



Medicines for lowering blood fats

Cholesterol Lowering

There are three main prescription medicines for lowering cholesterol - statins, ezetimibe, and PCSK9 inhibitors. All lower LDL cholesterol.

Evidence from more than 30 randomised trials, largely in statins, has consistently shown that reducing LDL cholesterol reduces the risk of cardiovascular (CV) events and that this benefit is proportional to the absolute reduction in LDL cholesterol.

All therapies that lower LDL (including ezetimibe, statins, PCSK9 inhibitors, bile acid sequestrants and dietary change) all act via the LDL-receptor pathway. They work by increasing the number of functioning LDL-receptors on the surface of liver cells. These receptors capture LDL cholesterol and remove it from the blood.

Statins – Atorvastatin, Rosuvastatin, Simvastatin, Pravastatin and Fluvastatin

Statins are the drug of choice for both the primary and secondary prevention of cardiovascular disease. They work by decreasing the activity of HMG-CoA reductase, which is a key enzyme involved in the production of cholesterol. By inhibiting this enzyme, statins slow down the liver's cholesterol production. This results in an increase in the number of LDL receptors on the surface of liver cells which in turn catch and remove more LDL cholesterol from the blood.

There are currently 5 statins available on prescription in the UK. Pravastatin and Rosuvastatin are broken down by different metabolic pathways and as a result there is potential for substitution if Atorvastatin or Simvastatin are poorly tolerated. The percentage cholesterol reduction depends upon the statin chosen and how much is given (see table). Clinical guidelines encourage doctors to prescribe a high potency statin/statin dose. Atorvastatin 20mg is advised for people who have not yet had a heart attack or stroke (primary prevention) and Atorvastatin 80mg for those that have had an event (secondary prevention). Simvastatin 80mg should only ever be prescribed in exceptional circumstances because it is associated with a higher risk of side effects.

People taking statins should be monitored for increased levels of liver enzymes and creatine kinase, an enzyme released from damaged muscle cells.

Percentage LDL cholesterol reduction from various statins and their doses

Dose (mg/day)	REDUCTION IN LDL CHOLESTEROL				
	5	10	20	40	80
Fluvastatin	-	-	21%	27%	33%
Pravastatin	-	20%	24%	29%	-
Simvastatin	-	27%	32%	37%	42%
Atorvastatin	-	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	-

20%-30%: Low intensity

31%-40%: Medium intensity

Above 40%: High intensity

Adapted from NICE CG181 2014

For most people statins are safe and well tolerated. The risk of side effects increases in people with a) advancing age b) other medications which compete for the same cytochrome P450 pathway, c) other medical conditions d) increasing alcohol consumption, and e) heavy exercise.

About 10-15% of patients report minor muscle problems such as muscle soreness and/or weakness (myalgia). Any side effects attributable to a statin are usually reversible when statins are stopped.

Cholesterol absorption inhibitor – Ezetimibe (Zetia) and Ezetimibe/statin combination (Inegy)

Ezetimibe reduces the absorption of cholesterol rich bile acids in the small intestine. Ezetimibe can reduce LDL cholesterol by 18-20% but has little effect on other lipoproteins. It can be used alone or in combination with a statin. It is available on its own or as a fixed dose combination tablet containing both ezetimibe and simvastatin.

PCSK9 Inhibitors – Evolocumab (Repatha) and Alirocumab (Praluent)

PCSK9 inhibitors (proprotein convertase subtilisin/kexin type 9 inhibitors) are a relatively new drug. They inhibit the action of the PCSK9 protein which under normal conditions binds to and destroys the LDL receptor. PCSK9 inhibitors prevent this action and allow the LDL receptor to be re-used to capture more LDL cholesterol from the circulation. Evolucomab and Alirocumab are a type of drug called a monoclonal antibody. Monoclonal antibodies have to be injected rather than taken orally. These PCSK9 inhibitors are therefore given either fortnightly or monthly by injection. They can reduce LDL cholesterol by over 50%.

The National Institute for Health and Care Excellence (NICE) have issued guidelines for their use in the UK. They are usually prescribed only by specialists for people at high risk who are on maximum tolerated conventional therapy and who are not reaching their LDL target. This includes people with Familial Hypercholesterolaemia (FH) and those with known cardiovascular disease.

Bile Acid Sequestrants (BAS) - Colesevelam (tablets), Colestipol (powder), Colestyramine (powder)

These drugs are also known as anion exchange resins. They bind to bile acids in the intestine, preventing them from being absorbed and re-cycled. As the liver is depleted of bile it needs to produce more. Bile is a breakdown product of cholesterol. The process of producing bile results in more cholesterol being removed from the circulation and broken down.

Colestipol and colestyramine (powders) are the older forms of BAS, and more recently a synthetic drug, colesevelam has been produced. Studies show a reduction in LDL cholesterol of between 18–25%. The powder preparations can interact with other prescribed drugs so they need to be taken separately to other medicines to reduce any possible interference. Colesevelam has less interactions and can be taken alongside other medications such as statins and ezetimibe. It should be taken at mealtimes. UK national guidelines do not recommend resins as the first choice for treating raised cholesterol and advise they should only be used under the supervision of a specialist.

Triglyceride Lowering

Fibrates – Bezafibrate, Ciprofibrate, Fenofibrate and Gemfibrozil

Known as **peroxisome proliferator activated receptor agonists**, fibrates act mainly by decreasing the amount of triglycerides in the blood. They have variable effects on LDL cholesterol and can raise HDL cholesterol. They are mainly used by specialists for people whose serum-triglyceride concentrations are greater than 10 mmol/L. They may be used alongside a statin. The combination of a statin with a fibrate increases the risk of muscle side effects and so they should be used cautiously. Statins should not be used alongside Gemfibrozil. Fibrates are only available for prescription by a specialist.

Novel Specialist Treatments

Lomitapide - Lojuxta

Lomitapide (marketed Lojuxta in the EU) directly binds and inhibits the microsomal triglyceride transfer protein (MTP) in the cell, which stops the synthesis of triglyceride carrying particles (chylomicrons and VLDL), which leads to a reduction in LDL cholesterol plasma levels. It is only available for individuals with the rare homozygous form of FH and can reduce LDL cholesterol by approximately 40%. It is a very expensive treatment with a high risk of gastro-intestinal side effects and requires patients to follow a fat restricted diet. It is only available through a restricted access programme. Lomitapide has received approval from European Medicines Agency (EMA) but has not as yet been used in the UK.

Mipomersen

Mipomersen is an antisense oligonucleotide. It is another treatment licenced only for people diagnosed with homozygous FH. It works by targeting the formation of apolipoprotein B-100, an important structural lipoprotein needed for the synthesis of fat carrying (VLDL and LDL) lipoproteins. Mipomersen did not receive approval from the EMA so is not available in Europe.

Alipogene tiparvec – Glybera

Glybera is a form of gene therapy. It is an injectable treatment for adults who have been diagnosed with the rare condition Lipoprotein Lipase Deficiency (LPLD). To be eligible people have to have experienced severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing and the treatment is only available to those who have detectable levels of the LPL protein.

Still in clinical trials

Cholesteryl Ester Transfer Protein Inhibitors (CETP inhibitors) – Anacetrapib, Evacetrapib

The cholesteryl ester transfer protein (CETP) promotes the transfer of cholesterol from HDL to LDL. CETP inhibitors prevent this from happening, thereby raising HDL levels (carriers of good cholesterol) and decreasing LDL (carriers of bad cholesterol) levels. Previous clinical trials into these drugs have not been successful in delivering clinical benefits, but newer inhibitors are currently being tested.

Volanesorsen

Volanesorsen is an antisense drug in development for rare metabolic disorders where triglycerides are severely raised and can cause severe pancreatitis. Volanesorsen is designed to reduce the production of ApoC-III, a protein produced in the liver that plays a central role in the regulation of plasma triglycerides.

Volanesorsen is currently still in stage three clinical trials but if approved should be available for people with Lipoprotein Lipase Deficiency (LPLD), a condition that results in a lack of an enzyme (lipoprotein lipase) that is needed to clear triglyceride rich particles from the blood after a meal. In addition Volanesorsen may be available to treat people with familial partial lipodystrophy (FPL) an equally rare disorder which results in an inability to store fat in normal locations and raised levels of triglycerides in the blood.