Statins Pharmacology

What are statins?

Statins are a class of drugs used in the treatment of hyperlipidemias or high blood cholesterol levels, They are cholesterol biosynthesis inhibitors.

Drugs that inhibit cholesterol biosynthesis are quite effective at lowering LDL cholesterol and total cholesterol.

Statins have revolutionized the management of hypercholesterolemia.

They have become essential in the management of patients with, or who are at risk of cardiovascular disease including coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD).

Indications of statins

Statins are indicated in both primary and secondary prevention of cardiovascular disease for many conditions.

Statins were primarily created to treat hypercholesterolemia, which is an independent risk factor for cardiovascular disease.

They are effective in reducing cholesterol levels in familial and nonfamilial hypercholesterolemias.

Statins can reduce LDL cholesterol levels dramatically, especially when used in combination with other cholesterol-lowering drugs.

These drugs are used commonly because they are effective and well tolerated.

Recent clinical trials have established that statins interfere with osteoclast-mediated bone resorption and may reduce osteoporosis.

These drugs may also interfere with the intracellular localization of certain oncogenes and thereby reduce the incidence of some cancers.

They also have weak anti-inflammatory activity.

They reduce the risk of coronary events and mortality in patients with ischemic heart disease, and they also reduce the risk of ischemic stroke.

Rosuvastatin, atorvastatin, and simvastatin have greater maximal efficacy than the other HMGCoA reductase inhibitors.

Fluvastatin has less maximal efficacy than the other drugs in this group.

Examples of statins

These drugs include

1. Lovastatin (mevinolin) (Mevacor),
2. Simvastatin (Zocor),
3. Pravastatin
4. (Pravachol), and
5. Fluvastatin (Lescol),
6. Atorvastatin (Lipitor), and
7. Rosuvastatin (Crestor).

Lovastatin and simvastatin are **prodrugs**, whereas the other HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, pravastatin, and rosuvastatin) are active as given.

Mechanism of action of statins

Statins work by competitively inhibiting 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis.

In turn, reduced cholesterol synthesis results in a compensatory increase in the hepatic uptake of plasma cholesterol mediated by an increase in the number of LDL receptors.

These drugs also reduce total cholesterol by as much as 30%–50%; LDL cholesterol can be reduced by as much as 60% (rosuvastatin).

The rate-limiting step in hepatic cholesterol synthesis is the conversion of hydroxymethyl glutaryl coenzyme A (HMG-CoA) to mevalonate by HMG-CoA reductase. The statins are structural analogs of HMG-CoA that competitively inhibit the enzyme

Although the inhibition of hepatic cholesterol synthesis contributes a small amount to the total serum cholesterol-lowering effect of these drugs, a much greater effect derives from the response to a reduction in a tightly regulated hepatic pool of cholesterol.

The liver compensates by increasing the number of high-affinity LDL receptors, which clear LDL and VLDL remnants from the blood. HMG-CoA reductase inhibitors also have direct anti-atherosclerotic effects and have been shown to prevent bone loss.

HMG-CoA is an enzyme found in hepatocytes of the liver. It converts HMG-CoA into mevalonic acid, which is a cholesterol precursor. The reduction in hepatic cholesterol production leads to the upregulation of hepatic LDL receptors that reduce circulating levels of LDL in the blood.

The enzyme is most active at night leading to the nocturnal administration of statins.

Statins can improve endothelial function, alter vascular smooth muscle proliferation, regulate cardiac hypertrophy, protect against ischaemic injury and exert anti-inflammatory properties.

These cholesterol-independent effects support the targeted use of statins even with normal cholesterol levels.

Dosage and administration

The most well-recognized statins available for clinical use include simvastatin, atorvastatin, rosuvastatin, and pravastatin.

Atorvastatin is typically started at 10-20 mg daily for primary prevention. This can be increased if necessary (every four weeks) to a max of 80 mg.

In secondary prevention, a high dose of atorvastatin at 80 mg (max dose) is usually prescribed.

Adverse drug reactions

Statins are associated with a number of mild side effects which include myositis, rhabdomyolysis, anxiety, irritability, hepatotoxicity, and elevations in aminotransferases. Mild elevations of serum aminotransferases are common but are not often associated with hepatic damage.

Patients with preexisting liver disease may have more severe reactions.

An increase in creatine kinase (released from skeletal muscle) is noted in about 10% of patients; in a few, severe muscle pain and even rhabdomyolysis may occur.

HGM-CoA reductase inhibitors are metabolized by the cytochrome P450 system; drugs or foods (eg, grapefruit juice) that inhibit cytochrome P450 activity increase the risk of hepatotoxicity and myopathy.

Because of evidence that the HMG-CoA reductase inhibitors are teratogenic, these drugs should be avoided in pregnancy.

The side effect range from gastrointestinal disturbances to headaches. Important serious or rare side effects include DILI, myopathy, and neuropathy. There are some statin-specific side effects like angioedema that are associated with atorvastatin.

Drug-induced liver injury. Statin therapy has been associated with the development of varying degrees of severity of DILI. If transaminases are >3 times the upper limit of normal, discontinue statin.

Myopathy describes any type of muscle disease. Statin therapy is associated with a spectrum of skeletal muscle disorders. These disorders include Myalgia, Myositis, and Rhabdomyolysis, Immune-mediate necrotizing myopathy.

Rhabdomyolysis can be a life-threatening condition associated with acute kidney injury, disseminated intravascular coagulation, and multi-organ failure. In patients with muscle cramps and elevated creatine kinase (CK), statins should be discontinued. In mild episodes of myopathy, statins can be reintroduced at a lower dose but expert advice should be sought.

Contraindications and cautions

Statins should be used with caution in patients with, or who are at risk, of liver diseases such as those who have a non-alcoholic fatty liver disease, high alcohol users, and those with raised transaminases.

Statins are contraindicated in patients with severe liver disease.

They are also contraindicated in patients with untreated hypothyroidism, a history of muscular disorders, and stroke.

Drug Interactions

Statins are known to have several drug interactions due to their metabolism by the hepatic cytochrome P450 enzymes.

They classically interact with Amiodarone and Clarithromycin, which are enzyme inhibitors.

Co-administration of an enzyme inhibitor leads to an increased risk of myopathy.

Pregnancy and monitoring

Statins are considered teratogenic in nature and should be avoided in pregnant mothers.

Patients on statin therapy should have blood test monitoring. Baseline lipid profile, Creatinine kinase, Urea and electrolytes, Liver function tests, and Thyroid function tests should be checked.

LFTs are recommended to be done at 3 and 12 months and HbA1c in high-risk patients.

It is important to consider dose adjustment in renal failure.