately 40 hours, but this value is highly variable among individuals.
- Warfarin has numerous drug interactions that may potentiate or attenuate its anticoagulant effect. For example: the **metronidazole can inhibit the metabolism of warfarin, while the barbiturates can potentiate it.**

Adverse effects:

- The principal adverse effect of warfarin is haemorrhage. So, it has a black box warning for bleeding risk. Therefore, it is important to frequently monitor the INR and adjust the dose of warfarin.
- Minor bleeding may be treated by withdrawal of the drug or administration of oral vitamin K1, but severe bleeding may require greater doses of vitamin K given intravenously. Whole blood, frozen plasma, and plasma concentrates of blood factors may also be used for rapid reversal of warfarin.
- Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with warfarin therapy.
- Warfarin is teratogenic and should never be used during pregnancy. If anticoagulant therapy is needed during pregnancy, heparin may be administered.

THROMBOLYTIC DRUGS

- Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin that support the fibrin hydrolysis and, thus, dissolves clots (Figure 3).
- Streptokinase, one of the first such agents to be approved, causes a systemic fibrinolytic state that can lead to bleeding problems.
- Alteplase acts more locally on the thrombotic fibrin to produce fibrinolysis. Urokinase is produced naturally in human kidneys and directly converts plasminogen into active plasmin.
- Fibrinolytic drugs may lyse both normal and pathologic thrombi.

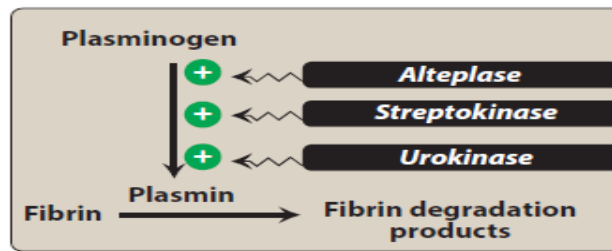


Figure 3: Activation of plasminogen by thrombolytic drugs.

Therapeutic use:

- Originally used for the treatment of DVT and serious PE, thrombolytic drugs are now being used less frequently for these conditions.
- Thrombolytic agents are usually administered intravenously.
- They are also used to dissolve clots that result in strokes.

Adverse effects:

- The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial haemostatic plug. Thus, haemorrhage is a major side effect.
- These drugs are contraindicated in pregnancy.

DRUGS USED TO TREAT BLEEDING

The use of anticoagulants may give rise to haemorrhage. Certain natural proteins and vitamin K, as well as synthetic antagonists, are effective in controlling this bleeding. Concentrated preparations of coagulation factors are available from human donors. However, these preparations carry the risk of transferring viral infections. Blood transfusion is also an option for treating severe haemorrhage.

Protamine sulfate

- Antagonises the anticoagulant effects of heparin.
- The positively charged protamine interacts with the negatively charged heparin forming a stable complex without anticoagulant activity.
- Adverse effects of drug administration include hypersensitivity as well as dyspnoea, flushing, bradycardia, and hypotension when rapidly injected.

Vitamin K

- Vitamin K1 (phytonadione) administration can stop bleeding problems due to warfarin by increasing the supply of active vitamin K1, thereby inhibiting the effect of warfarin.
- Vitamin K1 may be administered via the oral, subcutaneous, or intravenous route. [Note: Intravenous vitamin K should be administered by slow IV infusion to minimise the risk of hypersensitivity or anaphylactoid reactions.]
- For the treatment of bleeding, the subcutaneous route of vitamin K1 is not preferred, as it is not as effective as oral or IV administration. The response to vitamin K1 is slow, requiring about 24 hours to reduce INR (time to synthesise new coagulation factors). Thus, if immediate haemostasis is required, fresh frozen plasma should be infused.
- The Skin reaction and Anaphylaxis are the major side effects of vitamin K1.

Antihyperlipidemic Drugs

- **Hyperlipidaemia** is an increase (hyper) in the **lipids**, which are a group of fats or fatlike substances in the blood. **Cholesterol** and the **triglycerides** are the two lipids in the blood. Elevation of one or both of these lipids is seen in hyperlipidaemia.
- Serum cholesterol levels above 240 mg/dL and triglyceride levels above 150 mg/dL are associated with atherosclerosis.
- **Atherosclerosis** is a disorder in which lipid deposits accumulate on the lining of the blood vessels, eventually producing degenerative changes and obstruction of blood flow.
- Atherosclerosis is considered to be a major contributor in the development of heart disease.
- Triglycerides and cholesterol are insoluble in water and must be bound to a lipid-containing protein (**lipoprotein**) for transportation throughout the body.
- Although several lipoproteins are found in the blood, we will focus on the low-density lipoproteins (LDL), the high-density lipoproteins (HDL), and cholesterol.
 - **Low-density lipoproteins** (LDL) transport cholesterol to the peripheral cells. When the cells have all of the cholesterol they need, the excess cholesterol is discarded into the blood. This can result in an excess of cholesterol, which can penetrate the walls of the arteries, resulting in atherosclerotic plaque formation. Elevation of the LDL increases the risk for heart disease.
 - **High-density lipoproteins** (HDL) take cholesterol from the peripheral cells and bring it to the liver, where it is metabolised and excreted. The higher the HDL, the lower the risk for development of atherosclerosis. Therefore, it is desirable to see an increase in the HDL (the “good” lipoprotein) because of the protective nature of its properties against the development of atherosclerosis and a decrease in the LDL.

Hyperlipidaemia can be diagnosed by lipoprotein profile, which is a laboratory tests used to measure the blood lipid and can provide valuable information on the important cholesterol levels, such as:

- 1- Total cholesterol
- 2- LDL (the harmful lipoprotein)
- 3- HDL (the protective lipoprotein)
- 4- Triglycerides

Risk factors:

- 1- Elevated serum cholesterol and LDL levels
- 2- Family history of early heart disease (father before the age of 55 years and mother before the age of 55 years)
- 3- Cigarette smoking
- 4- High blood pressure

- 5- Age (men older than 45 years and women older than 55 years)
- 6- Low HDL levels
- 7- Obesity
- 8- Diabetes

Drugs for Hyperlipidemia

- 1- HMG-CoA reductase inhibitors
- 2- Bile acid sequestrants
- 3- Fibric acid derivatives
- 4- Niacin
- 5- Cholesterol absorption inhibitor.

- The target LDL level for treatment is less than 130 mg/dL. If the response to drug treatment is adequate, lipid levels are monitored every 4 months. If the response is inadequate, another drug or a combination of two drugs is used.
- Antihyperlipidemic drugs decrease cholesterol and triglyceride levels in several ways.
- Although the end result is a lower lipid blood level, each has a slightly different action.

HMG CoA reductase inhibitors

HMG-CoA (3- hydroxy-3-methylglutaryl coenzyme A) reductase is an enzyme that is a **catalyst** (a substance that accelerates a chemical reaction without itself undergoing a change) in the manufacture of cholesterol. These drugs appear to have one of two activities, namely, inhibiting the manufacture of cholesterol or promoting the breakdown of cholesterol. This drug activity lowers the blood levels of cholesterol and serum triglycerides and increases blood levels of HDLs. Examples of these drugs are Fluvastatin (Lescol), lovastatin (Mevacor), and simvastatin (Zocor). They are first line treatment for patients with elevated risk of ASCVD (atherosclerotic cardiovascular diseases) to reduce the occurrence of ASCVD events.

Therapeutic uses:

These drugs, along with a diet restricted in saturated fat and cholesterol, are used to treat hyperlipidaemia when diet and other nonpharmacologic treatments alone have not resulted in lowered cholesterol levels.

Adverse effects

- Elevated liver enzymes may occur with statin therapy. Therefore, liver function should be evaluated prior to starting therapy or if a patient has symptoms consistent with liver dysfunction as hepatic insufficiency can cause drug accumulation.
- Myopathy and rhabdomyolysis (disintegration of skeletal muscle; rare) have been reported.
- The HMG CoA reductase inhibitors may also increase the effect of warfarin. Thus, it is important to evaluate the international normalised ratio (INR) when initiating a statin or changing the dosage.
- These drugs are contraindicated during pregnancy, lactation, and active liver disease.

Bile Acid Sequestrants

Cholestyramine (Questran) and colestipol (Colestid) are examples of bile acid sequestrants. Bile, which is manufactured and secreted by the liver and stored in the gallbladder, emulsifies fat and lipids as these products pass through the intestine. Once emulsified, fats and lipids are readily absorbed in the intestine. These drugs

bind to bile acids to form an insoluble substance that cannot be absorbed by the intestine, so it is secreted in the feces. With increased loss of bile acids, the liver uses cholesterol to manufacture more bile. This is followed by a decrease in cholesterol levels.

Therapeutic uses

The bile acid sequestrants are used as adjunctive therapy for the reduction of elevated serum cholesterol in patients with hypercholesterolemia who do not have an adequate response to a diet and exercise program.

Adverse effects

- 1- A common side effects is constipation. Constipation may be severe and may occasionally result in faecal impaction. Haemorrhoids may be aggravated.
- 2- Additional adverse reactions include vitamin A and D deficiencies,
- 3- bleeding tendencies (including gastrointestinal bleeding) caused by a depletion of vitamin K (why), nausea, abdominal pain, and distention.

Fibric Acid Derivatives

Fibric acid derivatives work in a variety of ways.

- 1- Clofibrate (Atromid-S), acts to stimulate the liver to increase breakdown of very-low-density lipoproteins (VLDL) to low density lipoproteins (LDL), decreasing liver synthesis of VLDL and inhibiting cholesterol formation.
- 2- Fenofibrate (Tricor) acts by reducing VLDL and stimulating the catabolism of triglyceride-rich lipoproteins, resulting in a decrease in plasma triglyceride and cholesterol.
- 3- Gemfibrozil (Lopid) increases the excretion of cholesterol in the feces and reduces the production of triglycerides by the liver, thus lowering serum lipid levels.

Therapeutic uses:

- 1- Clofibrate and gemfibrozil are used to treat individuals with very high serum triglyceride levels who present a risk of abdominal pain and pancreatitis and who do not experience a response to diet modifications. Clofibrate is not used for the treatment of other types of hyperlipidaemia and is not thought to be effective for prevention of coronary heart disease.
- 2- Fenofibrate (Tricor) is used as adjunctive treatment for the reduction of LDL, total cholesterol, and triglycerides in patients with hyperlipidaemia.

Adverse effects

- Include nausea, vomiting, gastrointestinal upset, and diarrhea.
- Clofibrate, fenofibrate, and gemfibrozil may increase cholesterol excretion into the bile, leading to cholelithiasis (stones in the gallbladder) or cholecystitis (inflammation of the gallbladder). If cholelithiasis is found, use of the drug is discontinued.
- Fenofibrate may also result in abnormal liver function tests, respiratory problems, back pain, and headache.
- Gemfibrozil may cause dyspepsia, skin rash, vertigo, and headache.

Niacin (nicotinic acid)

Niacin reduces LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 g/day. Niacin can be used in combination with statins, and fixed-dose combinations of long-acting niacin with lovastatin and simvastatin are available.

Note: the addition of niacin to statin therapy has not been shown to reduce the risk of ASCVD events.

Mechanism of action

At gram doses, niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids. The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis. Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.

Adverse effects

- The most common adverse effects of niacin are an intense cutaneous flush accompanied by an uncomfortable feeling of warmth and pruritus. Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin-mediated.
- Some patients also experience nausea and abdominal pain. Slow titration of the dosage or use of the sustained-release formulation of niacin reduces bothersome initial adverse effects.
- Niacin inhibits tubular secretion of uric acid and, thus, predisposes patients to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported.

Cholesterol absorption inhibitor

- Ezetimibe selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
- Ezetimibe lowers LDL-C by approximately 18% to 23%. Due its modest LDL-C lowering, ezetimibe is often used as an adjunct to maximally tolerated statin therapy in patients with high ASCVD risk, or in statin-intolerant patients.
- Adverse effects are uncommon with the use of ezetimibe.

A summary of some actions of the antihyperlipidemic drugs is demonstrated in table 1.

Table 1: Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase Inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption Inhibitor	↓	↑	↓