# Hypolipidaemic Drugs: Statins and Potential Newer Targets

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***Abstract***

*Hyperlipidaemia is characterized by abnormally elevated levels of plasma lipids. It is one of the leading factors to be associated with cardiovascular and cerebrovascular diseases. Dietary and lifestyle modification is the first – line treatment in the management of hyperlipidaemia. If there are no satisfactory results, hypolipidaemic drugs are taken into consideration.*

*The most widely used hypolipidaemic drugs are statins. Statins inhibit the enzyme, HMG COA reductase, which catalyses the rate limiting step in cholesterol synthesis . Atorvastatin, approved in 1996 is the first drug of this class. It is indicated for heterozygous and homozygous familial hypercholesterolemia(FHC), mixed dyslipidaemia and as concomitant lipid lowering agent in coronary artery disease. Thereafter, Fluvastatin was approved for coronary atherosclerosis. Another agent, Lovastatin was approved in 1999 with the same indications as Atorvastatin. Since then, newer statins Rosuvastatin(2003), Pitarvastatin( 2009) and Simvastatin(2010) have been included in this class of drugs. A newly approved Cerivastatin was withdrawn due to the adverse effect of rhabdomyolysis and kidney failure. Later in 2013, a fixed drug combination of Ezetimibe and Atorvastatin was approved for treatment of hyperlipidaemia.*

*Further more researches point towards potential targets, which can have better effect on the lipid profile. The recent target include apolipoprotein B inhibitor, Mipomersen sodium, which is indicated as an adjunct to other lipid- lowering agents and diet. The inhibitors of a newer target, Proprotein Convertase Subtilisin Kexin Type 9(PCSK-9), Alirocumab, Evolocumab and Bococizumab have been developed as an adjunctive treatment in patients with heterozygous familial hypercholesterolaemia (FHC) or atherosclerotic diseases. Omega- 3- carboxylic acids is a new discovery as a lipid regulating agent and can be used as an adjunctive therapy.*

***Keywords***

*Hypolipidaemic drugs, Statins, Atorvastatin,PCSK-9*

**Introduction**

Hyperlipidemia causes about 17 million deaths worldwide each year and is leading cause for the development of heart and coronary diseases, and atherosclerosis.[1] Safety and efficacy of hypolipidemic therapy have been established for primary and secondary prevention of cardiovascular events in adults.[2]Treatment of dyslipidemia and prevention of cardiovascular disease with lipid-lowering drugs is one of the key issues in reducing cardiovascular mortality.[3]

Atherosclerosis is an inflammatory condition of arterial wall, leading to arterial wall thickening and its instability. This may affect coronary blood supply leading to myocardial infarction, cerebral and carotid blood supply causing ischemic stroke or peripheral arteries which may lead to limb amputation. One of the most important factors that accelerate atherosclerosis is hyperlipidemia. Dietary and lifestyle modification are the first –line treatment in the management of hyperlipidaemia. The focus should be on proper diet, physical activity and proper exercise. If there are no satisfactory results, hypolipidaemic drugs are taken into consideration. Major attention is given to LDL-C (low-density lipoprotein cholesterol) level as primary, and triglyceride level as secondary targets of therapy. All this can be achieved by the use of hypolipidemic drugs.[4]

**Statins**

The most widely used hypolipidaemic drugs are statins and their major effect is reduction of LDL levels. Statins are HMG Co-A(3-hydroxy -3-methyl gluteryl-co-enzyme A) reductase inhibitors. This enzyme reduce the conversion of HMG Co-A to Mevalonate which is a rate limiting step in the synthesis of cholesterol, thus preventing its formation. [5]**Atorvastatin** was the first statin to be used as an hypolipidemic and it was approved in 1996. It is used to treat Heterozygous Familial Hypercholesterolemia, Homozygous familial Hypercholesterolemia, mixed dislipidemia and also as a lipid lowering therapy in coronary heart disease. Its minimum dose is 10 mg once daily and maximum up to 80 mg can be used. The side effects include precipitation of diabetes mellitus, myopathy ,rhabdomyolysis,liver enzyme abnormality,arthralgia and diarrhea. **Pravastatin** is another statin approved in 1996 and it is also used to treat Heterozygous Familial Hypercholesterolemia,homozygous familial hypercholesterolemia ,mixed dislipidemia and in coronary heart disease. The dose range is 10-80mg per day and the most common side effects are mild skin irritation, transient rash and gastrointestinal upset

**Fluvastatin** was approved 1997. It is used in treatment of coronary atherosclerosis and has a dose range of 20-80 mg per day. The major side effects include rhabdomyolysis and liver enzyme abnormalities. Another statin **Lovastatin** was approved in 1999 and its dose range is 10-40 mg per day. The side effects associated with it are liver enzyme abnormalities,abdominal pain,gastrointestinal disturbances,muscle pain,dizziness and rarely hepatotoxicity. **Rosuvastatin** was approved in 2003 and its dose range is 5-40 mg once a day.Its side effects include pharyngitis, headache, diarrhea, dyspepsia,myalgia,asthenia,back pain,flu syndrome and urinary tract infection.According to a study done by Bener A et al Rosuvastatin (10 mg) is the most effective in reducing low-density lipoprotein cholesterol (LDL-C; 28.59%), followed by simvastatin 20 mg (16.7%), atorvastatin 20 mg,(15.9%), and pravastatin 20 mg (11.59.3%) in dyslipidemic diabetic patient.[6] **Pitavastatin** was approved in 2009 and it is indicated in primary hyperlipidemia and mixed lipidemia its dose range is 2-4 mg once a day and its side effects include back pain,constipation,diarrhea,myalgia and pain in extremity. **Simvastatin** was approved in 2010 and Its dose range is 5-40 mg once daily. Its side effects include

upper respiratory tract infections, headache, abdominal pain,constipation and nausea. One of the statins **Cerivistatin** was withdrawn from the market, due to drug related rhabdomyolysis leading to kidney failure.

**Liptruzet** is a newer hypolipidemic drug approved in 2013 which is fixed dose combination of Ezetimibe and Atorvastatin.[7] It thus treats two sources of cholesterol by inhibiting both the absorption of cholesterol in the digestive tract through Ezetimibe and the production of cholesterol in the liver through Atorvastatin. Liptruzet is indicated for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia. It is also indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. Liptruzet is supplied as a tablet for oral administration.The recommended starting dose of Liptruzet is combination of 10mg Ezetimibe and 10mg Atorvastatin or combination of 10 mg Ezetimibe with 20 mg Atorvastatin per day. Liptruzet can be administered as a single dose at any time of the day. Major side effects include liver enzyme abnormality and musculoskeletal pain.

**Newer targets**

An important new target for hypolipidemic drugs is Proprotein convertase subtilisin kexin type 9 enzyme which is a negative regulator of low density lipoprotein receptor, the drug binds to these receptors along with LDL-Cholesterol and facilitates its lysosomal degradation inside hepatocytes.[7] **Alirocumab** is a PCSK9 inhibitor antibody approved in 2015.[8] It is indicated for heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease. It is supplied as an injection for subcutaneous use. The recommended starting dose is 75 mg administered once every 2 weeks. Majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Nasopharyngitis,injection site reactions and influenza are the side effects of this drug. **Evolocumab** is another PCSK 9 inhibitor approved in 2015. It is a fully human monoclonal antibody to PCSK9. It is specifically indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia, clinical atherosclerotic cardiovascular disease. It is supplied as an injection for subcutaneous administration and the recommended dose is 140 mg every 2 weeks or 420 mg once monthly. Its side effects include, nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection site reactions.

**Mipomersen** is an ApoB-100 synthesis inhibitor approved in 2013. Mipomersen binds to messenger RNA coding for ApoB-100 molecule and stops its translation. ApoB-100 is a protein that plays a pivotal role in the production of low-density lipoprotein (LDL) thus reducing LDL-C concentration in blood.[8] It is specifically indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol, and non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia. It is supplied as a solution for subcutaneous injection and its dose is 200 milligrams (mg) once weekly. It comes under REMS(risk evaluation and mitigation strategy) programme of FDA due to hepatotoxicity. The side effects of this drug include injection site reactions,flu-like

symptoms,nausea,headache and elevations in serum transaminases. **Epanova** is an omega-3-carboxylic acid ,approved in 2014.[7] It is a lipid-regulating agent containing fish oil-derived free fatty acids, with at least 850 mg of polyunsaturated fatty acids, including multiple omega-3 fatty acids like eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]. Epanova is specifically indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe (>500 mg/dL) hypertriglyceridemia it is supplied as a capsule for oral administration and its recommended dose is 2 to 4 grams once daily. Its side effects include diarrhea,nausea,abdominal pain or discomfort and eructation.

**Conclusion**

The faulty dietary habits and a sedentary lifestyle of people today have contributed to the increasing dyslipidemias and complications associated with it like atherosclerotic vascular diseases. Hypolipidemic drugs available provides good lipid control and play important role in preventing co-morbidities associated with dyslipidemia. But these are not devoid of adverse affects which includes hepatotoxicity, myopathy ,rhabdomyolysis, respiratory tract infections and many more. Further development of newer targets may be required, which can give better control of the lipid levels and are safe.

**Reference**

1. Lopes RH et al.Antioxidant and hypolipidemic activity of the hydroethanolic extract of curatella americana l. leaves.Oxid Med and Cell Longev:May 9,2016.
2. K gazola, G B Vigna.Hypolipidemic drugs in elderly subjects: Indications and limits. J.Numecd; july 21 2016:1064-1070.
3. Szymanski FM et al, Utilization of the lipid-lowering therapies in outpatient settings in Poland - epidemiological survey Economedica Dyslipidemia.K.P: jan 9,2018.
4. Okopien B,Buldak L,Boldys .A Current and future trends in the lipid lowering therapy. Pharmacol Rep Aug 2016;68(4):737-47.
5. Thomas P.Bersot,drug therapy for hypercholesterolemia and dyslipidemia. Goodman and Gilman's Pharmocological basis of therapeutics.12 th edition.United States: McGraw-Hill companies,2011;p 894.
6. Abdulbari Bener, Muzeyyen Dogan, Lolwa Barakat,Abdulla O.A.A. Al-Hamaq, Comparison of efficacy, safety, and cost-effectiveness of various statins in dyslipidemic diabetic patients. Ind J P;February 2014.
7. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205060s000lbl.pdf
8. Chang Ho Ahn,Sung Hee Choi.New drugs for treating dyslipidemia:Beyond statins.Diabetes metab J.2015Apr;39(2):87-94