

Unmet Needs in LDL-C Lowering: When Statins Won't Do!

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Abstract The use of low-density lipoprotein cholesterol (LDL-C)-lowering medications has led to a significant reduction of cardiovascular risk in both primary and secondary prevention. Statin therapy, one of the cornerstones for the prevention and treatment of cardiovascular disease (CVD), has been demonstrated to be effective in lowering LDL-C levels and in reducing the risk for CVD and is generally well-tolerated. However, compliance with statins remains suboptimal. One of the main reasons is limitations by adverse events, notably myopathies, which can lead to non-compliance with the prescribed statin regimen. Reducing the burden of elevated LDL-C levels is critical in patients with CVD as well as in patients with very high baseline levels of LDL-C (e.g. patients with familial hypercholesterolaemia), as statin therapy is insufficient for optimally reducing LDL-C below target values. In this review, we discuss alternative treatment options after maximally

tolerated doses of statin therapy, including ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and cholesteryl ester transfer protein (CETP) inhibitors. Difficult-to-treat patients may benefit from combination therapy with ezetimibe or a PCSK9 inhibitor (evolocumab or alirocumab, which are now available). Updates of treatment guidelines are needed to guide the management of patients who will best benefit from these new treatments.

Key Points

Although statins have proven to be a valuable and efficacious low-density lipoprotein cholesterol (LDL-C)-lowering medication, they may not be sufficient or appropriate for every patient in need.

Some patients may benefit from additional or alternative approaches for LDL-C lowering, particularly those with familial hypercholesterolaemia and other patients in whom LDL-C lowering is not sufficient or who are intolerant to statins.

Alternative therapies should be considered for patients who do not reach their LDL-C target, for example, ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

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1 Introduction

Cardiovascular disease (CVD) is the main cause of death in Europe, accounting for over 4 million deaths each year [1]. Nearly half (47 %) of all deaths are from CVD (52 % of

deaths in women and 42 % in men). Just under half of all deaths from CVD in both men and women are from coronary heart disease (CHD), while stroke accounts for nearly one-third of deaths in women and one-quarter of deaths in men [1]. CVD has major economic and human costs: overall, it is estimated to cost the EU economy almost €196 billion a year. Of the total cost of CVD in the EU, around 54 % is due to direct healthcare costs, 24 % to productivity losses, and 22 % to the informal care of people with CVD [1].

The role of low-density lipoprotein cholesterol (LDL-C) in the pathophysiology of CVD is acknowledged and well-understood, and the use of LDL-C-lowering medications has led to a significant reduction of cardiovascular risk in both primary and secondary prevention. Notably, statin therapy has become a cornerstone for the prevention and treatment of CVD, and is generally safe and well-tolerated [2]. A number of large-scale clinical trials have demonstrated that statins substantially reduce cardiovascular morbidity and mortality in both primary and secondary prevention [3–7] and in high-risk patients [8]. Statins have also been shown to slow the progression or even promote regression of coronary atherosclerosis [9].

However, compliance remains suboptimal, even though long-term persistence with statin therapy is important for clinical benefits [10]. Moreover, in many patients, treatment with statin therapy is insufficient to optimally reduce LDL-C below target values. The most important reasons are very high baseline levels of LDL-C, for example in patients with familial hypercholesterolaemia (FH), and that the adverse effects of statin therapy can pose limitations, notably myopathies, which can lead to non-compliance with the prescribed statin regimen. Reducing the burden of elevated LDL-C levels is critical in these difficult-to-treat patient groups and there is a need for new treatment options and/or combination therapies that ultimately translate into improved clinical outcomes.

2 Treatment Aims and Low-Density Lipoprotein Cholesterol (LDL-C) Targets

LDL-C is the primary target of dyslipidemia management; it is tightly linked to outcomes and is therefore a reliable and widely used surrogate parameter. The 2010 Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis, which included 21 randomized trials of statin versus control in almost 130,000 patients and five trials of more versus less intensive statin regimens in almost 40,000 patients, confirmed a dose-dependent reduction in CVD with LDL-C lowering [3]. Among available statin therapies, more intensive regimens resulted in a significant further proportional 15 % risk reduction in major vascular events

associated with the mean 0.51 mmol/l further LDL-C reduction. In the meta-analysis of statin versus control, there was a significant risk reduction of 22 % with a 1.00 mmol/l LDL-C reduction. The most recent CTT meta-analysis, which focused on whether statin therapy is as effective in women as in men, found similar effectiveness for the prevention of major vascular events in both groups [5].

Target levels of LDL-C are defined by the patient's cardiovascular risk. All current guidelines on the prevention of CVD in clinical practice recommend the assessment of clinically manifest atherosclerotic CVD and cardiovascular risk because, in most people, atherosclerotic CVD is the product of a number of risk factors [2]. In primary prevention, many risk assessment systems are available, including Framingham, Systemic Coronary Risk Estimation (SCORE), Q-Risk, Prospective Cardiovascular Munster Study (PROCAM), the American Heart Association (AHA)/American College of Cardiology (ACC) Pooled Cohort Equations, and the World Health Organization (WHO) [11–13]. Most guidelines use risk estimation systems based on either the Framingham or the SCORE projects [2, 14, 15]. The SCORE system estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death. According to the European guidelines [2], the presence of atherosclerotic CVD, e.g. a history of acute myocardial infarction or stroke (i.e. secondary prevention), defines an LDL-C target <1.8 mmol/l (70 mg/dl). In primary prevention of patients with diabetes mellitus (T2DM), FH, or multiple risk factors leading to the estimation of high cardiovascular risk, an LDL-C level <2.6 mmol/l (100 mg/dl) should be targeted. If these absolute treatment goals are not reached, LDL-C levels should be at least halved.

The recent American guidelines (AHA/ACC 2013) no longer foresee any absolute target levels of LDL-C, but recommend using high-intensity statin treatment to reduce LDL-C levels by ≥ 50 % in patients with manifest atherosclerotic disease or high estimated risk, and to reduce LDL-C levels by 30–50 % in patients with moderate risk. Their new Pooled Cohort Equations risk calculator results in a larger population qualifying for treatment with statins, which has been a matter of debate [16, 17]. If more patients commence statin therapy because of an overestimated risk, this might be a reason for more cases of statin non-adherence due to treatment-related adverse effects [18].

3 Statin Non-Adherence and Intolerance

Despite the evidence that low adherence to statins is linked with worsening outcomes [19–21], numerous studies have documented high rates of non-adherence to statins [22, 23].

It is estimated that about half of patients discontinue statin therapy within the first year of treatment, with further decreases in adherence over time [24]. There are many reasons for non-adherence, including age, sex, income, comorbidities, and complexity of regimen [24]. Using clinical judgment alone, physicians are poor at identifying which patients have problems with adherence [25]. From a patient perspective, concerns about the adverse effects of statins are a dominant theme [26, 27]. Statin-related adverse effects include mainly muscle symptoms, but also headache, sleep disorders, dyspepsia, nausea, rash, alopecia, erectile dysfunction, gynecomastia, and/or arthritis [28]. Statin use has also been associated with an increased risk of T2DM [29–31]. Additionally, disparities in lipid control among patients with T2DM using statins have been reported [32]. Data reported from the PINNACLE registry showed that patients with T2DM were less likely to achieve LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) goals than other patients with dyslipidemia. Goals were not achieved for nearly 70 % of patients [33].

Most common adverse effects associated with statins are muscle related [28], and the most recent statement from the European Atherosclerosis Society (EAS) uses the term statin-associated muscle symptoms (SAMS) [34]. SAMS are one of the principal reasons for statin non-adherence and/or discontinuation, contributing to adverse cardiovascular outcomes [34].

The clinical features of SAMS include symptoms such as muscle aches or myalgia, weakness, stiffness, and cramps [35]. SAMS are usually defined as diffuse muscle symptoms that may or may not be accompanied by an elevation of plasma creatinine kinase (CK) activity [35, 36]. Rhabdomyolysis is a more severe form of statin-induced myopathy (usually associated with CK elevations >10 times the upper limit of normal [ULN]), resulting in severe skeletal muscle injury, lysis, and excretion of dark brown urine, indicating the presence of excess myoglobin and leading to kidney damage [37, 38].

It is estimated that SAMS occur in 2–6 % of the statin population (affecting about 1 million patients) [39] based on real-world data, the incidence rate of SAMS is approximately 5–10 % [40, 41]. Patient registries and clinical experience estimate the incidence of SAMS at between 7 and 29 %, and these may be an important contributor to the very high discontinuation rates observed with statin therapy [34, 40, 42–45]. In their investigation of long-term persistence with statin treatment, Chodick et al. [10] found that ≥ 75 % of patients discontinued therapy within 2 years of initiation.

The incidence of SAMS varies with different statins [28]. According to data from the PRIMO (Prediction of Muscular risk in Observational) and STOMP (Effects of Statins on Muscle Performance) studies, patients receiving

simvastatin or atorvastatin are reported to be at the highest risk of SAMS (18.2 and 9.4–14.9 %, respectively) [40, 46]; patients receiving lovastatin might have a high risk of SAMS [28]; and the lowest rates are described for patients receiving pravastatin and fluvastatin (10.9 and 5.1 %, respectively) [40].

One possible explanation for the low risk of myopathy seen with pravastatin and fluvastatin may be because they are more hydrophilic and hence have less muscle penetration [28] (although this argument is weaker in the case of fluvastatin, which is relatively lipophilic). However, they are also least potent in LDL-C lowering, and statins associated with more aggressive LDL-C lowering might be expected to result in a higher risk of muscular adverse effects [40, 47].

Higher incidences of rhabdomyolysis were reported with atorvastatin or cerivastatin therapy, both as monotherapy and in combination with fibrates [48]. This was partially due to drug interactions with inhibitors of P450 cytochrome (CYP) 3A4, the main CYP involved in the hepatic metabolism of the lipophilic statins [49]. In addition, several researchers have found that concurrent use of statins with fibrates or niacin significantly increases the risk of rhabdomyolysis compared with monotherapy, with a higher risk more often reported in statin–fibrate combinations than in statin–niacin combinations [35, 37, 38]. These muscle effects have usually been reported with the use of synthetic, potent, and more lipophilic statins [35, 37, 38].

An important consideration is the increased likelihood of adverse effects with higher dose/potency statins. A review by Golomb and Evans [50] summarized evidence supporting a dose/potency dependence of statin adverse effects (Table 1).

Despite treatment guideline recommendations, low achievement rates of LDL-C targets are reported, and a large proportion (10–20 %) of high-risk and very high-risk patients still do not meet their target, particularly those who are not receiving high-potency statins [39, 55, 56].

4 Familial Hypercholesterolaemia

FH is inherited as an autosomal dominant trait and is characterized by markedly elevated circulating levels of LDL-C from the time of birth as well as premature atherosclerotic CVD (ASCVD) [57–59]. With a prevalence of 1:200 [60] to 1:500 [61], heterozygous FH (HeFH) is very common. LDL-C levels in these patients are two- to threefold higher than normal [58, 59, 62, 63]. Homozygous FH (HoFH) is very rare, affecting one in 300,000–1,000,000 individuals [57, 64]. The paucity or even lack of any functional LDL receptors (LDLRs) leads

Table 1 Evidence of dose/potency dependence of statin adverse events (adapted from Golomb and Evans [50])

Study	AE	Comment
Silva et al. [51] (meta-analysis of RCTs)	All AEs	OR 1.44 (95 % CI 1.33–1.55; $p < 0.001$) intensive- vs. moderate-dose statin therapy
Silva et al. [51] (meta-analysis of RCTs)	AEs leading to treatment discontinuation	OR 1.28 (95 % CI 1.18–1.39; $p < 0.001$) intensive- vs. moderate-dose statin therapy
Dale et al. [52] (meta-analysis of RCTs)	CK elevation	OR 6.12 (95 % CI 1.36–27.5) higher- vs. lower- dose statin therapy (the odds appeared to be greater for lipophilic statins, which have more muscle penetration)
Silva et al. [51] (meta-analysis of RCTs)		OR 9.97 (95 % CI 1.3–77.9, $p = 0.028$) intensive- vs. moderate-dose statin therapy
Dale et al. [52] (meta-analysis of RCTs)	LFT elevation	LFT (transaminase) elevation OR 2.7 (1.5–5.0) higher- vs. lower- dose statin therapy (the effect appeared to be greater for hydrophilic statins)
Silva et al. [51] (meta-analysis of RCTs)		LFT elevation (alanine or aspartate aminotransferase ≥ 3 times the ULN) OR 4.5 (95 % CI 3.3–6.2) intensive- vs. moderate-dose statin therapy
SEARCH Collaborative Group [53] (randomized trial of 12,064 pts who received simvastatin 20 or 80 mg daily)	Rhabdomyolysis	49 cases of ‘definite myopathy’ in the simvastatin 80-mg group vs. 2 in the simvastatin 20-mg group. 49 cases of ‘incipient myopathy’ in the simvastatin 80-mg group vs. 6 in the simvastatin 20-mg group
Golomb et al. [54]	Non-CK elevating muscle symptoms	Recurrence of statin AEs was significantly higher when pts were rechallenged with same or higher potency statins vs. rechallenge with a lower potency statins (~ 95 vs. 55 %, $p < 0.01$)

AE adverse effect, CI confidence interval, CK creatinine kinase, LFT liver function test, OR odds ratio, RCT randomized controlled trial, ULN upper limit of normal

to LDL-C levels that are three- to sixfold higher than normal and a very early onset of atherosclerotic vascular disease, frequently in childhood or adolescence [58, 59, 62, 63]. Given the ASCVD complications associated with FH, reducing the burden of elevated LDL-C levels is critical [57–60]. Novel well-tolerated therapeutic strategies as add-ons to statin therapy, or as monotherapy in cases of statin intolerance, are therefore essential in the management of FH [60]. In patients with HeFH, LDL-C target levels are frequently not reached via statins alone because the baseline levels are very high. In patients with HoFH with no residual LDLR function, statins do not reduce LDL-C levels at all. In patients with HoFH with little residual LDLR activity, only modest reductions (10–25 %) in LDL-C serum concentrations are reached even at the highest doses of the most efficacious statins [58, 60]. These patients depend on extracorporeal LDL elimination by apheresis.

5 Prevention of Cardiovascular Events

The ‘LDL hypothesis’ is a concept suggesting that it is the reduction of LDL-C, regardless of the means (i.e. not just via statins), that produces a corresponding reduction in

cardiovascular events [65]. An alternative theory, the ‘statin hypothesis’, postulates that statins have unique efficacy in ASCVD that is not shared by other lipid-lowering agents and that LDL-C reduction is not the (only) basis for the beneficial effects of statins [65]. Notably, pleiotropic effects arising from the inhibition of 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase, rather than from LDL-C lowering, have been made responsible: inhibition of HMG CoA reductase not only limits the production of cholesterol, which is compensated by the upregulation of LDLRs and hence LDL uptake, but also the production of intermediary metabolites, which play important regulatory roles, for example by prenylation of many membrane proteins. This mechanism may explain muscle toxicity at high systemic exposure.

Recent data from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) emphasize the importance of LDL-C lowering as the primary strategy to prevent CHD [65]. After 7 years of follow-up of 18,144 patients who had experienced an acute coronary syndrome, the rate of the primary endpoint (a composite of cardiovascular death, major coronary event [non-fatal myocardial infarction, unstable angina, or non-fatal stroke]) was 2 % lower in the combination therapy group (simvastatin 40 mg plus ezetimibe 10 mg) than in

the simvastatin monotherapy group (33 vs. 35 %) [66]. One of the most important implications of this trial is that all reductions in LDL-C levels by enhanced hepatic LDL removal through the LDLR pathway are beneficial [65]. This is also suggested by the currently available outcome data on proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which are discussed in section 6.2.

Further evidence in support of the causal role of LDL and LDL-C in the pathogenesis of ASCVD has been derived from Mendelian randomization (MR) studies. A particular advantage of the MR approach is that it can provide information on the impact of a lifetime modulation of a biomarker [67]. In this respect, MR studies demonstrated that frequent variants in the *LDLR* gene, which increase LDL-C as early as in childhood by 15 mg/dl, result in stronger effects on coronary artery disease risk than predicted by epidemiological or clinical studies for such a degree of LDL variability [68]. Conversely, individuals carrying a rare PCSK9 allele, which lowers LDL way below population average (by 21–38 mg/dl), showed a marked 40–80 % reduced incidence of myocardial infarction [69].

6 Alternative Treatment Options After Statin Use

When the maximally tolerated dose of statin therapy fails to achieve the target LDL-C, clinicians need to consider alternative and/or add-on second- and third-line options. In these cases, combination therapy should be considered [70].

6.1 Ezetimibe

Ezetimibe is the first lipid-lowering agent that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients [70]. The interrupted enterohepatic circulation and enhanced fecal loss of cholesterol is compensated by upregulation of LDLR and LDL uptake into the liver. Combining ezetimibe with a statin (simvastatin) in IMPROVE-IT reduced LDL-C by an additional 24 % in stable patients who had experienced an acute coronary syndrome [66]. In addition, the statin–ezetimibe combination can decrease LDL-C by 60–70 % in patients with FH [60]. In view of the acceptable side-effect profile and high compliance, the EAS recommends co-administration of ezetimibe as an add-on to statin therapy [60]. IMPROVE-IT [66], the first trial to demonstrate an incremental clinical benefit from adding a non-statin agent (ezetimibe) to statin therapy, found no significant differences in rates of adverse events between the combination therapy and monotherapy groups [65]. The

IMPROVE-IT findings are in line with data from an MR study that found that mutations in *NPC1L1* are associated with reduced levels of LDL-C and reduced risk of ASCVD [71]. Together, the MR and trial data support the ‘LDL hypothesis’ regarding reduction of cardiovascular events in patients with cardiovascular risk factors.

6.2 Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

PCSK9 is a secreted protease that mediates LDLR degradation (Fig. 1a) [57, 59, 72, 73]. Its important contribution to the regulation of LDL-C levels was first demonstrated by the identification of gain-of-function mutations of the *PCSK9* gene of patients with FH who had no mutations in the *LDLR* or *apolipoprotein-B (apoB)* genes [69]. Additionally, individuals with loss-of-function mutations in PCSK9 were found to have reduced plasma levels of LDL-C and to be protected from CHD [69, 74].

Inhibition of PCSK9 has emerged as a new therapeutic option. Three monoclonal antibodies are available: evolocumab, alirocumab, and bococizumab.

The complementary mechanisms of action of statins, PCSK9 and PCSK9 inhibitors are shown in Figs. 1 and 2. Statins inhibit cholesterol biosynthesis, leading to increased cellular sterol-regulatory element-binding protein-2 (SREBP-2) activity that promotes transcription of SREBP-2-inducible LDLR and PCSK9 genes (Fig. 2). However, this co-regulation is counteractive, as the production of PCSK9 protein triggers LDLR protein trafficking for lysosomal degradation and results in an attenuated LDL-C-lowering effect of statins [75]. The introduction of a PCSK9 inhibitor disrupts the interaction between PCSK9 and LDLR, raises LDLR protein, and increases LDL-C lowering as compared with statins alone (Fig. 1b).

Evolocumab, alirocumab, and bococizumab are currently being studied in large clinical trial programs and appear to be highly effective at reducing LDL-C levels, achieving an additional 60–75 % reduction in patients treated with statins. Importantly, no significant increase in serious adverse events has been reported to date in phase III trials, in particular, no increase in myotoxicity when compared with statin-treated control patients [76].

In addition, small interfering RNAs—so-called antagomirs—have been developed to interfere with PCSK9 production in the liver. The previously published phase I trial is the first example of therapeutic RNA interference in humans [77].

Evolocumab PROFICIO Program PROFICIO (Programme to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations) is a large and comprehensive clinical trial program evaluating

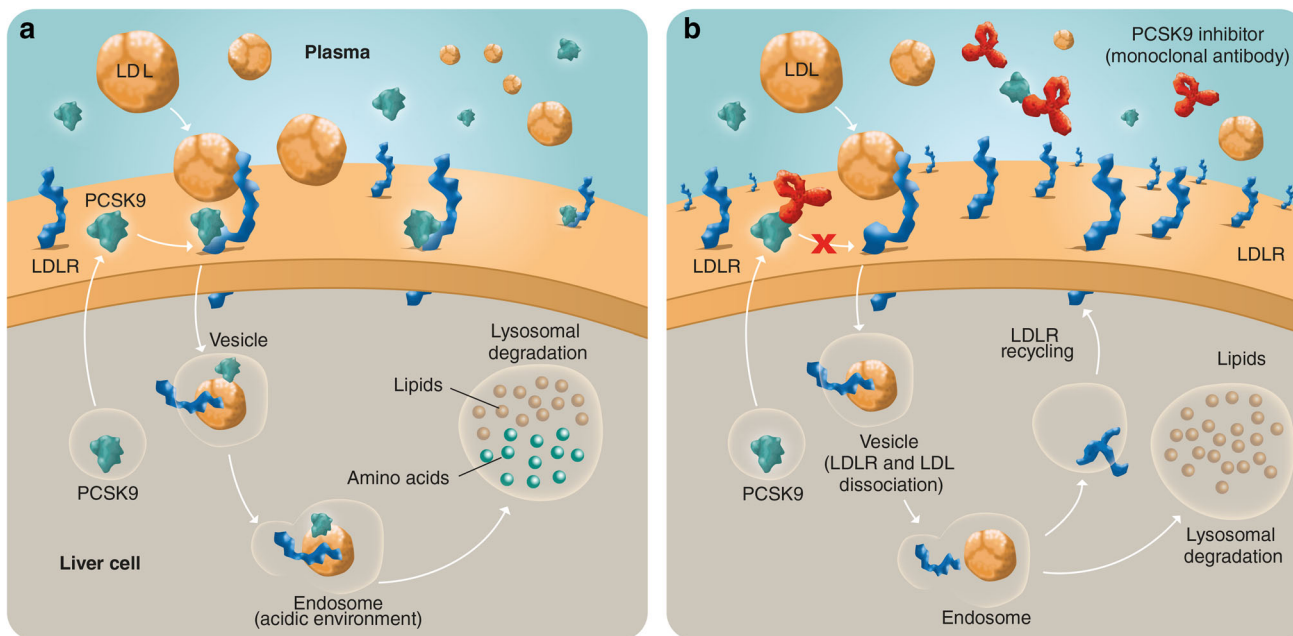


Fig. 1 Trafficking of LDLR in the presence of PCSK9 (a) or following PCSK9 inhibition by a monoclonal antibody (b). a Secreted PCSK9 binds to LDLR on the liver cell surface and mediates the lysosomal degradation of the complex formed by PCSK9, LDLR, and LDL [68]. b In the presence of a monoclonal antibody that binds to

PCSK9, the PCSK9-mediated degradation of LDLR is inhibited, resulting in an increased uptake of LDL-cholesterol by LDLR as more LDLR are recycled at the cell surface [72]. *LDL* low-density lipoprotein, *LDLR* low-density lipoprotein receptor, *PCSK9* proprotein convertase subtilisin/kexin type 9

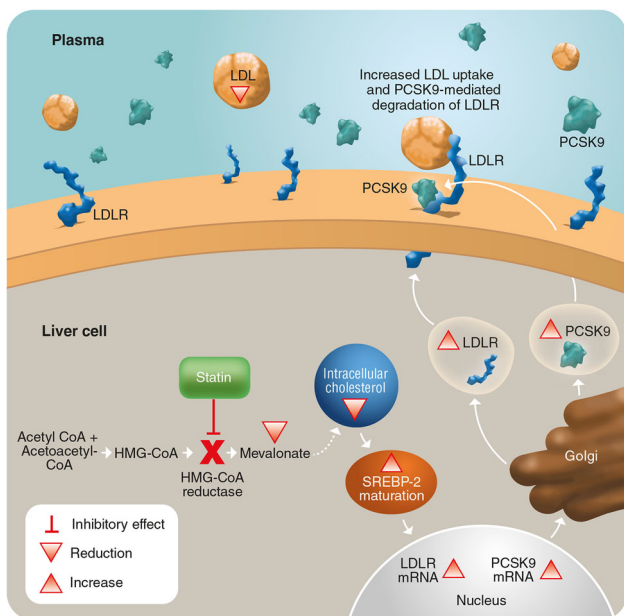


Fig. 2 Impact of statins on cholesterol metabolism. Statins inhibit the biosynthesis of intracellular cholesterol by inhibiting HMG-CoA reductase. This results in low levels of intracellular cholesterol, leading to increased SREBP-2 activity, which promotes the production of PCSK9 and LDLR, the degradation of which is mediated by PCSK9 [72]. *HMG CoA* 3-hydroxy-3-methyl-glutaryl-CoA, *LDL* low-density lipoprotein, *LDLR* low density lipoprotein receptor, *mRNA* messenger RNA, *PCSK9* proprotein convertase subtilisin/kexin type 9, *SREBP-2* sterol-regulatory element-binding protein

evolocumab. The PROFICIO phase III program includes 14 trials, with a combined planned enrolment of more than 28,000 patients.

The phase III studies will evaluate subcutaneous evolocumab 140 mg every 2 weeks and 420 mg monthly in multiple patient populations, and four of the studies will provide long-term safety and additional efficacy or cardiovascular outcome data. Table 2 summarizes the currently available data from individual studies in patients with unmet needs. The evidence from trials in these patients indicates that evolocumab might be an efficacious and tolerable option for them, a conclusion also drawn by Dadu and Ballantyne [78] in their review of lipid lowering with PCSK9 inhibitors.

In addition, in a pooled analysis of four phase III studies (MENDEL-2, LAPLACE-2, RUTHERFORD-2, GAUSS-2) that included 417 of 2729 patients with T2DM, the efficacy and safety of evolocumab was comparable in patients with or without T2DM and did not differ among T2DM sub-groups [85]. These findings were confirmed after 1 year of treatment in 4802 patients with, at high risk for, or at low risk for, diabetes mellitus who had completed one of 13 phase II or III parent studies of evolocumab (OSLER-1 and OSLER-2). Patients were randomized to receive either evolocumab 140 mg every 2 weeks or 420 mg monthly plus standard of care (SoC) or SoC alone [86, 87]. Results were similar irrespective of parent-study

Table 2 Summary of results from evolocumab trials in patient groups with unmet needs

Study	Population	Primary endpoints	Efficacy	Safety
GAUSS-2 [79] (evolocumab vs. ezetimibe)	Pts with hyperlipidemia who cannot tolerate statin therapy; <i>N</i> = 307	Percent change from BL in LDL-C level at the mean of weeks 10 and 12, and at week 12	Evolocumab reduced LDL-C from BL by 53–56 %: tx differences vs. ezetimibe of 37–39 % (<i>p</i> < 0.001)	Muscle AEs: 12 % of evolocumab-treated pts vs. 23 % of ezetimibe-treated pts; TEAEs and laboratory abnormalities comparable across tx groups
RUTHERFORD-2 [80] (evolocumab vs. PL)	Pts with HeFH, on stable lipid-lowering therapy; <i>N</i> = 329	Percent change from BL in LDL-C level at the mean of weeks 10 and 12, and at week 12	Evolocumab reduced mean LDL-C at week 12 (every-2-week dose: 59 % reduction, monthly dose: 61 % reduction; both <i>p</i> < 0.0001) and at the mean of week 10 and 12 (60 % reduction and 66 % reduction; both <i>p</i> < 0.0001)	Similar rates of AEs in both groups, except for nasopharyngitis (19 pts [9 %] in the evolocumab group vs. 5 [5 %] in the PL group) and muscle-related AEs (10 pts [5 %] in the evolocumab group vs. 1 [1 %] in the PL group)
TESLA [81] (evolocumab vs. PL)	Pts with HoFH, on stable lipid-lowering therapy; <i>N</i> = 49	Percentage change from BL in ultracentrifugation LDL-C level at week 12	Evolocumab reduced ultracentrifugation LDL-C at 12 weeks by 31 % (<i>p</i> < 0.0001)	TEAEs occurred in 10 (63 %) of 16 pts in the PL group and 12 (36 %) of 33 in the evolocumab group
DESCARTES [82] (evolocumab vs. PL)	Pts with hyperlipidemia and a wide range of CV risk, after a run-in period of background lipid-lowering therapy; <i>N</i> = 901	Percent change from BL in ultracentrifugation LDL-C level at week 52	Overall LSM (\pm SE) reduction in LDL-C 57 \pm 2 % (taking into account reduction in PL group) (<i>p</i> < 0.001); mean reduction 56 \pm 4 % in pts with diet alone as background therapy, 62 \pm 3 % with atorvastatin 10 mg, 57 \pm 5 % with atorvastatin 80 mg, and 49 \pm 5 % with combination of atorvastatin 80 mg and ezetimibe 10 mg (<i>p</i> < 0.001 for all comparisons)	Overall incidence of AE occurring during tx was similar in the evolocumab and PL groups: 448 of 599 pts (75 %) vs. 224 of 302 pts (74 %); most common AEs in the evolocumab group: nasopharyngitis, URTI, influenza, and back pain
LAPLACE-2 [83] (evolocumab vs. ezetimibe and PL)	Pts at risk for CVD receiving statin therapy; <i>N</i> = 1899	Percent change from BL in LDL-C level at mean of weeks 10 and 12 and at week 12	Evolocumab reduced LDL-C levels by 66–75 % (every 2 weeks) and by 63–75 % (monthly) vs. PL at mean of weeks 10 and 12 in the moderate- and high-intensity statin-treated groups; LDL-C reductions at week 12 were comparable	AEs reported in 36 %, 40 %, and 39 % of evolocumab-, ezetimibe-, and PL-treated pts, respectively; most common AEs in evolocumab-treated pts were back pain, arthralgia, headache, muscle spasms, and pain in extremity (all <2 %)
TAUSSIG [84] (evolocumab long-term open-label; interim results; estimated completion, January 2020)	Pts with HoFH, receiving stable lipid-lowering therapy; <i>N</i> = 100 (non-apheresis, <i>N</i> = 66; apheresis, <i>N</i> = 34)	Percentage change from BL in LDL-C at week 12	Evolocumab reduced LDL-C in the overall cohort by 21 % (<i>p</i> < 0.05); reduction maintained in the longer-term (up to 48 weeks); in a subset of non-apheresis pts, who uptitrated to 420 mg every 2 weeks (<i>N</i> = 28), LDL-C was reduced by a further 6 % (<i>p</i> = 0.01)	Evolocumab was well-tolerated

AE adverse effect, BL baseline, CV cardiovascular, CVD cardiovascular disease, HeFH heterozygous familial hypercholesterolaemia, HoFH homozygous familial hypercholesterolaemia, LDL-C low-density lipoprotein cholesterol, LSM least squares mean, PL placebo, pt(s) patient(s), SE standard error, TEAE treatment-emergent adverse effect, tx treatment, URTI upper respiratory tract infection

drug assignment. Evolocumab showed encouraging safety, with no measurable effect on skeletal muscle and glycemic parameters despite reducing LDL-C levels markedly.

Alirocumab ODYSSEY Program The ODYSSEY phase III program is expected to enroll more than 23,000 patients and currently includes 12 clinical trials of alirocumab, both in combination with other lipid-lowering agents and as monotherapy in patients with primary HeFH or non-FH or statin intolerance. Table 3 summarizes the currently available data from individual studies in patients with unmet needs. Similar to evolocumab, alirocumab appears to be effective in lowering LDL-C and well-tolerated.

In a sub-analysis of 2341 patients with or without T2DM from the ODYSSEY LONG TERM trial, the effects of alirocumab were also shown to be consistent, regardless of medical history of patients with T2DM at baseline [98].

Bococizumab SPIRE Program The bococizumab SPIRE program is currently underway in phase III trials. Table 4 describes these, although no results are yet available.

PCSK9 inhibitors For statin-intolerant patients specifically, promising results of the efficacy of PCSK9 inhibitors have already been shown in GAUSS 2 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects—2) (evolocumab vs. ezetimibe) (see Table 2); ODYSSEY ALTERNATIVE (alirocumab vs. ezetimibe) (see Table 3). The ongoing GAUSS-3 trial is the most recent statin intolerance study that incorporates a double-blind, placebo-controlled statin rechallenge prior to a 6-month evolocumab versus ezetimibe comparison, with a 2-year open-label extension. Further evidence will come from outcome trials; for now, LDL-C is an accepted marker for lipid-lowering therapies, and these data should be used for future guideline updates [104].

In conclusion, the available data on efficacy and safety of both evolocumab and alirocumab look very encouraging. Firm evidence will be obtained by clinical outcome trials that will be concluded in the near future [105, 106].

In 2015, evolocumab and alirocumab have received marketing authorization in the EU and the USA (Table 5). Despite their broad indications, the cost of monoclonal antibodies may restrict the use of PCSK9 inhibitors to patients with high LDL-C, where statins are not efficient enough, and to patients intolerant to statins, for whom these new treatment options may be the most cost effective [76, 107]. The substantial potential health benefits and savings in healthcare costs from preventing CHD events will need to be weighed against the possibility of adverse effects of long-term statin therapy and the costs of alternative treatments.

6.3 Other Statin Alternatives

Novel potent LDL-C-lowering therapies currently under investigation include mipomersen, an apoB synthesis inhibitor [110–115], and lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor [116–119]. Unlike statins or PCSK9 inhibitors, which ultimately lower LDL-C by increasing LDLR expression in the liver and hence hepatic clearance of LDL-C, mipomersen and lomitapide inhibit the production of chylomicrons, very low-density lipoprotein (VLDL), and LDL. Independence of the LDLR makes these two regimens particularly applicable for the treatment of HoFH. However, the prevention of VLDL production increases hepatic fat accumulation. Consequently, mipomersen (only in the USA) and lomitapide (in the USA and Europe) are currently authorized for treatment of HoFH only.

Cholesteryl ester transfer protein (CETP) transfers cholesterol esters from HDL to LDL. Patients with CETP deficiency have high levels of HDL-C and low levels of LDL-C. CETP inhibitors have been developed, five of which have been or currently are in different stages of clinical investigation [120]. Whereas dalcetrapib only increased HDL-C levels, torcetrapib (ILLUMINATE trial) [121], anacetrapib (DEFINE trial) [122], evacetrapib [123], and TA-8995 (TULIP trial) [124] also caused 14–45 % decreases in LDL-C. However, clinical endpoint trials on torcetrapib, dalcetrapib, and evacetrapib have been stopped prematurely because of excess rates of serious adverse events (torcetrapib) or futility (dalcetrapib, evacetrapib). The anacetrapib phase III trial was very recently announced to be continued.

Other therapies, such as bile acid sequestrants and nicotinic acid, have been evaluated but found to be poorly tolerated [79]. Furthermore, the addition of niacin to statins did not further decrease major adverse cardiac event rates in the AIM-HIGH trial [125]. Consequently, niacin is no longer available in Europe.

7 Controversies About Sub-Normally Low LDL-C Levels

The beginning of cholesterol-lowering therapy in the 1980s witnessed a fierce discussion on the harm of low cholesterol.

Cholesterol is a natural component of the body's metabolism: together with other lipids, it is an essential constituent of cell membranes and a constituent of steroid hormones, vitamin D, and bile acids [126]. Cholesterol is also an indispensable component of cell membranes in the

Table 3 Summary of results from alirocumab studies in patient groups with unmet needs

Study	Population	Primary/co-primary endpoints	Efficacy	Safety
ODYSSEY LONG TERM [88] (alirocumab vs. PL)	Pts with LDL-C >1.8 mmol/l on maximum-tolerated dose of statins with or without other lipid-lowering therapy; N = 2341	Percent change in calculated LDL-C level from BL to week 24	Alirocumab reduced LDL-C by 62 % ($p < 0.0001$) vs. PL by week 24	Alirocumab vs. PL injection-site reactions (6 vs. 4 %), myalgia (5 vs. 3 %), neurocognitive events (1 vs. 0.5 %), and ophthalmologic events (3 vs. 2 %). In a post hoc analysis, the rate of major adverse CV events was lower with alirocumab than with PL (2 vs. 3 %; $p = 0.02$)
ODYSSEY FH I and FH II [89] (alirocumab 75 mg every 2 weeks vs. PL)	Pts with HeFH and inadequate LDL-C control on maximally tolerated lipid-lowering therapy; N = 735	Percent change in calculated LDL-C from BL to week 24 (both studies)	Alirocumab reduced LDL-C 58 % vs. PL at week 24 in FH I and by 51 % vs. PL in FH II. LDL-C 1.8 mmol/l (was achieved at week 24 by 60 % and 68 % of alirocumab-treated pts in FH I and FH II, respectively)	AE-related tx discontinuation in 3 % of alirocumab-treated pts in FH I (vs. 6 % PL) and 4 % (vs. 1 %) in FH II. Injection-site reactions in alirocumab-treated pts 12 % in FH I and 11 % in FH II (vs. 11 % and 7 % with PL)
ODYSSEY HIGH FH [90] (alirocumab 150 mg every 2 weeks vs. PL)	Pts with HeFH and inadequate LDL-C control on maximally tolerated lipid-lowering therapy; N = 107	Percent change in LDL-C from BL to 24 weeks (ITT)	Alirocumab reduced LDL-C by 46 vs. 7 % with PL ($p < 0.0001$)	TEAEs were generally comparable between groups: 61 % of pts in the alirocumab group vs. 71 % of pts in the PL group
ODYSSEY OPTIONS I [91] (atorvastatin plus alirocumab vs. atorvastatin plus ezetimibe; or double atorvastatin; or rosuvastatin)	Pts with very high CVD risk and LDL-C >70 mg/dl or high CVD risk and LDL-C >100 mg/dl on BL atorvastatin 20 or 40 mg; N = 355	Percent change in LDL-C from BL to 24 weeks (ITT)	In atorvastatin 20 and 40 mg regimens, respectively: Add-on alirocumab reduced LDL-C levels by 44 % and 54 % ($p < 0.0001$ vs. all comparators) Add-on ezetimibe, 21 % and 23 % Double atorvastatin dose, 5 % in both cases Switching atorvastatin 40 mg to rosuvastatin 40 mg, 21 %	TEAEs occurred in 65 % of alirocumab pts vs. 64 % ezetimibe and 64 % double atorvastatin/switch to rosuvastatin (data were pooled)
ODYSSEY OPTIONS II [92] (rosuvastatin plus alirocumab vs. rosuvastatin plus ezetimibe; or double-dose rosuvastatin)	Pts with very high CVD risk and LDL-C >70 mg/dl or high CVD risk and LDL-C >100 on BL rosuvastatin 20 or 40 mg; N = 305	Percent change in LDL-C from BL to 24 weeks (ITT)	In the BL rosuvastatin 10-mg group, add-on alirocumab reduced LDL-C by 51 % vs. ezetimibe (14 %) and double-dose rosuvastatin (16 %) ($p < 0.0001$ in both cases). In the BL rosuvastatin 20-mg group, add-on alirocumab reduced LDL-C by 36 % vs. ezetimibe (11 %) and double-dose rosuvastatin (16 %) ($p = 0.0136$ and $p = 0.0453$, respectively; pre-specified threshold for significance, $p < 0.0125$)	TEAEs occurred in 56 % of alirocumab pts vs. 54 % ezetimibe and 67 % double-dose rosuvastatin (data were pooled)

Table 3 continued

Study	Population	Primary/co-primary endpoints	Efficacy	Safety
ODYSSEY ALTERNATIVE [93] (alirocumab vs. ezetimibe)	Statin-intolerant pts with very high BL LDL-C levels; <i>N</i> = 314	Percent reductions in LDL-C at week 24	Significantly more pts achieved LDL-C goals with alicrocumab than with ezetimibe (42 vs. 4 %, <i>p</i> < 0.0001)	Alicrocumab was better tolerated than atorvastatin (HR 1.63, <i>p</i> = 0.042) with a significantly lower rate of skeletal muscle adverse events (<i>p</i> < 0.05)
ODYSSEY COMBO I [94] (alirocumab vs. PL)	Pts with high CV risk with sub-optimally controlled hypercholesterolemia on maximum tolerated dose of statins with or without other lipid-lowering therapy; <i>N</i> = 316	Percent change in LDL-C from BL to 24 weeks (ITT)	Alicrocumab reduced LDL-C by 48 vs. 2 % with PL (<i>p</i> < 0.0001)	TEAEs (76 % of pts in both groups) and tx-emergent serious AEs (13 % of pts in both groups) were similar in the alicrocumab and PL groups
ODYSSEY COMBO II [95] (alirocumab vs. ezetimibe)	Pts with high CV risk with suboptimally-controlled hypercholesterolemia on maximum tolerated dose of statins; <i>N</i> = 720	Percent change in LDL-C from BL to 24 weeks (ITT)	Alicrocumab reduced LDL-C by 51 vs. 21 % with ezetimibe (<i>p</i> < 0.0001)	Percentages of pts experiencing at least one tx-emergent AE or serious AEs were comparable between the two groups: 71 and 19 %, respectively (alicrocumab) vs. 67 and 18 %, respectively (ezetimibe)
ODYSSEY CHOICE I [96] (alicrocumab 300 mg every 4 weeks vs. alicrocumab 75 mg every 2 weeks [calibrator arm] vs. PL)	Pts with moderate very high CVD risk on maximum tolerated dose of statins; pts with moderate CV risk not receiving statins; pts with moderate to very high CVD risk and statin intolerance; <i>N</i> = 803	Percentage LDL-C change from BL to week 24 and to averaged LDL-C for weeks 21–24	Alicrocumab 300 mg every 4 weeks mean differences vs. PL were –52 % (pts not receiving statin) and –59 % (pts receiving statins) (<i>p</i> < 0.0001); average reductions to weeks 21–24 were also greater in the alicrocumab 300-mg group vs. PL in pts not receiving statins (55 %) and in pts receiving statins (65 %) (<i>p</i> < 0.0001)	TEAEs ranged from 61 to 75 % (PL) and 72 to 78 % with alicrocumab 300 mg; higher rate of injection-site reactions with alicrocumab 300 mg vs. PL
ODYSSEY CHOICE II [97] (alicrocumab 150 mg every 4 weeks, alicrocumab 75 mg every 2 weeks [calibrator arm] or PL for 24 weeks)	Pts with moderate to very high CV risk and SAMS (inability to tolerate ≥2 statins due to muscle symptoms), or moderate CV risk without SAMS; <i>N</i> = 233	Percentage change in LDL-C from BL to week 24	Overall, 63.9 % of pts in the alicrocumab 150 mg every 4 weeks arm achieved pre-defined LDL-C target levels at week 24 vs. 1.8 % of PL pts (ITT analysis)	TEAEs occurred in 63.8 and 77.6 % of PL- and alicrocumab 150 mg every 4 wk-treated pts, respectively. Muscle symptoms were infrequent; the most common TEAEs were injection-site reactions, arthralgia, headache, and nasopharyngitis

AE adverse effects, BL baseline, CV cardiovascular, FH familial hypercholesterolemia, HeFH heterozygous familial hypercholesterolemia, HR hazard ratio, ITT intention to treat, LDL-C low-density lipoprotein cholesterol, PL placebo, *p*(t) patient(s), SAMS statin-associated muscle symptoms, TEAE treatment-emergent adverse effects, tx treatment

Table 4 Phase III bococizumab trials (ongoing)

Study	Population	Comparison	Estimated completion
SPIRE-HF [99] https://clinicaltrials.gov/ct2/show/NCT01968980	Pts with HeFH with high and very high CVD risk (with statin therapy)	Bococizumab vs. PL at 12 weeks	January 2016
SPIRE-HR [100] https://clinicaltrials.gov/ct2/show/NCT01968954	Pts with high and very high CVD risk (with statin therapy)	Bococizumab vs. PL at 12 weeks	January 2016
SPIRE-LDL [101] https://clinicaltrials.gov/ct2/show/NCT01968967	Pts with high and very high CVD risk (with statin therapy)	Bococizumab vs. PL at 12 weeks	December 2015
SPIRE-1 [102] https://clinicaltrials.gov/ct2/show/NCT01975376	Pts with high and very high CVD risk (with lipid-lowering therapy)	Bococizumab vs. PL at 5 years (effects on major CV events)	August 2017
SPIRE-2 [103] https://clinicaltrials.gov/ct2/show/NCT01975389	Pts with high and very high CVD risk (with lipid-lowering therapy)	Bococizumab vs. PL at 5 years (effects on major CV events)	August 2017

CV cardiovascular, CVD cardiovascular disease, HeFH heterozygous familial hypercholesterolemia, PL placebo

Table 5 PCSK9 inhibitors approved in Europe and the USA

PCSK9 inhibitor	Indications
Evolocumab [108] (evolocumab SmPC)	Adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in pts unable to reach LDL-C goals with the maximum tolerated dose of a statin or alone or in combination with other lipid-lowering therapies in pts who are statin intolerant or for whom a statin is contraindicated Adults and adolescents aged ≥ 12 years with homozygous FH in combination with other lipid-lowering therapies
Alirocumab [109] (alirocumab SmPC)	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidemia as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in pts unable to reach LDL-C goals with the maximum tolerated dose of a statin or alone or in combination with other lipid-lowering therapies in pts who are statin intolerant or for whom a statin is contraindicated

FH familial hypercholesterolemia, LDL-C low-density lipoprotein cholesterol, *pt(s)* patient(s), SmPC summary of product characteristics

brain [126]. Interestingly, there have been reports of higher all-cause mortality in populations with sub-normally low cholesterol levels [126]. For example, MRFIT (Multiple Risk Factor Intervention Trial) and other older studies suggested increased mortality of malignant and other disorders in individuals with serum cholesterol < 3.6 mmol/l (140 mg/dl) [126, 127]. However, this association may result from reverse causality: individuals with low cholesterol may have pre-clinical severe diseases that decrease cholesterol levels. After adjustment for body weight and smoking, the J-shaped relationship between cholesterol and total mortality disappeared. Moreover, 25 years of trial experience with statins do not indicate any increase in risk for serious life-threatening or life expectancy-limiting disease [126].

Nevertheless, the advent of very effective combination therapies for LDL-C lowering will revive the discussion on the potential threats from very low cholesterol levels. Innate errors of metabolism may give some information in this regard. Many carriers of loss-of-function mutations in PCSK9 or angiopoietin-like protein type 4 (ANGPTL4), as well as carriers of mutations preventing the synthesis of

full-length apoB, have very low levels of LDL-C. These conditions are not known to limit the life expectancy or quality of life of their carriers. Quite the opposite, they appear to dramatically reduce the risk of myocardial infarction [128, 129]. Only patients with homozygous hypobetalipoproteinemia and patients with abetalipoproteinemia (because of mutations in MTP) with complete absence of apoB-containing lipoproteins experience severe neurological disease such as ataxia and retinitis pigmentosa [130].

The adverse effects of extreme LDL-C lowering can be subclinical and overlooked for a long time. Thus, the increased risk of diabetes with statin treatment has been uncovered only recently, after 20 years of prior statin use. Initial data also point to increased loss of bone mass with statin treatment. However, the mechanism and hence extrapolation of the finding to non-statin interferences and LDL-C lowering in general is controversial. Some authors suggested that statins affect insulin secretion in beta cells as well as insulin signaling in peripheral target organs by interfering with the synthesis of bioactive intermediates in the mevalonate-cholesterol pathway [131, 132]. In this

case, non-statin mediated LDL-C lowering may not be diabetogenic. Others showed that LDL interferes with insulin secretion in an LDLR-dependent manner [133, 134], and that patients with FH are at reduced risk of diabetes [135]. In that case, non-statin interventions that upregulate the LDLR in pancreatic beta cells may also be diabetogenic.

However, follow-up of whether these changes in intermediary phenotypes lead to adverse clinical outcomes will be required. With respect to diabetes, it is important to highlight that statins reduce coronary event rates as well as the incidence of diabetic nephropathy.

Nonetheless, these examples indicate an urgent need to closely monitor the efficacy and safety of novel cholesterol-lowering regimens, such as PCSK9 inhibitors. For safety, it will be important to use methods that objectively measure specific endpoints, such as cognitive and other brain functions.

8 Conclusions

Statins are currently the SoC in the management of dyslipidemia. Treatment guidelines recommend optimization of statin dose when patients do not reach LDL-C targets. However, treatment aims may not be reached with statins in many patients at high risk of cardiovascular events, such as patients with FH or statin intolerance. Such patients require more effective treatment options and may benefit from combination therapy with ezetimibe or a PCSK9 inhibitor. PCSK9 inhibitors are now available, and treatment guidelines need to be updated to guide the management of patients who will best benefit from these new treatments.

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Compliance with ethical standards

Conflict of interest Stephan Krähenbühl is the local principal investigator of a clinical study sponsored by Amgen and has given talks about the pharmacology and safety of PCSK9 inhibitors in scientific meetings sponsored by Amgen and Sanofi. Arnold von Eckardstein received honoraria from Amgen, Sanofi-Aventis, and Merck Sharpe and Dohme for lectures or consultancies. Ivana Pavik-Mezour is an employee of Amgen and owns stocks.

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