REVIEW

Statin intolerance: new data and further options for treatment

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Purpose of review
Hypercholesterolemia is a major risk factor for cardiovascular diseases. Administration of statins represents the cornerstone of the prevention and treatment of cardiovascular disease, with demonstrated long-term safety and efficacy. This review aims to revisit statin intolerance mechanisms, as well as to discuss new data and therapeutic options.

Recent findings
Although statins are well tolerated, myopathy and other adverse effects are a challenging problem, being the main reason for poor adherence to treatment and failure in lowering cardiovascular risk. Statin intolerance is the subject of ongoing research, as these drugs are widely used. There are alternative options of treatment if statin intolerance emerges, that is, lowering the dose, intermittent dosages, and/or combining a statin with other drugs, such as ezetimibe, proprotein convertase subtilisin–kexin type 9 inhibitors, bempedoic acid, angiopoietin-like 3 protein inhibitors, and nutraceuticals. If even the lowest statin dose cannot be tolerated, a nonstatin regimen is recommended to reduce LDL cholesterol levels.

Summary
Treatment options in statin intolerance include combinations of a lower dose of statin with other lipid-lowering regimens or only nonstatin drugs in the presence of complete intolerance. New hypolipidemic therapies that address gene editing are emerging, and may prove useful in the future.

Keywords
angiopoietin-like 3 protein inhibitors, bempedoic acid, ezetimibe, proprotein convertase subtilisin–kexin type 9 inhibitors, statin intolerance

INTRODUCTION

Hypercholesterolemia is a major risk factor for atherosclerosis, coronary heart disease (CHD), and other cardiovascular diseases (CVDs) [1]. Since the discovery of statins, the reduction in CVD incidence, prevalence, and mortality has progressed, with a great impact on clinical guidelines and future research [2]. With the widespread use of statins, reports of adverse reactions have emerged prompting the medical community to accept the diagnosis of statin intolerance and the need to find other options for lipid-lowering treatment [3].

STATINS MECHANISMS OF ACTION

The biosynthesis of cholesterol involves an extensive pathway of enzymatic reactions. The conversion of β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) to mevalonate represents the most important step in cholesterol synthesis and thus, HMG-CoA reductase inhibition is an effective way to decrease circulating cholesterol levels [1]. The development of statins changed the entire history of cholesterol-induced CVD [1]. Statin therapy is one of the greatest medical developments and advances, with a long-proven ability to prevent and treat CVD [2].

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KEY POINTS

- Statin intolerance represents a challenging problem, being the leading cause of poor adherence to treatment.
- Therapeutic options in cases of statin intolerance include statin dose-lowering, intermittent dosages, switching to a different statin and combinations with other lipid-lowering drugs, including ezetimibe, proprotein convertase subtilisin–kexin type 9 inhibitors, bempedoic acid, and angiopoietin-like 3 inhibitors, as well as nutraceuticals.
- Emerging gene editing therapies should be further investigated.
- Treatment should be individualized.

Statins inhibit HMG-CoA reductase, thus lowering intracellular cholesterol, which increases the expression of surface LDL receptors that bind circulating LDL [3]. As a consequence, statins reduce the levels of LDL-cholesterol (LDL-C), the fraction that is implicated in atherosclerosis, myocardial infarction (MI), and stroke. Furthermore, statins can lower triglycerides levels, as well as raise HDL-cholesterol (HDL-C) and lipoprotein a levels [3]. Large statin trials showed that for every 39 mg/dl (1.0 mmol/l) decrease of LDL-C levels, the rates of major adverse CVD events are reduced by approximately 22% [3]. In addition, a meta-analysis of 26 randomized controlled trials (RCTs) ($n = 169\,138$ participants) reported that statin therapy reduces all-cause mortality by 10% for every 39 mg/dl (1.0 mmol/l) LDL-C lowering [rate ratio 0.90, 95% confidence interval (CI) 0.87–0.93; $P < 0.0001$], mainly through decreases in deaths due to CHD and other cardiac causes (rate ratio 0.80, 95% CI 0.74–0.87; $P < 0.0001$, and 0.89, 95% CI 0.81–0.98; $P = 0.002$, respectively) [4].

PATHOPHYSIOLOGY OF STATIN INTOLERANCE

Although statins are effective, safe, and generally well tolerated, they can exert adverse reactions, for example, on muscles and glucose metabolism, as reported in position papers and consensus panels [5,6]. Statin intolerance can be partial (to some statins, at some doses) or complete (regardless of the statin, in any dose) [2]. The most frequent adverse reactions are statin-associated muscle symptoms (SAMS), such as myalgia and muscle weakness, which are usually mild and completely reversible after treatment discontinuation [6]. Of note, 7–29% of patients may complain of SAMS (based on patient registries and clinical experience) that are usually related to normal or slightly elevated serum creatine kinase activity [6]. In rare cases, myositis can occur, with markedly increased serum creatine kinase activity (>10 times the upper normal limit) [6]. The most severe form of statin-induced muscle damage is rhabdomyolysis (with an incidence of ~1 in 100 000 statin-treated patients/year) manifested as severe myalgia, muscular necrosis, and myoglobinuria that can lead to renal failure, requiring hospitalization [6].

The risk factors associated with SAMS can be either endogenous [e.g., older age, female sex, Asian ethnicity, low BMI, presence of hypothyroidism, diabetes mellitus, chronic liver disease, chronic kidney failure, cytochrome P450 (CYP450) polymorphisms, vitamin D deficiency, and muscle diseases] or exogenous (e.g., surgery, heavy alcohol consumption, intense exercise, and excessive grapefruit or cranberry juice intake, in case of treatment with CYP3A4-metabolised statins like simvastatin and lovastatin) [3,4].

In the liver, pravastatin is metabolized by sulfonation, whereas other statins are metabolized by the CYP450 enzymes [7]. Atorvastatin, lovastatin, and simvastatin are metabolized by CYP3A4, an enzyme that can be inhibited by drugs like antifungals, warfarin, cyclosporine, macrolide antibiotics (e.g., clarithromycin), nondihydropyridine calcium channel blockers, HIV-protease inhibitors, amiodarone, and foods (grapefruit and cranberry) [8]. Fluvastatin and rosuvastatin are metabolized by CYP2C9, a common pathway for cimetidine, fluconazole, amiodarone, and trimethoprim [8]. Gemfibrozil inhibits the glucuronidation of statins, thus increasing the risk of statin-related myopathy [3].

The exact pathological mechanisms of SAMS are not yet fully elucidated, but in-vitro studies showed that statins decrease the beta-oxidation of fatty acids (FAs), hence the accumulation of lipids and inhibition of energy metabolism [9]. By reducing the intracellular cholesterol levels, cell membrane becomes unstable and prone to lysis [10]. Statins also inhibit the ubiquinone (coenzyme Q10) pathway involved in mitochondrial electron transport, thus decreasing energy production and increasing the intracellular level of reactive oxygen species [4]. This alteration of the respiratory chain affects the mitochondrial membrane permeability, with the release of cytochrome *C* in the cytosol, therefore, inducing mitochondrial dysfunction and apoptosis [4,10]. Overall, statin-induced effects that are potentially involved in SAMS include induced apoptosis, increases in sarcoplasmic calcium, decreased protein

synthesis, skeletal muscle dysfunction, and membrane lysis [6,11,12].

Another effect of statins is the decrease of post-translational protein modification (prenylation) of enzymes, derived from cholesterol synthesis, with an important role in signal transduction of *Ras*, *Rac*, *Rab*, and *Rho* G-coupled protein pathways [10]. Statin-induced insulin resistance can be explained by the same mechanism, as glucose transporter type 4 receptors are affected by *Rac* activity [5]. Although several studies demonstrated that dose-related statin treatment may lead to new-onset diabetes [13], via several pathways that affect insulin signaling, insulin sensitivity, pancreatic beta-cell function, and adipokine secretion [14] and weight gain [15], the benefits of CVD risk reduction outweigh any hyperglycemic effect [3,16,17].

PREVENTION AND TREATMENT OF STATIN INTOLERANCE

Statin intolerance is the leading cause of treatment discontinuation. Therefore, it is important to evaluate risk factors and the possibility of temporary withdrawal of statin in case of symptoms, as well as to monitor serum creatine-kinase activity [18]. Importantly, the onset of symptoms should be carefully assessed, as there may be a *nocebo* effect caused by the patient's awareness of statin-induced muscle pain [19]. Studies have now investigated the likely *nocebo* effect associated with statin treatment [20–22]. One placebo-controlled trial demonstrated that there was no significant difference between the placebo and statin-treated patients groups [20], and the reinitiation of statin in patients with myalgia as reported side effect did not increase the muscular symptoms as compared with placebo [21]. Significantly, at the completion time of both studies, the majority of patients were willingly to restart the statin therapy [20,21]. There are promising ongoing RCTs investigating the extent of statin intolerance in patients with MI (NCT04069598) [16] and intolerance recurrence after statin therapy reinitiation (NCT03889314) [23].

Vitamin D deficiency can coexist with SAMS, exerting similar symptoms like myalgia and fatigue. Although vitamin D deficiency is associated with more symptomatic statin intolerance, there is no proven benefit of preventive vitamin D supplementation when its serum levels are normal. The role of vitamin D in the cause of SAMS is not completely understood, due to the lack of evidence. Therefore, pathophysiological theories of vitamin D actions are still to be demonstrated [24]. A previous meta-analysis found that low vitamin D levels were associated with the presence of myalgia in statin-treated patients [25]. Statin lipophilicity may play a role in the development of myopathy in relationship with low vitamin D status, thus low lipophilic statins, like pravastatin and rosuvastatin, can exert fewer adverse reactions when a statin is reintroduced [26].

STATIN-BASED THERAPEUTIC OPTIONS

When statin intolerance occurs, certain treatment options should be considered in terms of lipid-lowering therapy, including a temporary decrease of statin dose, switch to a different statin at a lower dose and prescription of intermittent dosages (Fig. 1) [27,28,29▪]. Furthermore, ezetimibe combination with the maximal tolerated statin dose is currently recommended by the latest guidelines [3], as well as by the Working Group on Cardiovascular Pharmacotherapy, in their recent expert opinion article on statin adherence, to achieve LDL-C goals, with better outcomes and fewer adverse events [29▪]. Indeed, the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial demonstrated that high-risk patients and patients with diabetes mellitus have greater benefit from statin–ezetimibe combination vs. statin alone, with improved tolerability [30].

The combination of statins with a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor, such as evolocumab or alirocumab, was also reported to safely reduce CVD risk, by improving CVD outcomes, in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial [31] and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY) trial [32]. PCSK9 inhibitors are particularly useful in patients with atherosclerotic CVD and familial hypercholesterolemia to attain LDL-C goal and thus reduce cardiovascular risk [33▪]. In patients with statin intolerance, evolocumab (140 or 420 mg every 2 weeks) had a significantly greater effect on LDL-C lowering as compared with ezetimibe in doses of 10 mg daily (reduction of LDL-C levels by 53–56% for evolocumab and 37–39% for ezetimibe, $P < 0.001$), with fewer muscle adverse effects (12% for evolocumab, 23% for ezetimibe), as shown in the Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2 trial over a 3-month period [34]. Similar results were reported for alirocumab in the ODYSSEY ALTERNATIVE trial. In this trial, alirocumab reduced LDL-C by 45%, whereas ezetimibe only showed 14% reduction, with a mean difference of 30.4% ($P < 0.0001$) and a lower rate of muscle symptoms as compared with the latter (hazard ratio 0.61, 95% CI 0.38–0.99,

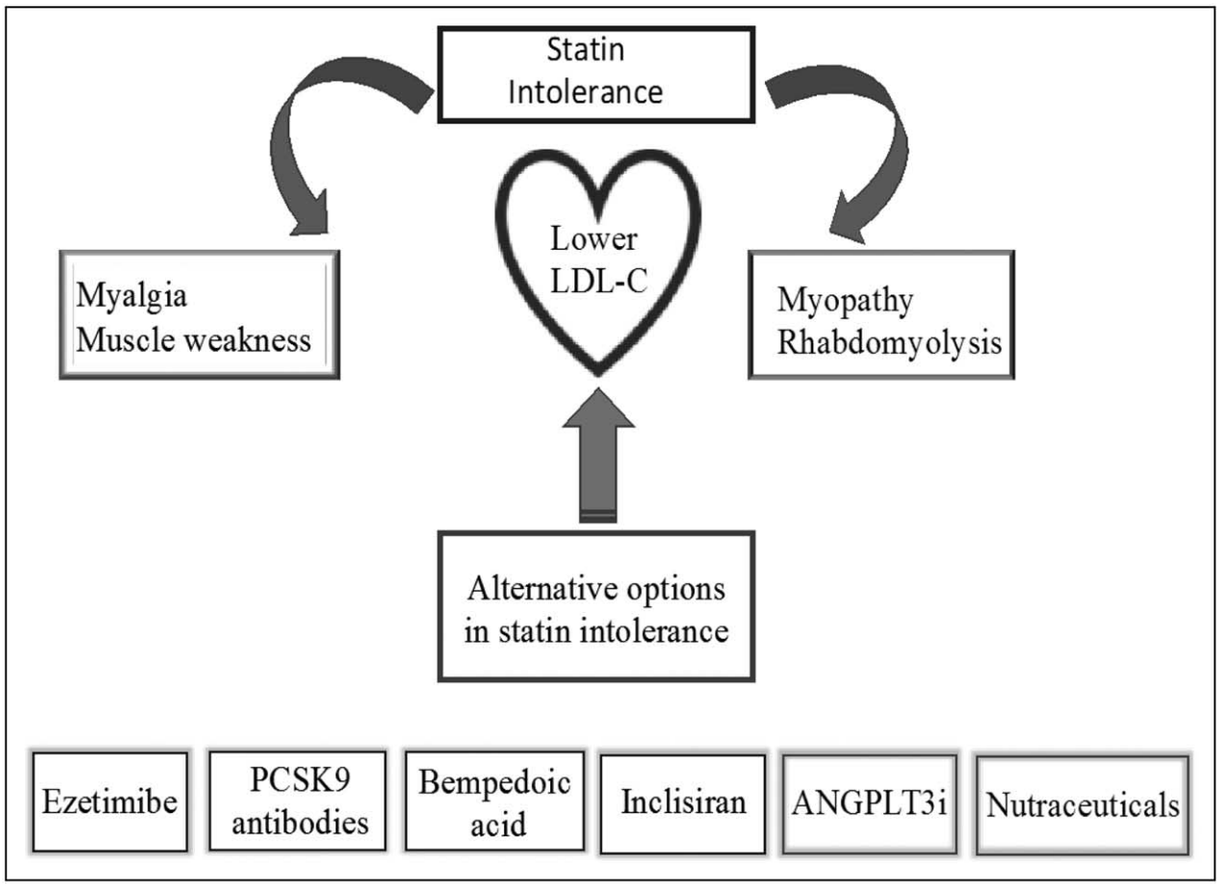

FIGURE 1. Statin intolerance treatment options.

$P = 0.042$) [35]. Current guidelines recommend the coadministration of PCSK9 inhibitors with the maximal tolerated statin dose to achieve LDL-C targets in the highest risk cases [3].

In a recent meta-analysis of three RCTs, inclisiran, a novel small interfering RNA molecule to PCSK9, significantly lowered LDL-C levels by 51% and decreased major adverse CVD events by 24% compared with placebo but this result was limited by small numbers of events [36]. Inclisiran modifies gene expression, leading to degradation of mRNA and decreased PCSK9 and LDL-C levels. One major advantage is the infrequent administration of this drug compared with other PCSK9 inhibitors (i.e., 2 vs. 12–16 injections/year) [33▪]. In a pooled analysis of the Inclisiran for Participants with Atherosclerotic Cardiovascular Disease and elevated LDL Cholesterol (ORION)-10 and ORION-11 trials involving 252 statin intolerant patients, inclisiran significantly lowered LDL-C levels compared with placebo (by 45.8%) with similar rates of myalgia (4.8 vs. 4.7% in the inclisiran vs. placebo groups) [37].

Bile acid sequestrants exert indirect benefits by limiting cholesterol absorption, followed by hepatic production of bile-rich cholesterol [38]. These drugs have many disadvantages, such as gastrointestinal intolerance and drug–drug interactions [38].

NONSTATIN THERAPIES AND INNOVATIVE HYPOLIPIDEMIC DRUGS

An mentioned above, both ezetimibe and PCSK9 inhibitors can be used in cases of statin intolerance, as recommended by the latest guidelines for the management of dyslipidemia [3].

Another therapeutic option in patients with statin intolerance are nutraceuticals, that is, molecules from natural sources with lipid-lowering properties [39,40]. For example, red yeast rice (RYR) contains monacolin K [41], a bioactive agent similar to lovastatin, that reversibly inhibits HMG-CoA reductase [42,43]. It has been shown that RYR potency to lower LDL-C is similar to moderate-intensity statins and that its safety profile is similar to that of low-dose statins [42]. Other nutraceuticals exerting lipid-lowering and atheroprotective properties include berberine, polydatin, *Opuntia ficus-indica*, curcumin, chlorogenic acid, bergamot, and

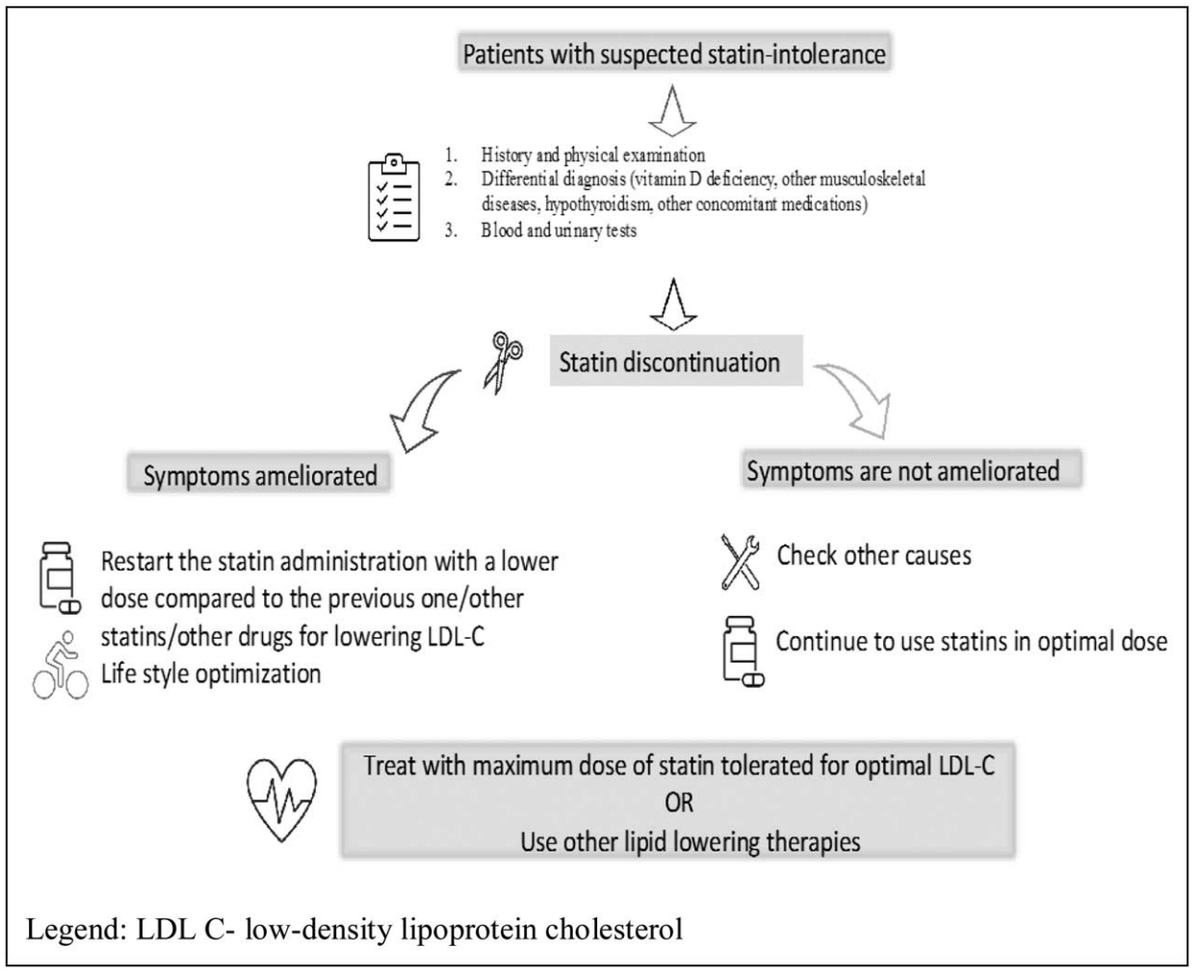

FIGURE 2. Statin intolerance proposed algorithm. LDL-C, LDL-cholesterol.

quercetin-3-O-b-d-glucoside [44–47]. Pharmaceuticals like $n-3$ PUFA-enriched fish oil, docosahexaenoic acid (DHA)-enriched canola oil, marine $n-3$ PUFAs have lipid-lowering effects and can be used [48].

Bempedoic acid represents a new lipid-lowering drug with a relatively significant potency, reducing LDL-C by 30% as monotherapy and 50% in combination with ezetimibe, and with minor side effects [3,33▪,49]. The mechanism of action involves ATP citrate lyase inhibition, an enzyme upstream of HMG-CoA reductase, thus lowering the cytosolic substrate for cholesterol synthesis. Bempedoic acid may also decrease high-sensitivity C-reactive protein levels and improve glycemic control [50]. Another advantage of this drug is the lack of muscle side effects, thus significantly increasing treatment adherence. The Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen 'CLEAR-Serenity' study showed that bempedoic acid significantly decreased LDL-C levels (by 21.4%) in patients with statin intolerance [51]. Furthermore, bempedoic acid was safe and well tolerated; myalgia occurred in fewer patients who received bempedoic acid than placebo (4.7 and 7.2%, respectively). The ongoing Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen NCT02993406 (CLEAR OUTCOMES) trial will provide evidence on the effects of bempedoic acid on lipids and CVD outcomes in statin intolerant patients [49,52].

Plant sterol ester supplements, either alone or in combination with $n-3$ FAs (eicosapentaenoic and DHA), are efficient in improving the lipid profile and nonalcohol fatty liver disease, as well as decreasing CVD risk, with evidence from RCTs [29▪,53]. Plant sterol esters or stanol esters can be used in statin-intolerant patients, with or without concomitant statin therapy [54].

Angiopoietin-like 3 (ANGPTL3) protein is a protein secreted by the liver, which inhibits lipoprotein lipase and endothelial lipase activity, thus increasing the levels of triglycerides and LDL-C and

hydrolyzing HDL-C [55]. The ANGPTL3 genetic variants with loss of function are associated with reduced levels of plasma lipoproteins, triglycerides, and cholesterol [56]. A fully human ANGPTL3 antibody, that is, evinacumab, has been recently developed, showing lipid-lowering effects in patients with homozygous familial hypercholesterolemia (HoFH) and severe mixed dyslipidemia [57–59]. The FDA very recently (February 2021) approved the use of evinacumab for the treatment of HoFH [59]. Apart from its efficacy, evinacumab is safe and well tolerated [60▪]. Further research is needed on its utility, especially in patients with statin intolerance.

There are other gene-editing therapies that should be evaluated in future research, including adenoviruses containing CRISPR–Cas9 (clustered regularly interspaced short palindromic repeats) that induce PCSK9 gene inhibition and adenoviral vector expressing BE3 that targets ANGPTL3 with promising results in murine studies [60▪].

CONCLUSION

Statins are generally well tolerated, representing the cornerstone of CVD and dyslipidemia treatment, with long-term demonstrated efficacy. However, statin intolerance may occur, leading to poor adherence to treatment and failure in lowering CVD risk. There are alternative therapeutic options if statin intolerance emerges, such as lowering statin dose, switching to a different statin, prescribing intermittent dosages and combining a statin with other lipid-lowering drugs, like ezetimibe, PCSK9 inhibitors, bempedoic acid, and ANGPTL3 inhibitors, as well as nutraceuticals (Fig. 2). In cases of complete statin intolerance, a nonstatin regimen is recommended to lower LDL-C levels. New therapies that address gene editing are emerging and may provide an additional treatment option in the future.

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- ▪ of special interest
- ▪▪ of outstanding interest

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