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Dyslipidemia management update

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Association of hypercholesterolemia and atherosclerotic cardiovascular disease (ASCVD) is well established. Reducing low-density lipoprotein-cholesterol (LDL-C) and raising high-density lipoprotein-cholesterol (HDL-C) have been the therapeutic targets to reduce the risk of ASCVD. Cholesterol-lowering medications have been used to provide both primary and secondary prevention of ASCVD for many years by reducing the absorption and reabsorption, promoting excretion, or decreasing the synthesis of cholesterol. Within the past five years, several new classes of cholesterol-lowering drugs have been tested and approved for patients with hypercholesterolemia that are not well controlled by conventional therapy (ezetimibe, bile-acid sequestrants, and statins). These drugs include proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies, apolipoprotein A-100 (Apo B-100) antisense, and microsomal triglyceride transfer protein (MTP) inhibitor. Clinical trials revealed that adding PCSK9 antibodies to the preexisting statin therapy can further reduce LDL-C by 60%. ApoB antisense and MTP inhibitor are currently approved for patients with homozygous familial hypercholesterolemia. Several HDL-raising drugs have also been tested, but the results are not promising. Studies suggest that specifically raising reverse cholesterol transport rather than HDL-C level could be a novel therapeutic approach to reduce cardiovascular risk.

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Treatment goal of anti-dyslipidemia

Total and LDL-cholesterol plasma levels increase throughout life in both men and woman. Although there are no established normal values for cholesterol, higher total and LDL-C is associated with the development of atherosclerotic heart diseases (ASCVD) including coronary heart disease (CHD), stroke, and peripheral arterial disease. Hypertriglyceridemia is considered to be a contributing factor, but after adjustment for other risk factors the contribution seems marginal at best. With respect to primary prevention, lowering cholesterol levels in healthy middle age men without CHD decreases the risk of CHD in proportion to the reduction in LDL-C, but is inconsistent at reducing all cause of mortality. However, in patients with known CHD, the evidence is strong that interventions lowering cholesterol reduce both the risk of secondary events and death. Finally, the evidence is less conclusive for the effectiveness of reducing triglycerides (TGs) in patients with or without history of CHD [1].

While hypercholesterolemia may be linked to specific genetic mutations, most cases of hypercholesterolemia are influenced by other factors, such as endocrine/metabolic diseases, lifestyle (diet and exercise) and drugs. A study found that without lipid-lowering medications, 5-year intensive lifestyle changes reduced LDL-C by 37% and reversed the progression of coronary atherosclerosis [2]. However, despite the intensive lifestyle changes, many people have LDL-C levels that remain high and have to be treated by the lipid-lowering agents. The drugs used to lower LDL-C levels have also been proven to reduce the risk of having an ASCVD event.

This review will summarize the currently FDA-approved lipid-modifying agents (Figure 6) and address some of the new agents in the development pipeline. These new agents may become options for patients who cannot tolerate the established lipid-modifying agents or who remain at high risk of ASCVD despite the treatment with the established lipid-modifying agents.

LDL-direct management

HMG-CoA inhibitors

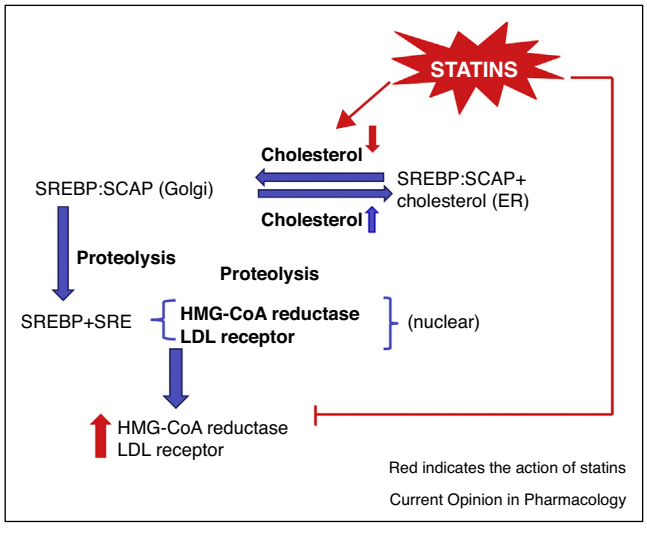
The statins are analogues of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase substrate. Currently available statins include atorvastatin, fluvastatin, lovastatin, pitvastatin, pravastatin, rosuvastatin, and simvastatin. Statins bind to HMG-CoA reductase and competitively inhibit the conversion of HMG-CoA to mevalonate, which is the rate-limiting step in *de novo* cholesterol synthesis. This inhibition leads to a transient and modest decrease in cellular cholesterol concentration [3]. As a monotherapy, statins are the most effective total cholesterol and LDL-C reducing agents and among the best tolerated. The most effective statins, atorvastatin, rosuvastatin and simvastatin also moderately reduce VLDL

triglyceride levels and increase HDL. Additionally, statins also increase the efflux of cholesterol from macrophages. Whether these additional effects are of clinical significance remain to be determined.

By reducing hepatic cholesterol levels, statins increase the expression of the LDL receptor gene [4], therefore enhancing the fractional metabolic rate of LDL and extraction of VLDL remnants, leading to reduction of LDL-C. This effect is mediated by activation of sterol regulatory element binding protein 2 (SREBP2), a transcription factor that up-regulates expression of the genes encoding HMG-CoA reductase and LDL receptors [5]. When cholesterol is at a normal level, SREBP2 binds to the cholesterol-sensing protein SREBP cleavage-activating protein (SCAP) and another ER protein named insulin-induced gene-1 (Insig-1). When cholesterol is depleted, SCAP escorts SREBP2 to the Golgi where it is cleaved by proteases allowing it to translocate to the nucleus and bind to the sterol regulatory binding element (SRE) of the HMG-CoA reductase and LDL receptor genes (Figure 1).

Statins decrease LDL-C by up to 60% and they are considered as the first-line agents for prevention of primary and secondary ASCVD. Lowering LDL-C is considered the major contributor to reduced risk of coronary heart disease [6–8]. In addition, the pleiotropic effects mediated by statins may also play a role in their beneficial effect in prevention of ASCVD. For example, statins inhibit inflammation by reducing expression of several proteins that are involved in atherosclerotic plaque formation, induce apoptosis leading to reduced hyperplasia and restenosis, inhibit immune cell proliferation and activation, and improve endothelial function. This improved endothelial function occurs because statins increase nitric oxide (NO) production, reduce reactive oxygen species (ROS) production resulting in decreased LDL oxidation, increase plaque stability, inhibit platelet adhesion and aggregation, and normalize sympathetic outflow [9,10].

Figure 1



Mechanism of statin-induced expression of LDL receptor. Statins lower intracellular cholesterol level, frees SREBP, and promotes SREBP bind to sterol regulatory binding element (SRE) of HMG-CoA reductase and LDL receptor, leading to increased expression of HMG-CoA reductase and LDL receptor.

Inhibitors of intestinal sterol absorption

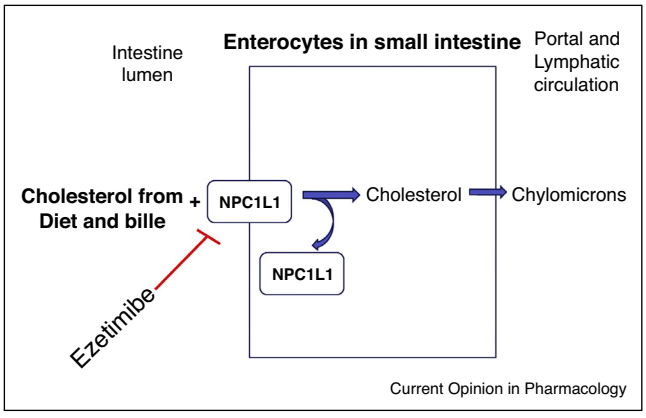
Ezetimibe inhibits the intestinal cholesterol and phytosterol absorption protein (Niemann-Pick C1-Like 1, NPC1L1) present on jejunal intestinal cells [11,12], effectively inhibiting intestinal cholesterol absorption from dietary sources and from bile, whether dietary cholesterol is present or not. It can reduce hepatic cholesterol concentration and circulating LDL-C to the same extent as the less potent statins, and as such, clinical studies may ultimately reveal similar outcomes (Figure 2).

Ezetimibe can achieve 20% of reduction in LDL-C and is approved for both primary and secondary prevention of ASCVD as a monotherapy in patients intolerant of statins or combined with statins in high risk or refractory patients with unsatisfactory statin therapy outcomes [13].

Bile acid-sequestering agents

Resins, including cholestipol, cholestyramine, and colesevelam, were the primary cholesterol lowering agents before statins were introduced. They share the same clinical indications with ezetimibe and can reduce LDL-C by up to 30%. Following oral administration, the negatively charged resins stay in the GI tract and bind to positively charged bile acids in the bile to form insoluble and non absorbable complexes in the intestines

Figure 2



Mechanism of action of ezetimibe.