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# Cholesterol-Lowering Drugs and Therapies in Cardiovascular Disease

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<http://dx.doi.org/10.5772/64762>

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## Abstract

Dyslipidemia is a major risk factor for cardiovascular disease (CVD). The relationship between low-density lipoprotein concentration and cardiovascular (CV) risk has been well established in numerous epidemiological studies. The benefit of cholesterol-lowering agents has been demonstrated in patients with known CVD. On the other hand, in patients without known CVD the decision to start therapy depends on their 10-year risk prediction of CV events. 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (“statins”), a mainstay of cholesterol-lowering therapy, have been shown to reduce both CV events and all-cause mortality. Other lipid-lowering measures (both pharmacological and nonpharmacological) have also been demonstrated in clinical trials to reduce CV outcomes. In this chapter, we review contemporary therapies used to treat dyslipidemia and discuss future directions including novel agents on the horizon.

**Keywords:** cholesterol treatment, cardiovascular disease, dyslipidemia, cardiovascular risk stratification, hypercholesterolemia

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## 1. Introduction

Atherosclerotic cardiovascular disease (CVD) affects more than 15 million Americans and is considered the leading cause of death in the United States (US) in both men and women (REF). Dyslipidemia is a major risk factor for atherosclerotic CVD [1]. We review current standard treatment of abnormal cholesterol levels and discuss future directions. Lipid-altering therapies favorably impact the lipid profile by lowering total cholesterol, low-density lipoprotein (LDL), and triglycerides (TGs), while beneficially increasing high-density lipoprotein (HDL; see **Table**

1) [2–4]. In addition, lipid-altering therapies cause a desirable shift toward less atherogenic cholesterol subparticles [5]. The benefit of lipid therapy has been borne out in studies evaluating their effects on coronary atherosclerosis regression (by angiography) and incidence of major adverse cardiovascular events (MACEs) [6–10]. The lipoprotein transport system mediates the movement of cholesterol and TG in plasma, in addition to numerous other important physiologic functions. These include transport of dietary fat absorbed in the intestines to the liver, transport of modified cholesterol to peripheral tissues for cell membrane and steroid hormone synthesis, and transport of free fatty acids that may be used for fuel [11]. Lipoproteins are typically classified by their size and density. The main lipoprotein carriers of cholesterol to peripheral tissues are LDL particles. They are internalized by LDL receptors, where they are then hydrolyzed. This is an important pathway in controlling plasma cholesterol levels, as evidenced in those with loss-of-function mutations of LDL receptors leading to an inherited hyperlipidemia [12]. Importantly, LDL particles vary in size. Those with fewer cholesteryl esters and more TGs are smaller, denser, and thus more atherogenic [11].

| Drug class                                    | LDL (%) | HDL (%) | TG (%)    |
|---|---------|---------|-----------|
| Bile acid sequestrants                        | ↓ 15–30 | ↑ 3–5   | No change |
| Cholesterol absorption inhibitors (Ezetimibe) | ↓ 17–22 | ↑ 2–5   | ↓ 4–11    |
| Fibrates                                      | ↓ 5–20  | ↑ 10–20 | ↓ 20–50   |
| Nicotinic acid (niacin)                       | ↓ 5–25  | ↑ 15–35 | ↓ 20–50   |
| PCSK9 inhibitors                              | ↓ 61–62 | ↑ 5–7   | ↓ 13–17   |
| HMG-CoA reductase inhibitors (Statins)        | ↓ 18–55 | ↑ 5–15  | ↓ 7–30    |

*Abbreviations:* LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglycerides.

**Table 1.** Potencies of various lipid lowering agents.

Increased concentrations of LDL have been shown in epidemiological studies to be associated with an increased risk of MACE. This was demonstrated in The Lipid Research Clinics Prevalence Study, where after 10 years of follow-up in patients with known coronary heart disease (CHD), a higher death rate was evident in those with higher levels of plasma total cholesterol and LDL [13]. In addition, those with inherited hyperlipidemia have early atherothrombosis [14]. Reducing LDL cholesterol is strongly linked to reductions in MACE, especially when using statins [10]. One-third of all middle-aged or older adults in the general population of the US and United Kingdom (UK) have an indication for statin therapy [15]. Notably decreased LDL and raising HDL levels have been associated with regression of atherosclerosis as evident in the Regression Growth Evaluation Statin Study (REGRESS) trial and several other trials [6–9].

Until recently, it was strongly recommended to treat to specific LDL targets [16]. These targets were based on post hoc analyses demonstrating greater reductions in MACE with LDL levels

below certain levels. However, subsequent head-to-head statin trials compared different agents at different doses. These studies did not investigate the effects of different LDL target levels [17]. For such reasons, the most recent US guidelines advocate for using high-intensity statins for patients at high risk of cardiovascular events. By contrast, guidelines in Europe and Canada have maintained their recommendation on using LDL targets [18].

Statins are well known for pleiotropic effects independent of cholesterol lowering, mainly anti-inflammatory properties [19]. In many statin trials, subjects with the largest reduction in high-sensitivity C-reactive protein (hsCRP) have decreased primary end points [20, 21]. In two statin trials, lower hsCRP and LDL levels were associated with a decrease in atheroma progression as assessed by serial intravascular ultrasound observation [22, 23]. Moreover, in the Justification for the Use of Statins in Prevention (JUPITER) trial, a decrease in MACE and all-cause mortality was seen in asymptomatic subjects with baseline elevated hsCRP levels and already low LDL level, which contemporary risk calculators would exclude from therapy. Notably, elevated LDL cholesterol is associated with MACE without the need for overt evidence of inflammation [24].

### **1.1. Cardiovascular risk stratification: Who to treat?**

In patients with known CVD, treatment with statins has been shown to reduce CV events and all-cause mortality, while other lipid-lowering agents have also been shown to reduce the incidence of CV events in patients not on statins [25–33]. However, in patients without known CVD, cholesterol-lowering agents have only been shown to be beneficial in those at a high risk of CV events. The absolute benefit of treatment is proportional to the underlying absolute CV risk. Therefore, it is important to target patients at a high risk of CV events rather than a specific LDL.

Various CV risk calculators have been used to identify patients at high risk. These calculators are modeled to a particular population; therefore, the choice of which risk calculator to use is important. Below, we will discuss the benefits and pitfalls of using risk calculators to guide decision to treat. The Framingham Risk score is a risk calculator based on a population from the northeastern US (<https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php#>). The most current version includes major CV outcomes, stroke, and heart failure. Notably, statins have shown to reduce the incidence of major CV outcomes and stroke, but not heart failure [34]. The American Heart Association/American College of Cardiology (AHA/ACC) Pooled Cohort Equations Cardiovascular risk calculator (ASCVD) is based on a population of non-Hispanic whites and African Americans in the US (<http://tools.acc.org/ASCVD-Risk-Estimator/>). Compared to the Framingham risk calculator, it predicts major CV outcomes that are reduced by statins. Limitations of the ASCVD include its dichotomization of diabetes mellitus without considering its duration or type. It also does not take into account family history of premature CV disease, thus underestimating CV risk in those with significant family history of CV events [35].

The Joint British Societies (JBS-3) guidelines calculator is based on a population from the UK (<http://www.jbs3risk.com/JBS3Risk.swf>). In those with a low 10-year risk of CV events, the JBS-3 recommends using the QRISK® lifetime CV risk calculator [36]. Both the ASCVD and

JBS-3 predict both 10-year risk and lifetime risk of CV events. Without the data with long-term effects of statins, there is a limitation to use lifetime risk prediction for using cholesterol-lowering agents. Therefore, the use of the 10-year risk predictions has been recommended when making such decisions. In patient with diabetes, the UK Prospective Diabetes Study calculator incorporates factors important to those with diabetics that are not found in the ASCVD calculator such as diabetes duration and type [37].

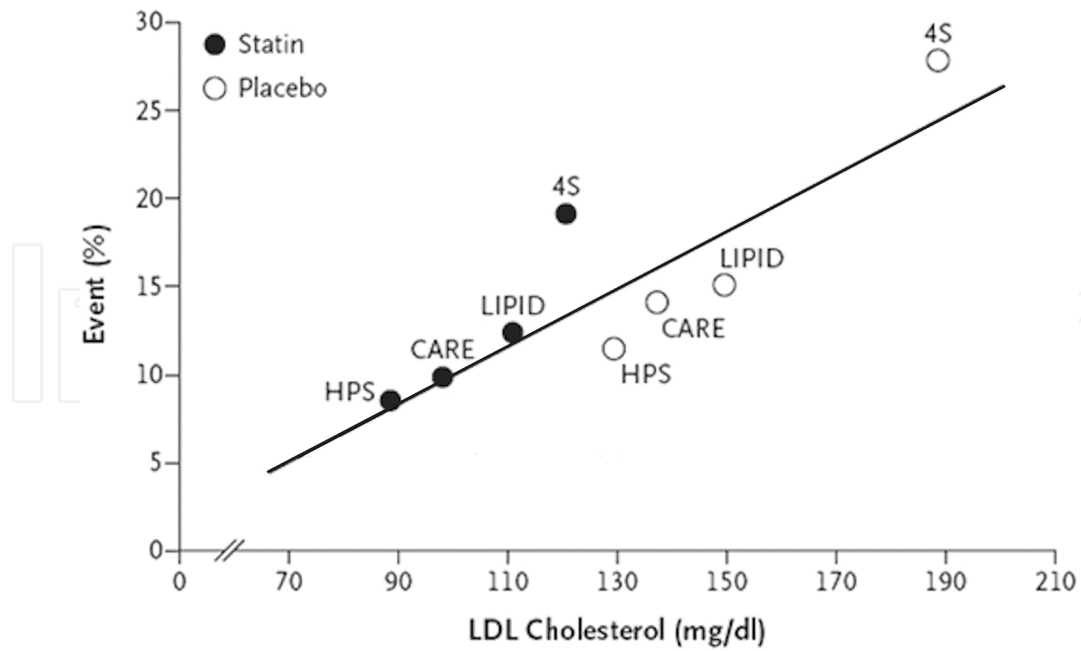
Another factor used when making the decision to treat on a population-based approach is cost-effectiveness. The 2013 AHA/ACC guidelines have recommended the use of a 10-year risk of CV events threshold of 7.5% when deciding to use cholesterol-lowering agents. This was found to be more cost-effective when compared with  $\geq 10\%$  threshold [38].

In older patients, over age 65, the decision to treat is also influenced by the presence of other comorbidities not taken into account in the calculators above. For example, a patient with a concurrent illness with high mortality, such as metastatic pancreatic cancer, is unlikely to benefit from a cholesterol-lowering agent. Thus, clinical trials of cholesterol-lowering agents have typically excluded older patients. However, a healthy elderly patient may potentially benefit from these therapies, and in fact the absolute number to treat is much lower in a healthy elderly population, given the dramatic increase in absolute risk of CV disease in this cohort [39]. A barrier to using cholesterol-lowering agents in the elderly has been the notion that it takes years to see the benefit of cholesterol-lowering agents; however, many studies have shown that they can be beneficial in as early as 6 months, as seen in the 4S trial [40].

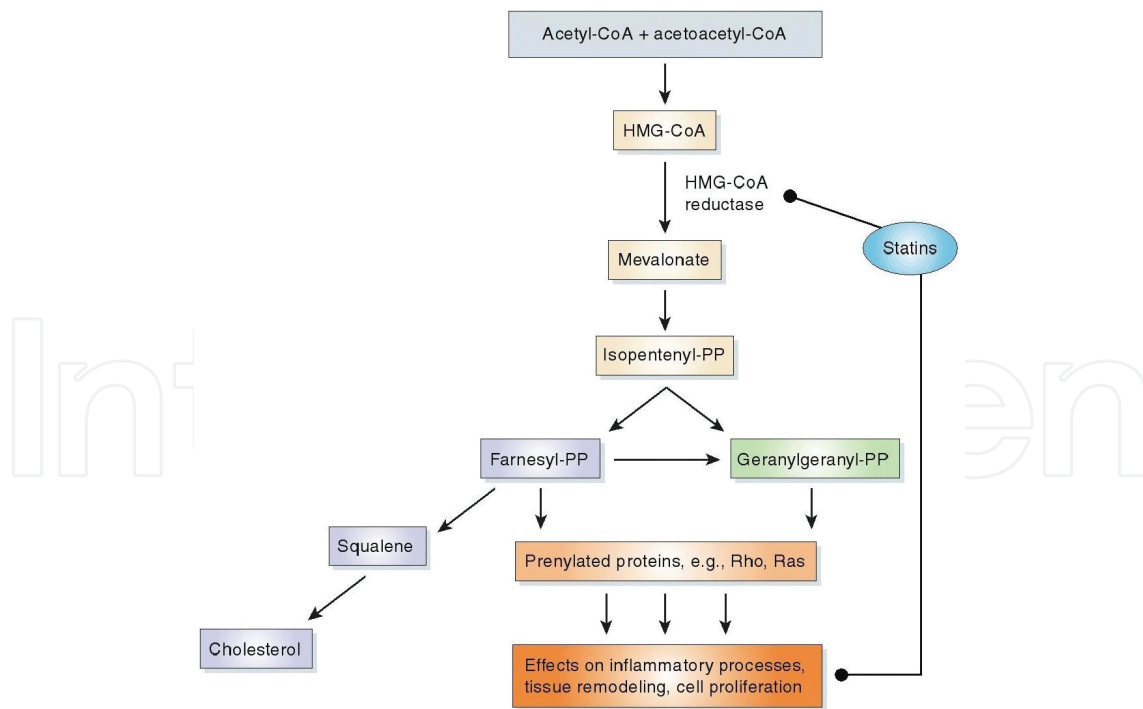
## 2. Pharmacological therapies

### 2.1. Statins

Statins have been shown to be beneficial in hypercholesterolemia for both primary and secondary prevention of CV events (see **Figure 1**) [41]. Their main mechanism of action involves competitive inhibition of an enzyme, 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a rate-limiting step in cholesterol synthesis (see **Figure 2**) [42, 43]. This prevents substrate from binding to the enzymatic active site resulting in a decrease in intrahepatic cholesterol synthesis [44]. The decrease in intrahepatic cholesterol leads to an increase in LDL receptors, and consequently an increase in LDL reuptake [45]. Other mechanisms described include alteration of hepatic Apolipoprotein B (Apo-B) secretion leading to a reduction in very low-density lipoprotein (VLDL) through decreased secretion and increased clearance. This consequently also contributes to the reduction in plasma TG [46]. Statins' effect on HDL has been attributed to their impact on hepatic microRNA33 (miR33) and consequent macrophage ATP-binding cassette transporter (ABCA)1-mediated efflux [47]. These additional mechanisms are thought to translate into clinical benefit through varied pathways including reversal of endothelial dysfunction, atheroma stabilization, and decreased thrombogenicity [48].



**Figure 1.** LDL, statins, and cardiovascular events. Reduction in cardiovascular event rates by lower low-density lipoprotein using statins in secondary prevention trials. *Abbreviations:* 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events Trial; HPS, Heart Protection Study; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease.



**Figure 2.** Mechanisms of HMG-CoA reductase inhibitors. Statins inhibit hepatic HMG-CoA reductase resulting in decreased downstream cholesterol production.

Statins are considered the most potent agents for lowering LDL cholesterol, and do so up to 63% [49]. They do have a predominant effect on small LDL particles leading to a shift in the LDL subfractions toward less atherogenic LDL [50]. Rosuvastatin has been shown to increase HDL by about 10%, appearing to be the most effective statins on HDL modification [51]. Regarding lowering TG, atorvastatin and rosuvastatin appear to be the most potent of the statins, with a dose-dependent decrease in TG of up to 33% [51].

Statins as a drug category demonstrate varying cholesterol-lowering potencies (see **Table 2**) [51–53]. Low-potency statins include simvastatin, lovastatin, pravastatin, and fluvastatin [51]. High-potency statins include atorvastatin and rosuvastatin [51]. Statins combined with a cholesterol absorption inhibitor (such as ezetimibe) or bile acid sequestrant show an additive cholesterol-lowering effect [54, 55].

| Statin       | TC (%)  | LDL (%) | HDL (%) | TG (%)  | Dose range (mg) |
|--------------|---------|---------|---------|---------|-----------------|
| Atorvastatin | ↓ 27–39 | ↓ 37–51 | ↑ 2–6   | ↓ 20–28 | 10–80           |
| Rosuvastatin | ↓ 33–40 | ↓ 46–55 | ↑ 8–10  | ↓ 20–26 | 10–40           |
| Simvastatin  | ↓ 20–28 | ↓ 28–39 | ↑ 5–6   | ↓ 12–15 | 10–40           |
| Pravastatin  | ↓ 15–22 | ↓ 20–30 | ↑ 3–6   | ↓ 8–13  | 10–40           |
| Fluvastatin  | ↓ 13–19 | ↓ 17–23 | ↑ 1–3   | ↓ 5–13  | 20–80           |
| Pitavastatin | ↓ 22–31 | ↓ 31–44 | ↑ 1–4   | ↓ 13–22 | 1–4             |

*Abbreviations:* NNT, number needed to treat; WOSCOPS, West of Scotland Coronary Prevention Study; AFCAPS/TEXCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CARDS, Collaborative Atorvastatin Diabetes Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; JUPITER, Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events trial; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease study; HPS, Heart Protection Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; TNT, Treating to New Targets; IDEAL, Incremental Decrease in End Points through Aggressive Lipid Lowering.

**Table 2.** Potencies of different statins.

Numerous clinical trials have shown a trend toward improved CV outcomes, but not all have demonstrated statistical significance [56]. Statins have been shown to be effective in primary prevention of CHD (see **Table 3**) 21, 25–28, 32, 41, 57–63]. This was demonstrated in the Heart Protection Study [25], CARDS trial [26], and MEGA trial [27], where statins led to a significant reduction in MACE. Statins have also been shown to be effective in the secondary prevention of CHD as well (see **Table 3**). This benefit was evident in the Scandinavian Simvastatin Survival study (4S) [28], Lipid trial [29], and MIRACLE [30], where statin use resulted in a significant reduction in MACE. In a meta-analysis, which included 17,617 patients randomized to statins from the Cholesterol and Recurrent Events (CARE), Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), and 4S trials, there was a significant reduction in MACE and all-cause mortality, but no effect on noncardiovascular mortality [31]. In addition, high-dose statin

therapy was shown to have a significant reduction in MACE when compared to lower-dose therapy, as seen in the Treating to New Target (TNT) trial [41] and PROVE IT-TIMI 22 trial [32].

| Study                | Year | Patients | Statin and daily dose                        | Mean baseline LDL (mg/dL) | Mean LDL reduction (%) | Reduction in coronary events (%) | NNT |
|----------------------|------|----------|--|---------------------------|------------------------|----------------------------------|-----|
| Primary prevention   |      |          |  |                           |                        |                                  |     |
| WOSCOPS              | 1995 | 6595     | Pravastatin 40 mg                            | 192                       | 26                     | 31 ( $P < 0.001$ )               | 42  |
| AFCAPS/TEXCAPS       | 1998 | 6605     | Lovastatin 20–40 mg                          | 150                       | 25                     | 37 ( $P < 0.001$ )               | 24  |
| ALLHAT-LLT           | 2002 | 10,355   | Pravastatin 40 mg                            | 146                       | 28                     | No significant reduction         |     |
| CARDS                | 2004 | 2838     | Atorvastatin 10 mg                           | 118                       | 40                     | 36 ( $P = 0.001$ )               | 32  |
| MEGA                 | 2006 | 7832     | Pravastatin 10–20 mg                         | 156                       | 18                     | 33 ( $P = 0.01$ )                | 119 |
| JUPITER              | 2008 | 17,802   | Rosuvastatin 20 mg                           | 108                       | 50                     | 44 ( $P < 0.001$ )               | 25  |
| Secondary prevention |      |          |  |                           |                        |                                  |     |
| 4S                   | 1994 | 4444     | Simvastatin 20–40 mg                         | 188                       | 35                     | 34 ( $P < 0.0001$ )              | 15  |
| CARE                 | 1998 | 4159     | Pravastatin 40 mg                            | 139                       | 32                     | 24 ( $P = 0.003$ )               | 33  |
| LIPID                | 2002 | 9014     | Pravastatin 40 mg                            | 150                       | 25                     | 24 ( $P < 0.0001$ )              | 33  |
| HPS                  | 2002 | 20,536   | Simvastatin 40 mg                            | 3.4                       | 1                      | 24 ( $P < 0.001$ )               | 20  |
| PROSPER              | 2002 | 5804     | Pravastatin 40 mg                            | 147                       | 34                     | 14 ( $P = 0.014$ )               | 47  |
| PROVE-IT             | 2004 | 4162     | Atorvastatin 80 mg versus Pravastatin 40 mg  | 106                       | 41                     | 16 ( $P = 0.005$ )               | 25  |
| TNT                  | 2005 | 10,003   | Atorvastatin 80 mg versus Atorvastatin 10 mg | 97                        | 21                     | 22 ( $P < 0.001$ )               | 46  |
| IDEAL                | 2005 | 8888     | Atorvastatin 80 mg versus Simvastatin 20 mg  | 121                       | 34                     | No significant reduction         |     |

**Table 3.** Primary and secondary prevention statin trials.

The most important side effects associated with statins are hepatic injury and myopathy [64, 65]. The risk of liver injury with the use of statins appears to be dose dependent and is most likely to occur in the first 3 months. This risk was demonstrated in a meta-analysis of 35 randomized trials that showed an excess risk of 4.2 cases per 1000 patients associated with statin use [66]. Multiple mechanisms of liver injury have been demonstrated with statins including hepatocellular and cholestatic [67]. Among the different statins, the risk of liver injury appears to be similar, except with fluvastatin that has a higher risk [68]. Numerous studies have found no significant difference in elevated aminotransferases when statins were compared to placebo [25, 28, 57]. It was for this reason that the Food and Drug Administration



(FDA) revised the recommendation for liver function testing with regard to statin therapy in 2012 [69]. In the setting of rising aminotransferases three times the upper limit of normal, it is recommended to lower the statin dose or change medication.

Statin muscle injury remains the most concerning side effect, despite severe myopathy occurring in only 0.1–0.5% of patients [70, 71]. The degree of injury ranges from myalgia, myopathy, myositis, myonecrosis, to rhabdomyolysis [65]. Rhabdomyolysis, the most severe of the statin myopathy spectrum, was largely seen when statins were used with gemfibrozil or cyclosporine [72, 73]. This is thought to be related to the decrease in mevalonic acid associated with HMG-CoA reductase inhibition. Other mechanisms attributed to muscle injury include statins' effects on coenzyme Q10, also called ubiquinone, which is involved in muscle energy production [74]. Different statins possess varying risk to cause muscle injury, with fluvastatin exhibiting the lowest risk and simvastatin exhibiting a higher risk of muscle injury, especially at 80 mg/day dose, as shown in the SEARCH trial that was the basis of the FDA restriction of this dose of simvastatin [64, 70, 75]. The major predisposing factor for statin-induced myopathy injury includes hypothyroidism, obstructive liver disease, and renal failure; these contribute to both hypercholesterolemia and myopathy. Thus, it is important to test for thyroid-stimulating hormone (TSH) levels prior to starting statins [76].

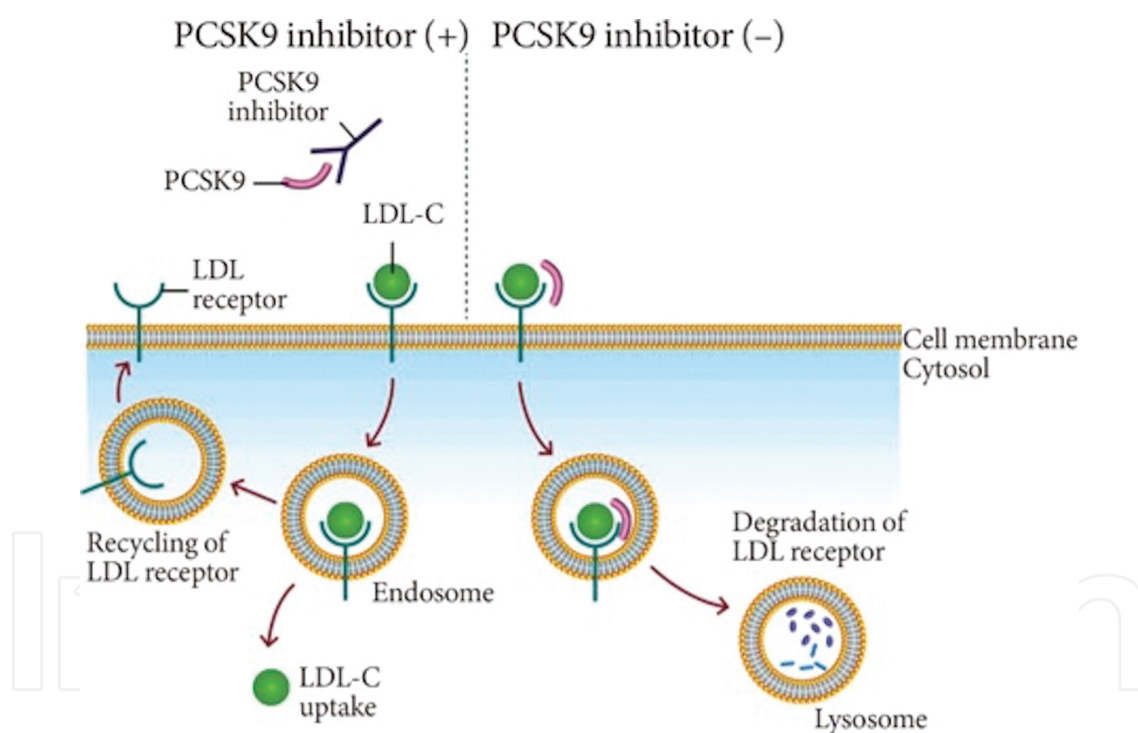
Other notable side effects include proteinuria that has been reported to the Food and Drug Administration with rosuvastatin and simvastatin, but no increased risk of renal failure has been described [77–79]. In addition, there have been several meta-analyses of randomized trials that found a small, yet increased risk of diabetes with high-dose statin therapy when compared to lower-dose statin therapies, possibly related directly to its inhibition of HMG-CoA reductase [80]. However, given that statins have been shown to reduce CV events in diabetics, these studies have suggested that the beneficial effects of statins on CV events outweigh this risk [80, 81].

Despite physicians in practice witnessing the discontinuation of statins due to “intolerance,” randomized control trials have failed to validate this finding. The difference between clinical practice and trials may relate to selection bias observed in clinical trials that limit their external validity [66, 82]. Intolerance is largely seen on the basis of muscle pain, leading to discontinuation of therapy. Another cause of intolerance is a rise in aminotransferases, which usually requires statins dose reduction, switch to another statin, or using an alternate drug. In patients, who are unable to tolerate statins, ezetimibe, fenofibrate, cholestyramine, and niacin have been recommended for those with known coronary heart disease (CHD) or at high-risk CV events (10-year risk >20%) [33]. Another option is the recently FDA-approved proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors.

## 2.2. PCSK9 inhibitors

PCSK9 is a serine protease that is mainly secreted by the liver in an inactive form, before undergoing catalytic changes in the endoplasmic reticulum. The mature PCSK9 is then released into the plasma where it has only one substrate, LDL receptors. Once in circulation, it regulates the LDL receptor recycling in the liver, intestines, pancreas, lungs, kidneys, and adipose tissue [83, 84]. PCSK9 binding to LDL receptors causes it to be internalized into

endosomal or lysosomal compartments, where they are destroyed. This leads to a decrease in LDL receptors on the surface of the cell. It has therefore been shown that serum PCSK9 levels are inversely proportional to the number of LDL receptors (see **Figure 3**) [85, 86]. Blood levels of PCSK9 are influenced by the diurnal trend in secretion (peak levels at 4 am), gender (higher in females), and fasting states (lower levels) [87, 88]. A mutation in PCSK9 was first described in French families in 2003. It is the third gene implicated in the autosomal dominant familial hypercholesterolemia (FH); the other two genes encode LDL receptor and Apo-B, a component of the LDL particle [89]. It is usually a gain-of-function mutation in PCSK9 that results in a low level of LDL receptors leading to a high level of LDL and consequently increased risk of premature CV disease [90, 91]. On the other hand, loss-of-function PCSK9 mutations result in high level of LDL receptors, and a decrease in LDL and significant reduction in CV events. Of note, the reduction of CV events observed with PCSK9 mutation is higher than that associated with statins. This difference is attributed to the persistently low LDL levels caused by the underlying genetic predisposition. This was demonstrated in the ARIC study, Copenhagen Heart Study, and the Zimbabwe population study [92–94].



**Figure 3.** Mechanisms of PCSK9 inhibitors. Secreted PCSK9 binds to LDL receptors on the cell surface and forms an endosome that undergoes lysosomal degradation. In the presence of PCSK9 inhibitors, the interaction between PCSK9 and LDL receptors is disrupted, resulting in the recycling of LDL receptors and increased hepatic uptake of LDL from the bloodstream. *Abbreviations:* LDL, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin 9.

Statins have been described to increase the concentration of PCSK9 inhibitors by 14–47% in a dose- and time-dependent fashion. This is via a decrease in endogenous cholesterol synthesis caused by statin inhibition of HMG-CoA reductase with consequent up-regulation in LDL

receptors. It has therefore been demonstrated that a PCSK9 mutation increases the response to statins [95–98]. Neutralizing antibodies to PCSK9 were first described in 2009, and in subsequent studies it was shown to decrease LDL levels by 30% in animal models [99].

Although statins are the most effective cholesterol-lowering agents for preventing CV events, there is a need for additional therapies in those patients who are (1) unable to take statins or (2) already on maximal statin doses with residual CV risk. The National Lipid Association in the US estimates that about 12% of patients discontinue statin therapy, of whom 62% experienced adverse effects [100]. These data signal the need for alternative effective agents, such as PCSK9 inhibitors, to be used with or instead of statins. As monotherapy, PCSK9 inhibitors lower LDL by up to approximately 66% [101]. In conjunction with statins, PCSK9 inhibitors reduce LDL by an additional 60% beyond statins [102]. Examples of monoclonal antibody PCSK9 inhibitors available in the market include evolocumab and alirocumab. Phase I, II, and III clinical trials have shown an additional decrease in LDL levels with the use of PCSK-9 inhibitors (monoclonal antibodies) in combination with statin therapy, as well as a significant decrease in CV events including mortality (hazard ratio (HR): 0.47–0.52) [2, 3]. Other PCSK9 inhibitors include the small interfering RNA (siRNA) molecules that block the synthesis of PCSK9 inhibitors and have been shown to decrease LDL by 40% in a phase I clinical trial when used at the highest dose compared to placebo [103].

Regarding their side effects, there were no significant differences in the incidence of adverse drug events between PCSK9 inhibitors (alirocumab, evolocumab) and placebo in the latest phase III trials, except for neurocognitive events, myalgia, injection site reactions, and ophthalmologic events [2, 3]. A major concern with PCSK9 inhibitors revolves around their cost and the very low LDL levels achieved (as low as 18 mg/dL compared to 44 mg/dL with rosuvastatin in the JUPITER study). Potential short- and long-term consequences of very low LDL levels include neurocognitive impairment, hemorrhagic stroke, hemolytic anemia, vitamin, and hormonal deficiencies [21, 104].

### **2.3. Ezetimibe**

Ezetimibe inhibits the intestinal absorption of dietary and biliary cholesterol without affecting the absorption of fat-soluble vitamins or TG [105]. This possibly occurs by the inhibition of Niemann-Pick C1-like 1 (NPC1L1) protein function that is expressed in the intestines and liver [106]. The benefits of ezetimibe were demonstrated in the IMPROVE-IT trial where the addition of ezetimibe to statin therapy led to a decrease in CV events, excluding all-cause and CV mortality [54]. Ezetimibe is helpful in avoiding high doses of statin and the associated dose-dependent statin side effects, especially in patients who do not meet cholesterol targets. It has been well tolerated with the incidence of myopathy and serum transaminase elevations being similar when compared to placebo [54].

### **2.4. Bile acid sequestrants**

Bile acid sequestrants, such as cholestyramine, colestevlam, and colestipol, lower cholesterol by binding to bile acids in the intestine preventing them from being reabsorbed [107]. The

consequent decrease in intrahepatic cholesterol leads to an increase in LDL receptors that bind LDL from plasma with consequent small increase in HDL via increased intestinal synthesis of HDL [108]. They are relatively potent and exhibit a dose-dependent response achieving 10–25% reduction in LDL, exhibiting a synergistic effect when used with statins or niacin [55, 109, 110].

Major side effects have limited its overall use. Those described include abdominal discomfort with nausea, bloating, cramping, and rise in aminotransferases. Of the bile acid sequestrants, colestevlam is the better-tolerated drug. They also interact with common CV medications (warfarin and digoxin) by binding and inhibiting their absorption. This can be avoided by administering the other medications 1 h before or 4 h after ingestion of bile acid sequestrants [107].

## 2.5. Fibrates

Fibrates include gemfibrozil and fenofibrate [111]. The mechanism of action of fibrates is via activation of transcription factor, peroxisome proliferator-activated receptors (PPARs). It decreases TG via reduction in hepatic VLDL secretion, and stimulation of lipoprotein lipase that consequently leads to increased clearance of TG-rich lipoproteins. It also raises HDL by direct stimulation of HDL Apolipoprotein A-I/A-II synthesis and increased transfer of Apo A-I from HDL to VLDL [112].

This class of drugs lowers serum TG by 35–50%, and have also been shown to increase HDL by 5–20% directly proportional to the degree of hypertriglyceridemia [113–115]. Fibrates have not demonstrated any significant effect on cardiovascular outcomes, as seen in the FIELD trial [115], except in those with high TG (>200 mg/dL) or low HDL (<40 mg/dL) and metabolic syndrome, as was seen in the BIP trial [116].

The main side effect associated with fibrates is muscle injury. Muscle injury is often seen in patients who are already on a statin, and is thought to be mediated by fibrate-related inhibition of CYP3A4 with consequent decrease in statin metabolism [117]. Fibrates have also been shown to raise serum creatinine levels, but it remains unknown if there is direct parenchymal or tubular renal injury. Nevertheless, elevated creatinine has been found to be reversible on discontinuation of the medication, as was demonstrated in the FIELD trial [118]. Another noteworthy side effect is pancreatitis, which has been seen in patients with normal TG. However, the absolute risk remains low (number needed to harm over 5 years = 935) [119].

## 2.6. Nicotinic acid (niacin)

Nicotinic acid acts by inhibiting the hepatic production of VLDL and consequently decreasing LDL. It also increases HDL by reducing lipid transfer from HDL to VLDL, thus delaying HDL clearance [120]. This class of drugs has positive effects on HDL that occurs at relatively low dosages (1–1.5 g/day result in about 33% increase in HDL). Higher nicotinic acid doses are needed to lower LDL (3 g/day results in about 23% LDL decrease) [121, 122]. This class of drugs is also associated with a significant reduction of MACE in the HATS trial and ARBITER 6-HALTS trial when niacin was added to statin therapy [123, 124]. Contrary to these studies, the

AIM-HIGH, ARBITER-2, and HPS2-THRIVE trials found no significant benefit of adding niacin to statin therapy [125–127].

Unfortunately, its use is limited by poor tolerability. The most common side effect is flushing, which occurs in the majority (up to 80%) of patients at standard recommended doses. Other notable side effects include paresthesia, pruritis, and nausea, each of which occurs in 20% of patients at standard doses [120].

### 3. Lifestyle modification

All patients with an elevated LDL should be advised to attempt and undergo for therapeutic lifestyle changes. Therapeutic lifestyle changes involve weight loss (even in those who are only slightly overweight), exercise, and improvement in diet. Numerous studies have investigated and demonstrated the benefits of lifestyle modification. In the United Kingdom Lipid Clinics Program study, 2508 subjects who underwent diet modification experienced a 5–7% reduction in serum total and LDL cholesterol [128]. In the Lifestyle Heart Trial, 53 patients were randomized to either control diet (National Cholesterol Education Program-NCEP step 2 diet) or vegetarian therapy with exercise and relaxation therapy (intervention group). After 5 years of follow-up, the intervention group demonstrated a decrease in CV events (0.89 vs 2.25 events per patient) [129]. In the Lyon Diet Heart Study, 605 patients were randomized after a first myocardial infarction to either a Mediterranean diet or a control diet. After 4 years of follow-up, the Mediterranean diet group demonstrated lower rates of death and myocardial infarction [130].

### 4. Other potential therapy options

Statins are the preferred therapy for most patients with dyslipidemia, especially those with elevated total cholesterol and LDL cholesterol. However, in patients on maximal tolerated statin dose with a persistently elevated LDL, other therapies may be considered. These include niacin, bile acid sequestrants, and ezetimibe. Not uncommonly, these additional agents may not be sufficient to “normalize” abnormal cholesterol profiles, especially in patients with severe hypercholesterolemia and familial cholesterol diseases. Therapeutic options in this group of patients, who remain “at risk” for CV events, include LDL apheresis, lomitapide, surgical options, and gene therapy. Preferably, this cohort of patients should be managed by a specialist.

#### 4.1. LDL apheresis

LDL apheresis is a procedure that involves extracorporeal removal of circulating Apo B-containing lipoprotein (e.g., LDL, VLDL, and lipoprotein-a). Regimens include weekly or biweekly depending on the rate LDL returns to baseline after therapy [131].

The National Lipid Associated Expert Panel on familial hypercholesterolemia recommended LDL apheresis in those with FH if LDL targets are not achieved with maximal tolerated medical

therapy. These targets include LDL of  $\geq 300$  mg/dL in those with functional homozygous or heterozygous FH, LDL of  $\geq 200$  mg/dL in those with functional heterozygous FH, and  $\geq 2$  risk factors or high lipoprotein-a ( $\geq 50$  mg/dL), or LDL of  $\geq 160$  mg/dL in those established CAD, CV disease, or diabetes [132]. In the absence of statin therapy, LDL apheresis lowers LDL by 50–75% acutely, by 30% after 6 months, and 38% after 18 months [133]. There are numerous studies showing benefit in outcomes such as myocardial infarction and reduction in arterial inflammation, but none have shown a survival benefit [134, 135]. Limitations to using LDL apheresis include patient burden, problems related to venous access, frequent long visits, and high costs [136].

#### **4.2. Lomitapide**

Lomitapide is a microsomal TG transfer protein inhibitor which inhibits the transfer of TG to Apo-B for the production of VLDL in the liver. However, lomitapide is metabolized by CYP3A4 and is also an inhibitor of CYP 3A4 and P-glycoprotein leading to numerous drug interactions. It was FDA approved in 2012 for use in patients with homozygous FH. It is used in addition to standard therapy, as well as other therapies such as LDL apheresis or liver transplantation. It has been shown to significantly decrease LDL (up to 50%) in a phase 3, open-label, non-randomized, dose-escalating study [137].

#### **4.3. Mipomersen**

Mipomersen is an injected antisense oligonucleotide that inhibits the production of Apo-B. Mipomersen binds to the Apo-B mRNA, affects Apo-B production, and consequently reduces the levels of LDL, VLDL, and intermediate dense lipoprotein. It has been approved by FDA in 2013 for use in homozygous FH patients; however, it is not approved in Europe. It has been shown that mipomersen can significantly decrease LDL in those patients with homozygous FH (up to 25%) [138]. Similar findings were found in studies involving other populations, including those with heterozygous FH and have CAD, statin intolerant, and at high risk of CV disease, and in those without FH who have or are at high risk of CVD [139–143].

#### **4.4. Cholesteryl ester transfer protein inhibitors**

Cholesteryl ester transfer protein (CETP) inhibitors, such as anacetrapib, have shown to significantly increase in HDL and lower LDL; however, there are no studies showing clinical benefit. In fact, in the REALIZE trial, despite a significant reduction in LDL in the intervention group compared to placebo, there was a significant increase in CV events, hence limiting its clinical use [144].

#### **4.5. Anti-resistin antibodies**

Anti-resistin antibodies inhibit resistin function, an adipokine (protein derived from adipose tissue) that is increased in obese individuals and positively correlated with atherosclerosis. In *in vitro* studies, resistin can decrease LDL receptor expression and increase PCSK9 expression.

By using anti-resistin antibodies, studies have shown an increase in LDL receptors in obese individuals [145].

#### **4.6. Small molecule regulator of lipid metabolism**

ETC-1002 is a small molecule regulator of carbohydrate and lipid metabolism. In a study of 177 subjects with LDL between 130 and 220 mg/dL not on statin therapy, patients were randomized to ETC-1002 (one of three different doses) or placebo. After 12 weeks of follow-up, treated subjects at the highest dose demonstrated a 27% decrease in LDL. There were no changes in TG or HDL. ETC-1002 also demonstrated a limited side effect profile [146, 147].

#### **4.7. Recombinant Apo-A-I milano**

Apo-A-I milano is a variant of the Apolipoprotein A-I (Apo-A-I). This variant leads to rapid mobilization of cholesterol with rapid regression of atherosclerosis. Subjects with Apo-A-I Milano have very low levels of HDL (10–30 mg/dL), longer survival, and reduced atherosclerosis compared to what is expected for their HDL levels [148]. Infusion of recombinant Apo-A-I milano (ETC-216) in an RCT was shown to lead to a significant regression of coronary atherosclerosis [149].

#### **4.8. Lipoprotein-associated phospholipase A<sub>2</sub>**

Lipoprotein-associated phospholipase A<sub>2</sub> is also known as platelet-activating factor acetylhydrolase. It is a protein with pro-inflammatory properties that co-travels with circulating LDL particles and is found abundantly in atherosclerotic plaques [150]. Lipoprotein-associated phospholipase A<sub>2</sub> has been shown in a meta-analysis to significantly increase CHD and is an independent predictor of CHD and ischemic stroke [151]. However, in a large phase III randomized control trial (STABILITY trial), the lipoprotein-associated phospholipase A<sub>2</sub> inhibitor, darapladib, failed to show any CV benefit [152].

## **5. Conclusion**

Over the last several years, the role of cholesterol-lowering agents in reducing cardiovascular disease and mortality has been further established. Statin therapy remains the cornerstone of lipid-lowering therapy; however, in patients already on maximal dose of statins or intolerant to statins with residual CV risk, other options are also available. As evidenced by the recent bench to bedside development of a new drug class (PCSK9), the emergence of drugs to specifically target a population, in this case, familial hypercholesterolemia, the national call for precision medicine is on the horizon. By continuing to scientifically probe biologic mechanisms in preclinical models related to cholesterol perturbation, drug development and translation to human clinical studies marks a bright and promising future.

## Conflicts of interest

None.

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