Chapter 5

Cholesterol-Lowering Drugs and Therapies in Cardiovascular Disease

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Additional information is available at the end of the chapter

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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

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

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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 pleotropic 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 ≥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].

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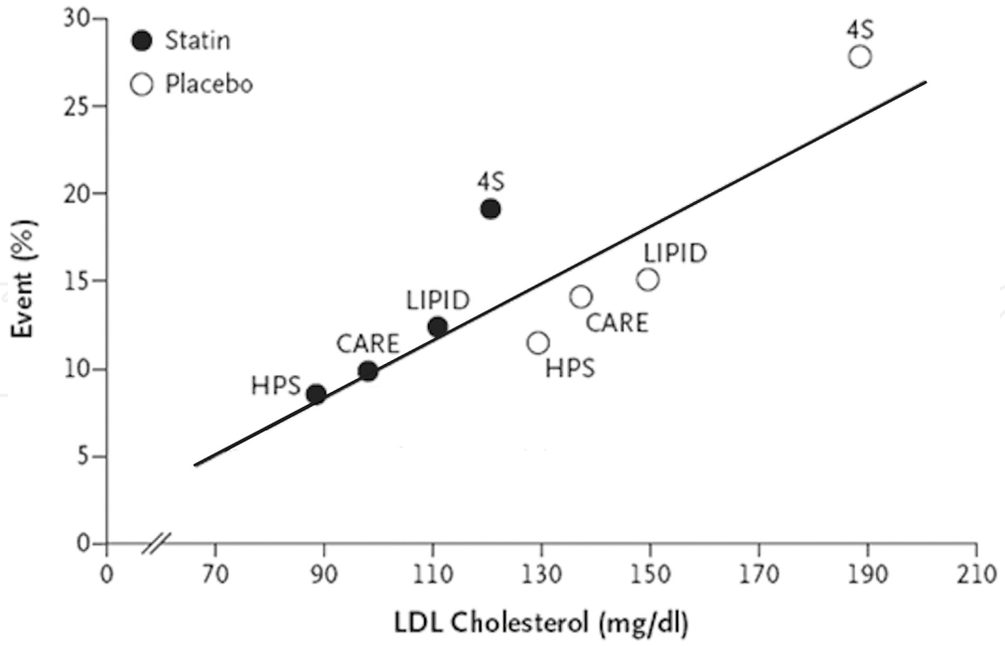

Figure 1. LDL, statins, and cardiovascular events. Reduction in cardiovascular event rates by lower low-density lipoprotein using statins in secondary prevention trials. *Abbreviations*: 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events Trial; HPS, Heart Protection Study;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

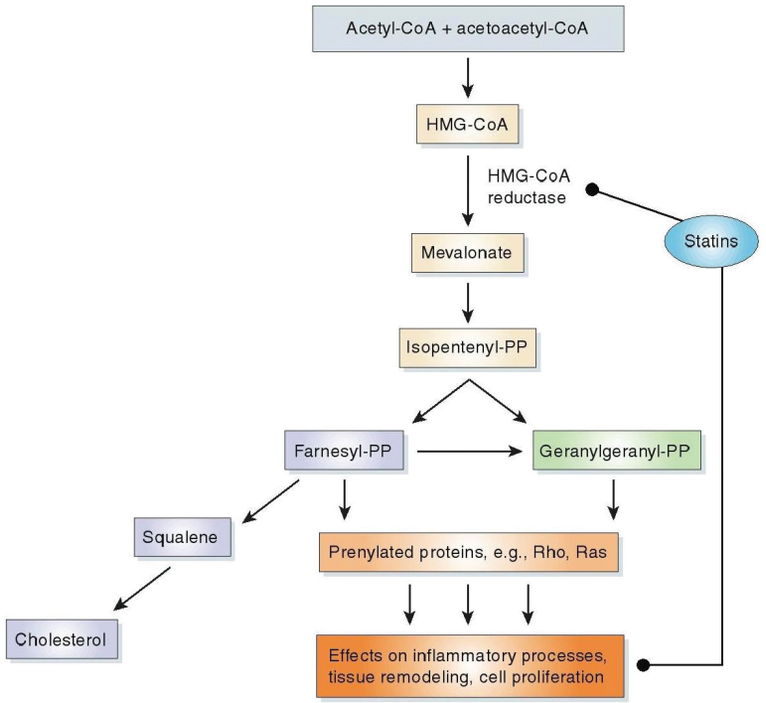

Figure 2. Mechanisms of HMG-CoA reductase inhibitors. Statins inhibit hepatic HMG-CoA reductase resulting in decreased downstream cholesterol production.

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

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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

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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].

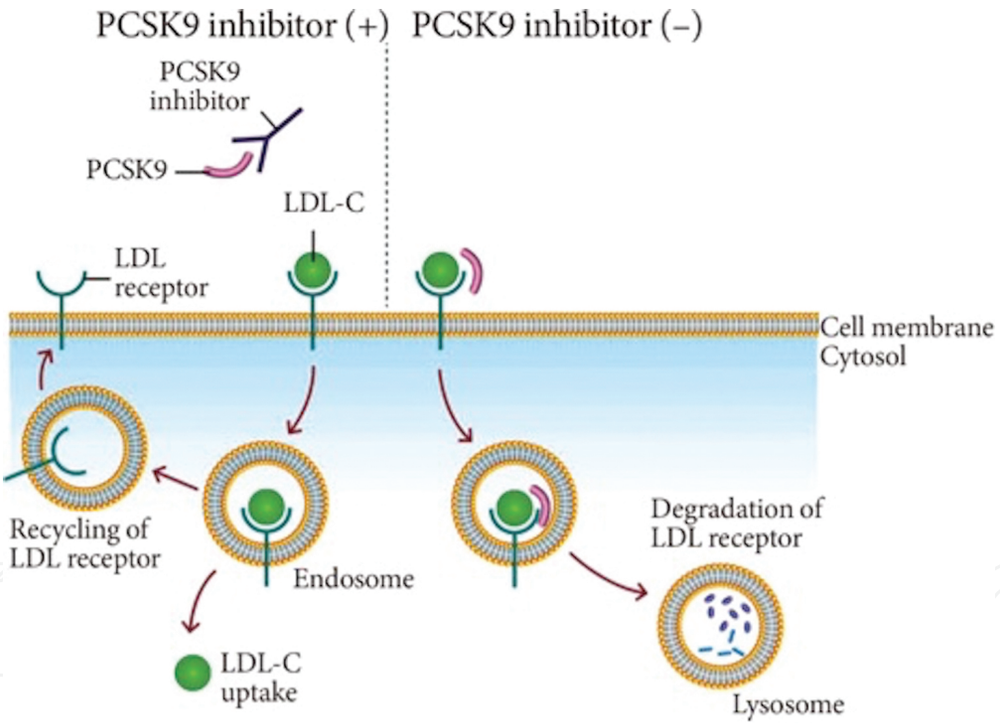

Figure 3. Mechanisms of PCSK9 inhibitors. Secreted PCSK9 binds to LDL receptors on the cell surface and forms an endosome that undergoes lysosomal degradation. In the presence of PCSK9 inhibitors, the interaction between PCSK9 and LDL receptors is disrupted, resulting in the recycling of LDL receptors 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, colesevelam, and colestipol, lower cholesterol by binding to bile acids in the intestine preventing them from being reabsorbed [107]. The

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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, colesevelam 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

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therapy. These targets include LDL of ≥300 mg/dL in those with functional homozygous or heterozygous FH, LDL of ≥200 mg/dL in those with functional heterozygous FH, and ≥2 risk factors or high lipoprotein-a (≥50 mg/dL), or LDL of ≥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_2

Lipoprotein-associated phospholipase A_2 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_2 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_2 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.

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Conflicts of interest

None.

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References

[1] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6.

[2] Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):1500–9.

[3] Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):1489–99.

[4] Expert Panel on Detection E. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486.

[5] Salonen R, Nyyssönen K, Porkkala-Sarataho E, Salonen JT. The Kuopio Atherosclerosis Prevention Study (KAPS): effect of pravastatin treatment on lipids, oxidation resistance of lipoproteins, and atherosclerotic progression. Am J Cardiol. 1995;76(9):34C–9C.

[6] Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). Circulation. 1995;91(10):2528–40.

[7] Schartl M, Bocksch W, Koschyk DH, Voelker W, Karsch KR, Kreuzer J, et al. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering

therapy on plaque volume and composition in patients with coronary artery disease. Circulation. 2001;104(4):387–92.

[8] Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004;291(9):1071–80.

[9] Lee JM, Robson MD, Yu LM, Shirodaria CC, Cunnington C, Kylintireas I, et al. Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function: a randomized, placebo-controlled, magnetic resonance imaging study. J Am Coll Cardiol. 2009;54(19):1787–94.

[10] Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581–90.

[11] Genest J. Lipoprotein disorders and cardiovascular risk. J Inherit Metab Dis. 2003;26(2–3):267–87.

[12] Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009;29(4):431–8.

[13] Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med. 1990;322(24):1700–7.

[14] Collaboration PS. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. Lancet. 2007;370(9602):1829–39.

[15] Pencina MJ, Navar-Boggan AM, D'Agostino RB, Sr., Williams K, Neely B, Sniderman AD, et al. Application of new cholesterol guidelines to a population-based sample. N Engl J Med. 2014;370(15):1422–31.

[16] Panel NCEPNE. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143.

[17] Hayward RA, Krumholz HM. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. Circ Cardiovasc Qual Outcomes. 2012;5(1):2–5.

[18] Ray KK, Kastelein JJ, Boekholdt SM, Nicholls SJ, Khaw KT, Ballantyne CM, et al. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. Eur Heart J. 2014;35(15):960–8.

[19] Bu DX, Griffin G, Lichtman AH. Mechanisms for the anti-inflammatory effects of statins. Curr Opin Lipidol. 2011;22(3):165–70.

[20] Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010;152(8):488–96, W174.

[21] Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol< 50 mg/dl with rosuvastatin: the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol. 2011;57(16):1666–75.

[22] Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005;352(1):29–38.

[23] Puri R, Nissen SE, Libby P, Shao M, Ballantyne CM, Barter PJ, et al. C-reactive protein, but not low-density lipoprotein cholesterol levels, associate with coronary atheroma regression and cardiovascular events following maximally intensive statin therapy. Circulation. 2013:CIRCULATIONAHA. 113.004243.

[24] Varbo A, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. Circulation. 2013;128(12):1298–309.

[25] Collins R, Armitage J, Parish S, Sleight P, Peto R, Collaboration HPS. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo controlled trial. Lancet. 2002;360(9326):7–22.

[26] Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685–96.

[27] Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368(9542):1155–63.

[28] Group SSSS. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383–9.

[29] Marschner IC, Colquhoun D, Simes RJ, Glasziou P, Harris P, Singh BB, et al. Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. LIPID Study Investigators. J Am Coll Cardiol. 2001;38(1):56–63.

[30] Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285(13):1711–8.

[31] LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA. 1999;282(24):2340–6.

[32] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495–504.

[33] Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. Ann Intern Med. 2015;163(1):40–51.

[34] D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care the Framingham Heart Study. Circulation. 2008;117(6):743–53.

[35] Muntner P, Colantonio LD, Cushman M, Goff DC, Jr., Howard G, Howard VJ, et al. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. JAMA. 2014;311(14):1406–15.

[36] Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014;100(Suppl 2):ii1–67.

[37] Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study G. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond). 2001;101(6):671–9.

[38] Pandya A, Sy S, Cho S, Weinstein MC, Gaziano TA. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. JAMA. 2015;314(2):142–50.

[39] Grundy SM, Cleeman JI, Rifkind BM, Kuller LH. Cholesterol lowering in the elderly population. Coordinating Committee of the National Cholesterol Education Program. Arch Intern Med. 1999;159(15):1670–8.

[40] Miettinen TA, Pyorala K, Olsson AG, Musliner TA, Cook TJ, Faergeman O, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation. 1997;96(12):4211–8.

[41] LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352(14):1425–35.

[42] Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science. 2001;292(5519):1160–4.

[43] Haslinger-Löffler B. Multiple effects of HMG-CoA reductase inhibitors (statins) besides their lipid-lowering function. Kidney Int. 2008;74(5):553–5.

[44] Ness GC, Zhao Z, Lopez D. Inhibitors of cholesterol biosynthesis increase hepatic low-density lipoprotein receptor protein degradation. Arch Biochem Biophys. 1996;325(2): 242–8.

[45] Ness GC, Chambers CM, Lopez D. Atorvastatin action involves diminished recovery of hepatic HMG-CoA reductase activity. J Lipid Res. 1998;39(1):75–84.

[46] Arad Y, Ramakrishnan R, Ginsberg HN. Lovastatin therapy reduces low density lipoprotein ApoB levels in subjects with combined hyperlipidemia by reducing the production of ApoB-containing lipoproteins: implications for the pathophysiology of ApoB production. J Lipid Res. 1990;31(4):567–82.

[47] Niesor EJ, Schwartz GG, Perez A, Stauffer A, Durrwell A, Bucklar-Suchankova G, et al. Statin-induced decrease in ATP-binding cassette transporter A1 expression via microRNA33 induction may counteract cholesterol efflux to high-density lipoprotein. Cardiovasc Drugs Ther. 2015;29(1):7–14.

[48] Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation. 2004;109(23 Suppl 1):III27–32.

[49] Rosenson RS, Otvos JD, Hsia J. Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome: a randomized, double-blind, controlled study. Diabetes Care. 2009;32(6):1087–91.

[50] Otvos JD, Shalaurova I, Freedman DS, Rosenson RS. Effects of pravastatin treatment on lipoprotein subclass profiles and particle size in the PLAC-I trial. Atherosclerosis. 2002;160(1):41–8.

[51] Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol. 2003;92(2):152–60.

[52] Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). Am J Cardiol. 1998;81(5): 582–7.

[53] Stender S, Budinski D, Gosho M, Hounslow N. Pitavastatin shows greater lipid-lowering efficacy over 12 weeks than pravastatin in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia. Eur J Preventive Cardiol. 2013;20(1):40–53.

[54] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25): 2387–97.

[55] Knopp RH, Brown WV, Corder CN, Dobs AS, Dujovne CA, Goldberg AC, et al. Comparative efficacy and safety of pravastatin and cholestyramine alone and combined in patients with hypercholesterolemia. Arch Int Med. 1993;153(11): 1321–9.

[56] Salonen R, Nyyssonen K, Porkkala E, Rummukainen J, Belder R, Park JS, et al. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. Circulation. 1995;92(7):1758–64.

[57] Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279(20):1615–22.

[58] Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005;294(19):2437–45.

[59] Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360(9346):1623–30.

[60] Group WS. Baseline characteristics and screening experience in the West of Scotland Coronary Prevention Study. Am J Cardiol. 1995;76:485–91.

[61] Furberg CD, Wright JT, Davis BR, Cutler JA, Alderman M, Black H, et al. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care—the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA—J Am Med Assoc. 2002;288(23):2998–3007.

[62] Lewis SJ, Moye LA, Sacks FM, Johnstone DE, Timmis G, Mitchell J, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. Ann Intern Med. 1998;129(9):681–9.

[63] Group LS. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. The Lancet. 2002;359(9315):1379–87.

[64] Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36(17):1012–22.

[65] Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert P. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol. 2014;8(3 Suppl):S58–71.

[66] Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006;114(25):2788–97.

[67] Russo MW, Hoofnagle JH, Gu J, Fontana RJ, Barnhart H, Kleiner DE, et al. Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network. Hepatology. 2014;60(2):679–86.

[68] Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010;340:c2197.

[69] Marcum ZA, Vande Griend JP, Linnebur SA. FDA drug safety communications: a narrative review and clinical considerations for older adults. Am J Geriatr Pharmacother. 2012;10(4):264–71.

[70] Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004;292(21):2585–90.

[71] Dujovne CA, Chremos AN, Pool JL, Schnaper H, Bradford RH, Shear CL, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results: IV. Additional perspectives on the tolerability of lovastatin. Am J Med. 1991;91(1B):25S–30S.

[72] Norman DJ, Illingworth DR, Munson J, Hosenpud J. Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. N Engl J Med. 1988;318(1):46–7.

[73] Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA. 1990;264(1):71–5.

[74] Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Arch Neurol. 2004;61(6):889–92.

[75] Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet. 2010;376(9753):1658–69.

[76] Bar SL, Holmes DT, Frohlich J. Asymptomatic hypothyroidism and statin-induced myopathy. Can Fam Phys. 2007;53(3):428–31.

[77] Howard W. The issue of statin safety: where do we stand? Grundy SM (University of Texas Southwestern Med Ctr, Dallas) Circulation 111:301 (6–9), 2005. Year Book Endocrinol. 2006;2006:126–7.

[78] Jacobson TA. Statin safety: lessons from new drug applications for marketed statins. Am J Cardiol. 2006;97(8A):44C–51C.

[79] Alsheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. Circulation. 2005;111(23):3051–7.

[80] Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, et al. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. Lancet. 2015;385(9965):351–61.

[81] Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305(24):2556–64.

[82] Armitage J. The safety of statins in clinical practice. Lancet. 2007;370(9601):1781–90.

[83] Benjannet S, Rhainds D, Essalmani R, Mayne J, Wickham L, Jin W, et al. NARC-1/PCSK9 and its natural mutants: zymogen cleavage and effects on the low density lipoprotein (LDL) receptor and LDL cholesterol. J Biol Chem. 2004;279(47):48865–75.

[84] Seidah NG, Benjannet S, Wickham L, Marcinkiewicz J, Jasmin SB, Stifani S, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. Proc Natl Acad Sci USA. 2003;100(3):928–33.

[85] Alborn WE, Cao G, Careskey HE, Qian YW, Subramaniam DR, Davies J, et al. Serum proprotein convertase subtilisin kexin type 9 is correlated directly with serum LDL cholesterol. Clin Chem. 2007;53(10):1814–9.

[86] Ahn CH, Choi SH. New drugs for treating dyslipidemia: beyond statins. Diabetes Metab J. 2015;39(2):87–94.

[87] Cui Q, Ju X, Yang T, Zhang M, Tang W, Chen Q, et al. Serum PCSK9 is associated with multiple metabolic factors in a large Han Chinese population. Atherosclerosis. 2010;213(2):632–6.

[88] Persson L, Cao G, Stahle L, Sjoberg BG, Troutt JS, Konrad RJ, et al. Circulating proprotein convertase subtilisin kexin type 9 has a diurnal rhythm synchronous with cholesterol synthesis and is reduced by fasting in humans. Arterioscler Thromb Vasc Biol. 2010;30(12):2666–72.

[89] Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34(2):154–6.

[90] Maxwell KN, Breslow JL. Proprotein convertase subtilisin kexin 9: the third locus implicated in autosomal dominant hypercholesterolemia. Curr Opin Lipidol. 2005;16(2):167–72.

[91] Humphries SE, Whittall RA, Hubbart CS, Maplebeck S, Cooper JA, Soutar AK, et al. Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. J Med Genet. 2006;43(12):943–9.

[92] Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354(12):1264–72.

[93] Benn M, Nordestgaard BG, Grande P, Schnohr P, Tybjaerg-Hansen A. PCSK9 R46L, low-density lipoprotein cholesterol levels, and risk of ischemic heart disease: 3 independent studies and meta-analyses. J Am Coll Cardiol. 2010;55(25):2833–42.

[94] Hooper AJ, Marais AD, Tanyanyiwa DM, Burnett JR. The C679X mutation in PCSK9 is present and lowers blood cholesterol in a Southern African population. Atherosclerosis. 2007;193(2):445–8.

[95] Brown MS, Goldstein JL. A proteolytic pathway that controls the cholesterol content of membranes, cells, and blood. Proc Natl Acad Sci USA. 1999;96(20):11041–8.

[96] Dubuc G, Chamberland A, Wassef H, Davignon J, Seidah NG, Bernier L, et al. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis-regulated convertase-1 implicated in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2004;24(8):1454–9.

[97] Nohturfft A, DeBose-Boyd RA, Scheek S, Goldstein JL, Brown MS. Sterols regulate cycling of SREBP cleavage-activating protein (SCAP) between endoplasmic reticulum and Golgi. Proc Natl Acad Sci USA. 1999;96(20):11235–40.

[98] Berge KE, Ose L, Leren TP. Missense mutations in the PCSK9 gene are associated with hypocholesterolemia and possibly increased response to statin therapy. Arterioscler Thromb Vasc Biol. 2006;26(5):1094–100.

[99] Chan JC, Piper DE, Cao Q, Liu D, King C, Wang W, et al. A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. Proc Natl Acad Sci USA. 2009;106(24):9820–5.

[100] Toth PP, Harper CR, Jacobson TA. Clinical characterization and molecular mechanisms of statin myopathy. Expert Rev Cardiovasc Ther. 2008;6(7):955–69.

[101] Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385(9965):331–40.

[102] Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012;367(20):1891–900.

[103] Fitzgerald K, Frank-Kamenetsky M, Shulga-Morskaya S, Liebow A, Bettencourt BR, Sutherland JE, et al. Effect of an RNA interference drug on the synthesis of proprotein

convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial. Lancet. 2014;383(9911):60–8.

[104] LaRosa JC, Pedersen TR, Somaratne R, Wasserman SM. Safety and effect of very low levels of low-density lipoprotein cholesterol on cardiovascular events. Am J Cardiol. 2013;111(8):1221–9.

[105] Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation. 2002;106(15):1943–8.

[106] Altmann SW, Davis HR, Jr., Zhu LJ, Yao X, Hoos LM, Tetzloff G, et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science. 2004;303(5661): 1201–4.

[107] Davidson MH, Dillon MA, Gordon B, Jones P, Samuels J, Weiss S, et al. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. Arch Intern Med. 1999;159(16):1893–900.

[108] Shepherd J, Packard CJ, Morgan HG, Third JL, Stewart JM, Lawrie TD. The effects of cholestyramine on high density lipoprotein metabolism. Atherosclerosis. 1979;33(4): 433–44.

[109] Insull W, Toth P, Mullican W, Hunninghake D, Burke S, Donovan JM, et al., editors. Effectiveness of colesevelam hydrochloride in decreasing LDL cholesterol in patients with primary hypercholesterolemia: a 24-week randomized controlled trial. Mayo Clinic Proceedings; 2001: Elsevier.

[110] Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of Apolipoprotein B. N Engl J Med. 1990;323(19):1289–98.

[111] Oliver MF, Heady JA, Morris JN, Cooper MJ. Who cooperative trial on primary prevention of ischemic-heart-disease with clofibrate to lower serum-cholesterol—final mortality follow-up. Lancet. 1984;2(8403):600–4.

[112] Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation. 1998;98(19): 2088–93.

[113] Birjmohun RS, Hutten BA, Kastelein JJ, Stroes ES. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2005;45(2):185–97.

[114] Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999;341(6):410–8.

[115] Investigators FS. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. The Lancet. 2005;366(9500):1849–61.

[116] Group BS. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease the bezafibrate infarction prevention (BIP) study. Circulation. 2000;102(1):21–7.

[117] Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, Didangelos TP, Carina MV, Kranitsas DF, et al. Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia. Am J Cardiol. 1997;80(5): 608–13.

[118] Davis TM, Ting R, Best JD, Donoghoe MW, Drury PL, Sullivan DR, et al. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the fenofibrate intervention and event lowering in diabetes (FIELD) study. Diabetologia. 2011;54(2): 280–90.

[119] Preiss D, Tikkanen MJ, Welsh P, Ford I, Lovato LC, Elam MB, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA. 2012;308(8):804–11.

[120] Illingworth DR, Stein EA, Mitchel YB, Dujovne CA, Frost PH, Knopp RH, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia. A prospective trial. Arch Intern Med. 1994;154(14):1586–95.

[121] Probstfield JL, Hunninghake DB. Nicotinic-acid as a lipoprotein-altering agent—therapy directed by the primary physician. Arch Int Med. 1994;154(14):1557–9.

[122] Grundy SM, Mok HY, Zech L, Berman M. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. J Lipid Res. 1981;22(1):24–36.

[123] Zhao XQ, Morse JS, Dowdy AA, Heise N, DeAngelis D, Frohlich J, et al. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). Am J Cardiol. 2004;93(3):307–12.

[124] Villines TC, Stanek EJ, Devine PJ, Turco M, Miller M, Weissman NJ, et al. The ARBITER 6-HALTS Trial (arterial biology for the investigation of the treatment effects of reducing cholesterol 6-HDL and LDL treatment strategies in atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration. J Am Coll Cardiol. 2010;55(24):2721–6.

[125] Investigators A-H, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255–67.

[126] Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER) 2: a double-blind,

placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004;110(23):3512–7.

[127] Group H-TC. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371(3):203.

[128] Butowski PF, Winder AF. Usual care dietary practice, achievement and implications for medication in the management of hypercholesterolaemia. Data from the U.K. Lipid Clinics Programme. Eur Heart J. 1998;19(9):1328–33.

[129] Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA. 1998;280(23):2001–7.

[130] Michel de Lorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction. Heart Failure. 1999;11(6): 779–785.

[131] Thompson GR, Catapano A, Saheb S, Atassi-Dumont M, Barbir M, Eriksson M, et al. Severe hypercholesterolaemia: therapeutic goals and eligibility criteria for LDL apheresis in Europe. Curr Opin Lipidol. 2010;21(6):492–8.

[132] Ito MK, McGowan MP, Moriarty PM, National Lipid Association Expert Panel on Familial H. Management of familial hypercholesterolemias in adult patients: recommendations from the National Lipid Association Expert Panel on familial hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S38–45.

[133] Hemphill LC. Familial hypercholesterolemia: current treatment options and patient selection for low-density lipoprotein apheresis. J Clin Lipidol. 2010;4(5):346–9.

[134] Mabuchi H, Koizumi J, Shimizu M, Kajinami K, Miyamoto S, Ueda K, et al. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group. Am J Cardiol. 1998;82(12):1489–95.

[135] van Wijk DF, Sjouke B, Figueroa A, Emami H, van der Valk FM, MacNabb MH, et al. Nonpharmacological lipoprotein apheresis reduces arterial inflammation in familial hypercholesterolemia. J Am Coll Cardiol. 2014;64(14):1418–26.

[136] Stefanutti C, Vivenzio A, Di Giacomo S, Mazzarella B, Bosco G, Berni A. Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis. Transfusion. 2009;49(7):1461–70.

[137] Cuchel M, Meagher EA, du Toit Theron H, Blom DJ, Marais AD, Hegele RA, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381(9860):40–6.

[138] Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, Cromwell WC, et al. Mipomersen, an Apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations

in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375(9719):998–1006.

[139] Kastelein JJ, Wedel MK, Baker BF, Su J, Bradley JD, Yu RZ, et al. Potent reduction of Apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of Apolipoprotein B. Circulation. 2006;114(16):1729–35.

[140] Akdim F, Stroes ES, Sijbrands EJ, Tribble DL, Trip MD, Jukema JW, et al. Efficacy and safety of mipomersen, an antisense inhibitor of Apolipoprotein B, in hypercholesterolemic subjects receiving stable statin therapy. J Am Coll Cardiol. 2010;55(15):1611–8.

[141] Stein EA, Dufour R, Gagne C, Gaudet D, East C, Donovan JM, et al. Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation. 2012;126(19):2283–92. doi: 10.1161/CIRCULATIONAHA.112.104125.

[142] Visser ME, Wagener G, Baker BF, Geary RS, Donovan JM, Beuers UH, et al. Mipomersen, an Apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. Eur Heart J. 2012;33(9):1142–9.

[143] Thomas GS, Cromwell WC, Ali S, Chin W, Flaim JD, Davidson M. Mipomersen, an Apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2013;62(23):2178–84.

[144] Kastelein JJP, Besseling J, Shah S, Bergeron J, Langslet G, Hovingh GK, et al. Anacetrapib as lipid-modifying therapy in patients with heterozygous familial hypercholesterolaemia (REALIZE): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet. 2015;385(9983):2153–61.

[145] Tavori H, Fan D, Blakemore JL, Yancey PG, Ding L, Linton MF, et al. Serum proprotein convertase subtilisin/kexin type 9 and cell surface low-density lipoprotein receptor: evidence for a reciprocal regulation. Circulation. 2013;127(24):2403–13.

[146] Pinkosky SL, Filippov S, Srivastava RA, Hanselman JC, Bradshaw CD, Hurley TR, et al. AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. J Lipid Res. 2013;54(1):134–51.

[147] Ballantyne CM, Davidson MH, Macdougall DE, Bays HE, Dicarlo LA, Rosenberg NL, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. J Am Coll Cardiol. 2013;62(13):1154–62.

[148] Sirtori CR, Calabresi L, Franceschini G, Baldassarre D, Amato M, Johansson J, et al. Cardiovascular status of carriers of the Apolipoprotein A-I milano mutant. The Limone sul Garda Study. Circulation. 2001;103(15):1949–54.

[149] Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA. 2003;290(17):2292–300.

[150] Karabina SA, Ninio E. Plasma PAF-acetylhydrolase: an unfulfilled promise? Biochim Biophys Acta. 2006;1761(11):1351–8.

[151] Collaboration L-PS. Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, Kaptoge S, et al. Lipoprotein-associated phospholipase A2 and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet. 2010;375(9725): 1536–44.

[152] Investigators S, White HD, Held C, Stewart R, Tarka E, Brown R, et al. Darapladib for preventing ischemic events in stable coronary heart disease. N Engl J Med. 2014;370(18): 1702–11.