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Management of patients with statin intolerance

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Abstract

Atherosclerotic cardiovascular disease is a leading cause of morbidity and mortality, and statins have become a cornerstone in its treatment and prevention. Despite the well-documented benefits of statins, many patients stop taking them, with adverse muscle symptoms being a commonly cited reason. Although some statin-associated adverse muscle effects are real, some can be attributed to the nocebo effect, which is the patient's perception of harm. The purpose of this article is to review the literature on statin safety, particularly that related to muscle, to analyze adverse effects, and to propose various treatment strategies for the statin intolerant patient.

Keywords

statins; statin intolerance; statin-associated muscle symptoms; nocebo effect; bempedoic acid

Introduction (A)

Cardiovascular disease (CVD) remains the leading cause of death in the United States (U.S.), and identifying methods to reduce risk has become a top priority in the medical community (1). Since lovastatin became the first statin marketed in the U.S. in 1987, statins have become a critical approach for CVD risk reduction and are among the most prescribed medications in the U.S. (2). Numerous randomized controlled clinical trials (RCTs) and subsequent meta-analyses have proved that statins significantly reduce CVD, including myocardial infarction (MI) and stroke, as well as death from cardiovascular causes (3,4). The 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/ multispecialty cholesterol guidelines recommended that patients with clinical atherosclerotic

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cardiovascular disease (ASCVD) should have low-density lipoprotein cholesterol (LDL-C) levels lowered with high intensity statin or maximally tolerated statin therapy (5). Depending on the patient's ASCVD history and risk factors, treatment thresholds can be LDL-C greater than 70 or 100 mg/dL with a goal of ≥ 30% to 50% reduction in LDL-C levels.

Although statins are first line therapy for lowering LDL-C, long term adherence to statin therapy is not optimal. It is estimated that 10% of statin prescriptions are discontinued, which is associated with an increase in CVD events (6–9). Discontinuation is usually due to side effects attributed to the statin, reported by either the patient or the prescriber. Several adverse effects have been attributed to statins, with muscle symptoms being the most common. One definition of statin intolerance specifies that it is a clinical syndrome characterized by the inability to tolerate at least two statins: one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, reproducible by re-challenge and with other known determinants being excluded (10). The aim of this article is to review the extent and factors contributing to statin intolerance, discuss real versus nocebo effects, and describe treatment strategies for patients intolerant to statins.

Statin Pharmacology (A)

Statins decrease cholesterol production by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes the rate-limiting step in cholesterol synthesis. This causes depletion of intracellular cholesterol and induces the production of LDL receptors and increased uptake of LDL from the circulation (11,12). Seven statins are on the U.S market: lovastatin, simvastatin, atorvastatin, rosuvastatin, pravastatin, pitavastatin, and fluvastatin. Lovastatin and simvastatin differ structurally from the other statins in that they are closed-ring lactone pro-drugs and require conversion to the open ring form in the liver and gastrointestinal tract to become biochemically active. The other statins exist as open ring hydroxy acids (12). Statins are taken orally and generally have low bioavailability. Bioavailability, defined as the percentage of administered drug that reaches the systemic circulation, is low for most statins, particularly simvastatin and lovastatin (≈5%) which undergo extensive hepatic first pass metabolism (11). Pitavastatin has the highest bioavailability of approximately 60% (12). Drugs with very low bioavailability (i.e. simvastatin and lovastatin), tend to be more vulnerable to drug-drug interactions.

There are three categories of statin intensity based on efficacy in lowering LDL-C levels: high-, moderate-, and low-intensity statin doses. High-intensity statin doses lower LDL-C levels by ≥50%, moderate-intensity by 30% to 49%, and low-intensity by <30% (5). High-intensity statin therapy is atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily. Moderate-intensity is atorvastatin 10–20 mg daily, rosuvastatin 5–10 mg daily, simvastatin 20–40 mg daily, pravastatin 40–80 mg daily, lovastatin 40–80 mg daily, fluvastatin 40 mg BID, fluvastatin XL 80 mg daily, or pitavastatin 1–4 mg daily. Low-intensity statin therapy is simvastatin 10 mg daily, pravastatin 10–20 mg daily, lovastatin 20 mg daily, or fluvastatin 20–40 mg daily (5).

Statin metabolism begins with uptake into hepatocytes, primarily mediated by the organic anion transporting polypeptides OATP1B1 (organic anion transporting polypeptide 1B1) and OATP1B3 (organic anion transporting polypeptide 1B3) (11). Once inside hepatocytes, statins rapidly undergo oxidation through microsomal cytochrome P450 (CYP450) enzymes. The CYP3A4 isoenzyme metabolizes lovastatin, simvastatin, and atorvastatin, whereas CYP2C9 metabolizes fluvastatin, pitavastatin, and rosuvastatin. Pravastatin is not metabolized by the CYP isoenzyme family. Efflux of statins from cells is mediated by the ATP-binding cassette subfamily B (ABCB) transporters (12). Statins are eliminated from the body by either the liver via bile into feces or the kidneys into urine. Atorvastatin and rosuvastatin have the longest half-lives (20 hours) followed by pitavastatin (10–12 hours) (11,12). The other statins have shorter half-lives of 4 hours or less. Although hepatic cholesterol biosynthesis reaches a peak at night, there is minimal difference in cholesterol lowering between morning and evening dosing of short-acting statins (13). Thus, all statins can be dosed at any time of day.

Adverse Effects (A)

Several adverse effects have been attributed to statins including hepatotoxicity, diabetes mellitus, renal impairment, and central nervous system dysfunction. However, this review will focus on muscle effects. The AHA scientific statement on statin safety (11) provides an extensive review of these concerns.

Muscle Symptoms (B)

Muscle symptoms are the most cited reason for statin discontinuation (7,14), and the terminology used to describe the effects of statins on muscle varies (Table 1). This article will use the definition that has been accepted by the FDA and that is specified in the current prescribing information for all statins that provide a definition (11,15). Myopathy is defined as unexplained muscle pain or weakness, or both, plus an increase in creatine kinase (CK) concentration >10 times the ULN. Rhabdomyolysis is a severe form of myopathy with a less consistent definition, usually defined as markedly elevated CK levels (often >40 times the ULN), requiring hospitalization, and associated with acute renal failure due to toxic effects of myoglobin on the kidneys (11). Myalgia is defined as muscle pain or aches. Statin-associated muscle symptoms (SAMS) is a term used to describe muscle symptoms that occur in the presence of statin use, but it does not imply causation by the statin (11). Muscle symptoms are typically bilateral and symmetrical and confined to skeletal muscle. Cardiomyopathy has not been associated with any statins (11).

Based on data from large RCTs, statin-associated myopathy is rare and occurs in 0.1–0.3% of patients on statins, which does not significantly differ from placebo (16,17). The risk of myopathy tends to be highest in the first year of therapy and is also related to the statin dose and other drug interactions (18) (See below). Rhabdomyolysis is rare with a risk of less than 0.1% (16–18). In a retrospective cohort study, Graham et al. searched the hospital records of 252,460 statin users and identified 24 patients who had been admitted to the hospital for rhabdomyolysis (19). For the statins commonly used at the time of the study (atorvastatin, simvastatin, and pravastatin), the rate of hospitalization due to

rhabdomyolysis was estimated as 0.44 per 10,000 patient-years (95% CI, 0.20–0.84) when used as monotherapy and 5.98 per 10,000 patient-years (95% CI, 0.72–216.0) when used together with a fibrate (primarily gemfibrozil). With monotherapy, cases occurred after a mean length of therapy of 348 days for atorvastatin or simvastatin (range, 21–1050 days), and 77 days for gemfibrozil (range, 21–179 days). The mean time to onset after initiation of combined statin-fibrate therapy was 32 days (range, 18–78 days). Factors that have been associated with increased risk of myopathy and rhabdomyolysis include older age (>65 years), renal impairment, preexisting muscle disease, hypothyroidism, and East Asian descent (11,19).

Before myopathy or rhabdomyolysis is attributed to a statin, it is prudent to exclude other causes such as unusual or strenuous exercise and hypothyroidism since these conditions can be associated with muscle weakness and elevated CK levels. Measurement of vitamin D may be useful because vitamin D deficiency can cause muscle pain and weakness independently of statin use (20). CK should be measured in any patient presenting with significant unexplained muscle symptoms or unexplained increases in transaminases greater than 3 times the ULN because these enzymes are found in both muscle and liver (11). If CK is elevated >10 times the ULN (or >5 times the ULN in a vulnerable patient), the statin should be stopped immediately and high fluid intake started. If the patient is at high risk of renal failure, hospital admission may be needed. If the CK elevation is moderate (between 3 and 4 times the ULN), and symptoms are mild, the statin can be continued and the CK level repeated within a few days. If the CK level is decreasing or stable, the statin can be continued with timing of follow up to be guided by degree of CK elevation, symptoms, and medical history. Coenzyme Q10 supplementation has been proposed for the treatment or prevention of SAMS, but RCT data regarding its efficacy is mixed and does not consistently support this (21–23). The same is true for vitamin D supplementation (24–26).

Autoimmune Myopathy (B)

In most cases of statin-associated myopathy, symptoms will abate after discontinuation of the statin. In exceptionally rare cases, an autoimmune myopathy may develop. Statin-associated autoimmune myopathy (SAAM) has an estimated incidence of 2 to 3 of every 100,000 patients treated with statins (27). Onset of symptoms is variable and can range from occurring immediately to years after statin initiation. In a systematic review by Nazir et al (28), 16 articles describing 100 patients with SAAM were identified. The mean age of presentation was 64.72 years, and 54.44% were males. The mean duration of statin use prior to myopathy symptom onset was 40.48 months.

On physical examination, patients with SAAM typically present with proximal muscle weakness, typically difficulty rising from a chair, ascending steps, and lifting heavy objects. Some patients may have mild joint pains or rash. On laboratory evaluation, the CK level is universally and persistently elevated in patients with active disease; and in nearly 90% of cases, the level exceeds 2000 IU/L, more than 10 times the ULN (27). Nazir et al, found mean CK was 6853 IU/L, which was 45 times the ULN (28). On muscle biopsy, the most prominent histologic features in patients with SAAM are muscle cell necrosis and infiltration by macrophages. The presence of autoantibodies against HMG-CoA reductase in

the context of statin exposure, muscle symptoms, and elevated CK supports the diagnosis of SAAM (27). However, autoantibodies against HMG-CoA reductase have also been observed in patients with autoimmune myopathy who have never been exposed to a statin (29); so clinical history is important for establishing the diagnosis. Nazir et al noted that anti-HMG-CoA reductase antibodies were positive in all the patients who were tested (57/57, 100%) (28).

Treatment of SAAM involves lifelong avoidance of statins and, in most cases, requires a course of immunosuppression. Steroids are usually first line, with starting doses equivalent to prednisone 1 mg/kg per day (27). Unless the patient has only mild weakness, another agent such as methotrexate, azathioprine, or mycophenolate mofetil, should be included at the outset. In those in whom severe weakness develops or in whom the condition does not respond to the initial combination of medications after 8 to 12 weeks, intravenous (IV) immune globulin or another agent, such as rituximab, may be added. Once patients recover strength, immunosuppressive medications should be gradually tapered while paying close attention to signs of recurrence. Some patients may relapse and require long term treatment. Employing the expertise of a neurologist or rheumatologist is helpful for the management of patients with this rare condition.

SAMS in the Absence of CK elevation and the Nocebo Effect (B)

True statin-associated myopathy is rare, but statin-associated muscle symptoms (SAMS) in the absence of CK elevation are common. Analysis of multiple large RCTs has shown that the incidence of SAMS in treatment arms is generally not statistically or clinically different from placebo. In a meta-analysis of safety data, Collins et al (30) reported symptomatic musculoskeletal event rates from 15 major statin RCTs included in the Cholesterol Treatment Trialists (CTT) collaboration. This included information on myalgia or muscle aching (or muscle-specific events with a similar description) in 12 trials with >100,000 participants along with a meta-analysis of this outcome in the 12 trials. Nine contributing trials found no significant increase in myalgia or muscle aching in patients allocated to a statin relative to those allocated to placebo. Three trials, (HOPE-3 [Heart Outcomes Prevention Evaluation-3], JUPITER [Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin], and ASPEN [Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints]) reported small but statistically significant increases in muscle symptoms (up to 1.4% absolute difference) between statin- and placebo-treated groups. The pooled results of the 12 trials found a nonsignificant difference in these muscle symptoms in participants allocated to statins [5162 (11.7%)] versus in participants allocated to placebo [5015 (11.4%); P=0.10] (11).

Myalgia may affect 5 to 10% of patients taking statins (31); and although some SAMS could be a true effect of the statin, there is likely a nocebo effect as well. The word nocebo comes from Latin and means “I will harm,” the opposite of placebo or “I will please” (11,32). The nocebo effect refers to adverse effects, usually subjective, that result from expectations of harm from a drug, placebo, other therapeutic intervention, or a nonmedical situation. These expectations can be driven by many factors such as warnings about adverse effects communicated by clinicians when prescribing a drug, the informed consent form

in a clinical trial, information on the Internet and social media, health scares propagated by broadcast and print media, and observation of symptoms and behavior of others (32). The nocebo and placebo effects reflect normal human neuropsychology and are real to the patient. Clinicians should avoid being dismissive of patient concerns or implying they are fabricated since doing so can undermine patient trust and hurt future chances of continuing therapy.

Multiple studies have shown that many patients with statin-associated muscle symptoms do not have muscle symptoms that are specifically due to statins (21,33,34). N-of-1 studies have been helpful in determining response to statins on an individual level. Wood et al (35) performed a double-blind, three-group, n-of-1 trial in 60 patients (49 of whom completed the full 12-month trial) who had previously discontinued statins because of side effects that occurred within 2 weeks after the initiation of treatment. The patients were given four bottles containing atorvastatin 20 mg tablets, four bottles containing placebo tablets, and four empty bottles; each bottle was to be used for a 1-month period according to a random sequence. Patients rated their symptoms daily on a scale from 0 (no symptoms) to 100 (worst symptoms imaginable). The primary end point was symptom intensity as assessed with the use of the nocebo ratio (i.e., the ratio of symptom intensity induced by taking placebo to the symptom intensity induced by taking a statin). At the end of the study period, the pooled nocebo ratio was 0.9. Among all 60 patients, the mean symptom intensity was 8.0 during no-tablet months (95% CI, 4.7 to 11.3), 15.4 during placebo months (95% CI, 12.1 to 18.7; $P<0.001$ for the comparison with no-tablet months), and 16.3 during statin months (95% CI, 13.0 to 19.6; $P<0.001$ for the comparison with no-tablet months and $P=0.39$ for the comparison with placebo months). Thus, in patients who had discontinued statin therapy because of side effects, 90% of the symptom burden elicited by a statin challenge was also elicited by placebo. Half of the trial patients (30/60) were able to successfully restart statins. Herrett et al performed N-of-1 studies in a larger cohort of patients (N=151) who were randomized to a sequence of six double blinded treatment periods (two months each) of atorvastatin 20 mg daily or placebo (36). There was no significant difference in muscle symptoms between the statin and placebo treatment periods, and two thirds of those completing the trial reported restarting long term treatment with statins.

Factors that Contribute to Statin Adverse Effects (A)

Many factors can influence the development of statin-associated adverse effects, and they range from pharmacologic to inherent patient attributes. Some of these factors are listed in Table 2 and discussed further below.

Drug-Drug Interactions (B)

A drug-drug interaction (DDI) is a pharmacokinetic or pharmacological influence of one medication on another that differs from the known or anticipated effects of each agent alone (37). A DDI may result in a change in either drug efficacy or drug toxicity for one or both of the interacting medications. In the case of statins, this is most often due to inhibition of one of the enzymes or transporters involved in statin metabolism that leads to an increase in the systemic plasma concentration of the statin or its active metabolites. Statins are

generally the “victim” of DDIs, not the “perpetrator” (11). Thus, it is usually the other drug that leads to toxic levels of the statin, not the other way around. The exception to this is warfarin, for which some statins (simvastatin, lovastatin, fluvastatin, and rosuvastatin) have been shown to decrease dose requirements and slightly increase INR and bleeding risk (37). The proposed mechanism involves inhibition of CYP2C9 or CYP3A4 (38). Simvastatin and lovastatin are the most vulnerable statins to DDI. They are metabolized by CYP3A4 and undergo extensive elimination of nearly 95% via the liver which leads to low bioavailability of roughly 5% (11). Therefore, even minor inhibition of hepatic elimination can greatly increase their plasma concentrations.

In 2016, the AHA published a report with recommendations for noteworthy statin DDIs in patients with CVD. Of the statin DDIs described, the combinations most likely to cause harm were gemfibrozil and the immunosuppressive agents cyclosporine, tacrolimus, sirolimus, and everolimus (37). Gemfibrozil has been shown to increase the area under the curve (AUC) of simvastatin, lovastatin, and pravastatin by 2–3-fold, which increases the risk of muscle toxicity. The increases in AUC for other statins is smaller. In 2001, cerivastatin was withdrawn from the U.S. market due to increased cases of rhabdomyolysis and death when combined with gemfibrozil (39), which occurred despite a black box warning to avoid combination with gemfibrozil. This interaction with statins is especially problematic in patients who have concurrent hypertriglyceridemia. Fenofibrate is efficacious in lowering triglycerides but has minimal effects on statin plasma concentrations and is less likely to cause muscle toxicity. Therefore, fenofibrate is the preferred fibrate for treatment of hypertriglyceridemia in patients who are already on a statin (5).

Bempedoic acid is an emerging lipid-lowering agent that has been shown to increase the AUC for simvastatin and pravastatin; doses of these statins should not exceed 20 mg and 40 mg daily, respectively (40). Dose adjustments of other statins with bempedoic acid are not required. Other important drug interactions with statins include cyclosporine, tacrolimus, sirolimus, anti-retroviral medications, some anti-infection drugs, and amiodarone. Some of these DDIs are summarized in Table 3. For a comprehensive listing of DDIs, the prescription labels for each statin and pharmacology websites can be referenced.

Pharmacogenetics (B)

Pharmacogenetics, the study of how genes can impact drug disposition, has been helpful in understanding how individuals metabolize and respond to drugs. In the case of statin-induced myopathy, a 2008 genome-wide association study (GWAS) reported the first pharmacogenetic association: solute carrier organic anion transporter family member 1B1 (SLCO1B1), which encodes the hepatic transporter OATP1B1 (41,42). Since then, studies of other genes involved in statin metabolism including cytochrome P450 isoenzymes and ABC subfamilies have been performed with mixed results (41). Only the 5* allele of the SLCO1B1 gene has so far been consistently associated with statin-induced myopathy, and only with simvastatin (11). Given the ambiguity in findings, more research in elucidating the pharmacogenomic impact of these genes is needed before routine genetic testing for statin intolerance can be recommended.

Advanced Age (B)

Elderly patients are susceptible to drug toxicity due to decreased glomerular filtration by the kidney and less effective enzymatic metabolism in the liver. Polypharmacy is also a common problem with the potential for multiple drug interactions. Statins are often part of the problem. None of the statins require dose reduction based on age-related pharmacokinetic factors alone (11). Some of the large statin RCTs with thousands of patients excluded elderly patients. However, PROSPER enrolled patients 70 to 82 years of age (43). In this trial comparing pravastatin 40 mg to placebo, serious adverse event rates were similar between groups, and there were no cases of rhabdomyolysis. Safety data were published for the patients 65 to 75 years of age who participated in CARDS and for patients ≥70 years of age in JUPITER (44,45). No differences were observed in the rate of adverse events between older and younger patients and between older patients allocated to treatment versus those allocated to placebo. Despite their safety, data to support the prescribing of statins for primary prevention of ASCVD in those ≥75 years of age are mixed, The AHA/ACC guidelines recommend a shared decision-making approach to decide if the benefits of statin use outweigh the risks in this population (5).

Asian Ancestry (B)

Many people of East Asian descent have genetic mutations in enzymes and transporters involved in statin metabolism that lead to increased plasma levels of some statins or their active metabolites (46,47). Therefore, a lower starting dose may be needed in this population, such as 5mg daily for rosuvastatin (48).

Media (B)

Clinicians must contend with a plethora of health information available online. What patients read on the internet can contribute to the nocebo effect and avoidance of beneficial therapies. One study by Khan et al sought to elucidate whether the number of websites about statin side effects found with the search engine Google was associated with the prevalence of statin intolerance (49). The prevalence of statin intolerance in 13 countries across 5 continents was established from a web-based survey of 810 primary care providers and specialists. Using the Google search engine for each country, the number of websites about statin side effects was determined and standardized to the number of websites about statins overall. English-speaking countries (Australia, Canada, United Kingdom, United States of America) had the highest prevalence of statin intolerance and the largest standardized number of websites about statin side effects. The sample Pearson correlation coefficient between these two variables was 0.868 showing a possible correlation between the prevalence of statin intolerance and the amount of information pertaining to statin adverse effects available online.

In addition, many websites propose unproven alternative cholesterol-lowering therapies such as special diets or supplements that are not regulated by the FDA. An internet search for the term “dietary supplements to lower cholesterol” yields thousands of results advocating such products as garlic capsules, policosanol, lavender oil, green tea capsules, artichoke leaf extract, red yeast rice, and many others (50). To combat misinformation, clinicians must

be diligent in educating patients about the facts pertaining to statins and lipid-lowering therapies.

Approaches to Management of Statin Intolerance (A)

Statin discontinuation in patients at risk of ASCVD is associated with an increase in major adverse cardiovascular events (MACE) and mortality. Although statins are well tolerated in clinical practice, convincing patients who report adverse effects with statin use, especially muscle symptoms, to continue a statin can be difficult. Rather than abandoning statin therapy after one failed attempt of a maximum dose statin, helpful strategies include rechallenge of the statin with a lower dose, intermittent dosing, or switching to a different statin.

The first step in a statin rechallenge is to stop the statin and allow a 2-week washout period to see if the symptoms resolve (51). After the washout period, the same statin can be tried at a lower dose, or a different statin can be tried. Switching to a statin that is metabolized by a different pathway may work for some patients. For example, if a patient was unable to tolerate atorvastatin which is lipophilic and primarily cleared by the liver, they may have better tolerance with rosuvastatin which is hydrophilic and cleared by both the kidneys and liver (52). For patients who are very reluctant to try a statin or who have failed more than one statin at daily doses, intermittent dosing with an extended half-life statin (rosuvastatin, atorvastatin, and pitavastatin) may be a viable option. Dosing can start with one tablet per week and then an additional tablet can be added weekly every 1 to 2 weeks as tolerated. Giving the patient control over the titration schedule can be helpful. Ideally patients would reach daily dosing, but every other day (EOD) dosing can be effective in lowering LDL-C levels. In a retrospective study of 51 patients intolerant to statins, Backes et al found that 72.5% (37/51) were able to tolerate an EOD rosuvastatin (mean dose 5.6 mg) regimen for 4 ± 2.9 (mean ± SD) months (53). Mean LDL-C decreased 34.5% ($p<0.001$) in patients who tolerated the regimen, enabling approximately 50% to achieve their LDL-C goal.

If the decision is made to try a non-statin lipid-lowering agent, factors such as side effects, route of administration, and cost should be kept in mind. Statins and ezetimibe are inexpensive at roughly $5 and $10 a month, respectively (54). Without insurance coverage, the costs of PCKSK9 inhibitors and bempedoic acid (discussed below) are much higher at roughly $500 and $400 a month, respectively.

Ezetimibe (B)

For patients unable to achieve adequate LDL-C levels with maximally tolerated statin, ezetimibe is recommended as the next agent (5). Ezetimibe targets the Niemann–Pick C1–like 1 (NPC1L1) protein, thereby reducing absorption of cholesterol from the intestine (55). The IMPROVE-IT trial demonstrated a cardiovascular outcomes benefit with the addition of ezetimibe to simvastatin in patients with a history of acute coronary syndrome. Ezetimibe lowered LDL-C levels by an additional 24% compared with simvastatin alone (55). No significant between-group differences were seen in the percentage of patients who had ALT elevations greater than 3 times the ULN or muscle-related adverse effects.

Prescribers must effectively communicate that ezetimibe is not a statin because patients are commonly under the impression that it is a statin (51). An important counseling point with ezetimibe involves the limited systemic effects and low potential for causing adverse muscle effects. The standard dose for ezetimibe is 10 mg daily; however, fearful patients could start with one-half tablet daily.

PCSK9 Inhibitors (B)

Patients unable to achieve adequate LDL-C levels with maximally tolerated statin and ezetimibe may benefit from proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (5). Inhibition of PCSK9 leads to increased expression of the LDL receptor on hepatocytes and thus increased clearance of LDL-C from the systemic circulation (56). In clinical trials, alirocumab and evolocumab significantly lowered LDL-C levels by 50–60% compared to standard therapy alone (57, 58). The ODYSSEY-ALTERNATIVE and GAUSS-3 trials done in patients with statin intolerance showed that these medications led to few muscle side effects (33,59). Due to their randomized, double-blind designs, these trials also showed that many patients with muscle symptoms attributed to statins tolerated moderate dose statin during the study.

Bempedoic Acid (B)

In February 2020, the FDA approved the use of the novel agent bempedoic acid for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established ASCVD who require additional lowering of LDL-C (60,61). Bempedoic acid is a small molecule that lowers LDL cholesterol levels by inhibiting ATP citrate lyase, a key enzyme in the cholesterol biosynthesis pathway that acts upstream of HMG-CoA reductase, the target for statins (62). Because bempedoic acid has a different mechanism of action compared with other lipid-lowering therapies, it provides complementary LDL-C lowering with concomitant statin, ezetimibe (blocking intestinal cholesterol absorption), and/or PCSK9 inhibitor (preventing LDL receptor degradation) therapy (40). It is a prodrug that is activated only in the liver. There is the potential for fewer muscle side effects since active medication is not present in muscle. CLEAR-Wisdom and CLEAR-Harmony were phase 3 double-blind placebo-controlled RCTs that studied the efficacy of bempedoic acid in a combined total of nearly 3,000 patients who had LDL-C levels greater than 70 mg/dL on maximally tolerated lipid-lowering therapy (62,63). At 12 weeks, bempedoic acid led to significant reductions in LDL-C of 15–16% compared to placebo (between treatment group differences 17–18%). The LDL-C reduction was sustained at 52 weeks. Bempedoic acid also led to significant improvements in non-high-density lipoprotein cholesterol (HDL-C), total cholesterol, apolipoprotein B (apoB), and high-sensitivity C-reactive protein (hsCRP). An increased incidence of hyperuricemia was observed with bempedoic acid. There were no significant differences in muscle symptoms, CK elevations, or liver enzyme elevations between the treatment groups. The CLEAR Serenity trial focused on the efficacy and safety of bempedoic acid in 345 patients with statin intolerance and showed significant reductions in LDL-C (placebo-corrected difference, −21.4% [95% CI, −25.1% to −17.7%]; P<0.001), non-HDL-C, total cholesterol, apoB, and hsCRP compared to placebo at 12 weeks with no significant difference in muscle adverse events (64). A cardiovascular outcomes trial with bempedoic acid is in progress (65).

Lipid-lowering effects are greater when bempedoic acid is combined with ezetimibe. In a phase 3 double-blind RCT by Ballantyne et al (66), 301 patients with risk factors for ASCVD who had uncontrolled LDL-C levels on maximally tolerated statin therapy were randomized 2:2:2:1 to oral, once-daily treatment with bempedoic acid 180 mg plus ezetimibe 10 mg, bempedoic acid 180 mg, ezetimibe 10 mg, or placebo for 12 weeks. The mean baseline LDL-C level was 149.8 mg/dL. At week 12, the fixed-dose combination lowered LDL-C (–36.2%) significantly more than placebo (1.8% (placebo-corrected difference –38.0%); $P < 0.001$), ezetimibe alone (–23.2%; $P < 0.001$) or bempedoic acid alone (–17.2%; $P < 0.001$). The fixed-dose combination lowered LDL-C levels similarly across subgroups, including patients receiving high-intensity, other-intensity or no statin therapy. Improvements with the fixed-dose combination were also observed in secondary efficacy endpoints, including hsCRP. In this trial, fixed-dose combination treatment had a similar safety profile compared with bempedoic acid, ezetimibe or placebo. The CLEAR Tranquility trial studied the safety and efficacy of adding bempedoic acid to baseline lipid-lowering therapy that included ezetimibe in 269 patients with statin intolerance and showed significant reductions in LDL-C (−23.5% bempedoic acid, +5.0% placebo, $p < 0.001$), non-HDL-C, total cholesterol, apoB, and hsCRP compared to placebo plus ezetimibe with no significant difference in muscle adverse events and other adverse events (67). Less common adverse effects of bempedoic acid include mild creatinine increase, decreased hemoglobin, and rare instances of tendon rupture (40).

The above studies showed the efficacy of bempedoic acid in patients on maximally-tolerated statin therapy, but recent data has shown that bempedoic acid is also effective in patients who are not on any statin. Laufs et al performed a pooled analysis of data from patients enrolled in four phase 3 bempedoic acid studies (12 to 52 weeks in duration) who were not taking concomitant statins and a phase 3 bempedoic acid plus ezetimibe fixed-dose combination study (68). They found that in patients with hypercholesterolemia unable to take statins, bempedoic acid lowered LDL-C levels by a mean of 26.5% vs placebo and bempedoic acid + ezetimibe fixed-dose combination lowered LDL-C by 39.2%. The treatments were generally well tolerated, suggesting that bempedoic acid may be efficacious and well tolerated in this challenging-to-treat patient population.

Inclisiran (B)

Inclisiran is another novel lipid-lowering agent that was approved by the FDA in December 2021 for adults with HeFH or clinical ASCVD on maximally-tolerated statin therapy who require additional lowering of LDL-C (69). Inclisiran is a small interfering RNA (siRNA) that reduces hepatic synthesis of PCSK9 and has the convenience of dosing once every 6 months (70). The ORION-10 and ORION-11 phase 3 clinical trials combined recruited over 3,100 patients with ASCVD or ASCVD risk equivalent(s) and elevated LDL-C levels in spite of maximally tolerated statin therapy and randomized them 1:1 to receive inclisiran or placebo. At 90 and 540 days of treatment, inclisiran led to significant LDL-C reductions of roughly 50% compared to placebo. Adverse events were generally similar in the inclisiran and placebo groups in each trial, although injection-site adverse events were more frequent with inclisiran than with placebo.

Conclusions (A)

Atherosclerotic cardiovascular disease is a leading cause of morbidity and mortality. Thus, developing effective preventive therapies is crucial. Statins have been shown to decrease the risk of MACE, but many patients are unable or unwilling to take them. Muscle complaints are a major reason for statin discontinuation. It is important to recognize that the nocebo effect is real. Careful attention to informing patients of the true risks and benefits of statins is essential. Several current and upcoming lipid-lowering therapies such as ezetimibe, PCSK9 inhibitors, bempedoic acid, and inclisiran can be effective in helping patients at risk of ASCVD achieve their lipid goals when they are unable to do so with a maximally tolerated statin. Trials studying the efficacy and long-term outcomes of these agents are needed to guide clinical practice. Employing shared decision-making with patients can go a long way towards building trust and improving the odds of therapeutic success.

References

1. FastStats 2021/10/20/T03:48:58Z 2021; https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm. Accessed 2021/11/01
2. The Top 300 of 2019 https://clincalc.com/DrugStats/Top300Drugs.aspx. Accessed 2021/11/01
3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet Oct 8 2005;366(9493):1267–78. doi:10.1016/s0140-6736(05)67394-1 [PubMed: 16214597]
4. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet Nov 13 2010;376(9753):1670–81. doi:10.1016/s0140-6736(10)61350-5 [PubMed: 21067804]
5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation Jun 18 2019;139(25):e1082–e1143. doi:10.1161/cir.0000000000000625 [PubMed: 30586774]
6. Vinogradova Y, Coupland C, Brindle P, Hippisley-Cox J. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. Bmj Jun 28 2016;353:i3305. doi:10.1136/bmj.i3305 [PubMed: 27353261]
7. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. Journal of Clinical Lipidology Sep-Oct 2013;7(5):472–83. doi:10.1016/j.jacl.2013.03.001 [PubMed: 24079289]
8. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Annals of Internal Medicine*. Apr 2 2013;158(7):526–34. doi:10.7326/0003-4819-158-7-201304020-00004 [PubMed: 23546564]
9. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. European Heart Journal Mar 14 2016;37(11):908–916. doi:10.1093/eurheartj/ehv641 [PubMed: 26643266]
10. Guyton JR, Bays HE, Grundy SM, Jacobson TA, The National Lipid Association Statin Intolerance P. An assessment by the Statin Intolerance Panel: 2014 update. Journal of Clinical Lipidology May-Jun 2014;8(3 Suppl):S72–81. doi:10.1016/j.jacl.2014.03.002 [PubMed: 24793444]
11. Newman CB, Preiss D, Tobert JA, et al. Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association. Arteriosclerosis, Thrombosis, and Vascular Biology Feb 2019;39(2):e38–e81. doi:10.1161/atv.0000000000000073 [PubMed: 30580575]
12. Sirtori CR. The pharmacology of statins. Pharmacological Research Oct 2014;88:3–11. doi:10.1016/j.phrs.2014.03.002 [PubMed: 24657242]

13. Hunninghake DB, Mellies MJ, Goldberg AC, et al. Efficacy and safety of pravastatin in patients with primary hypercholesterolemia. II. Once-daily versus twice-daily dosing. Atherosclerosis Dec 1990;85(2–3):219–27. doi:10.1016/0021-9150(90)90114-x [PubMed: 2129319]

14. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. Journal of Clinical Lipidology May-Jun 2012;6(3):208–15. doi:10.1016/j.jacl.2012.03.003 [PubMed: 22658145]

15. Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. American Journal of Cardiology Nov 11 1988;62(15):28j–34j. doi:10.1016/0002-9149(88)90004-5

16. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine Nov 20 2008;359(21):2195–207. doi:10.1056/NEJMoa0807646 [PubMed: 18997196]

17. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. New England Journal of Medicine Aug 10 2006;355(6):549–59. doi:10.1056/NEJMoa061894 [PubMed: 16899775]

18. Armitage J, Bowman L, Wallendszus K, 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 Nov 13 2010;376(9753):1658–69. doi:10.1016/s0140-6736(10)60310-8 [PubMed: 21067805]

19. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. Jama Dec 1 2004;292(21):2585–90. doi:10.1001/jama.292.21.2585 [PubMed: 15572716]

20. Dawson-Hughes B Vitamin D and muscle function. Journal of Steroid Biochemistry and Molecular Biology Oct 2017;173:313–316. doi:10.1016/j.jsbmb.2017.03.018 [PubMed: 28341251]

21. Taylor BA, Lorson L, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. Atherosclerosis 2015;238(2):329–335. doi:10.1016/j.atherosclerosis.2014.12.016 [PubMed: 25545331]

22. Derosa G, D'Angelo A, Maffioli P. Coenzyme q10 liquid supplementation in dyslipidemic subjects with statin-related clinical symptoms: a double-blind, randomized, placebo-controlled study. Drug Design, Development and Therapy 2019;13:3647–3655. Published 2019 Oct 21. doi:10.2147/DDDT.S223153 [PubMed: 31695332]

23. Bookstaver DA, Burkhalter NA, Hatzigeorgiou C. Effect of coenzyme Q10 supplementation on statin-induced myalgias. The American Journal of Cardiology 2012;110(4):526–529. doi:10.1016/j.amjcard.2012.04.026 [PubMed: 22608359]

24. Wu Z, Camargo CA Jr, Khaw KT, et al. Effects of vitamin D supplementation on adherence to and persistence with long-term statin therapy: Secondary analysis from the randomized, double-blind, placebo-controlled ViDA study. Atherosclerosis 2018;273:59–66. doi:10.1016/j.atherosclerosis.2018.04.009 [PubMed: 29684661]

25. Taylor BA, Lorson L, White CM, Thompson PD. Low vitamin D does not predict statin associated muscle symptoms but is associated with transient increases in muscle damage and pain. Atherosclerosis 2017;256:100–104. doi:10.1016/j.atherosclerosis.2016.11.011 [PubMed: 27993387]

26. Kurnik D, Hochman I, Vesterman-Landes J, et al. Muscle pain and serum creatine kinase are not associated with low serum 25(OH) vitamin D levels in patients receiving statins. Clinical Endocrinology (Oxf) 2012;77(1):36–41. doi:10.1111/j.1365-2265.2011.04321.x

27. Mammen AL. Statin-Associated Autoimmune Myopathy. New England Journal of Medicine Feb 18 2016;374(7):664–9. doi:10.1056/NEJMra1515161 [PubMed: 26886523]

28. Nazir S, Lohani S, Tachamo N, Poudel D, Donato A. Statin-Associated Autoimmune Myopathy: A Systematic Review of 100 Cases. Journal of Clinical Rheumatology Apr 2017;23(3):149–154. doi:10.1097/rhu.0000000000000497 [PubMed: 28277343]

29. Werner JL, Christopher-Stine L, Ghazarian SR, et al. Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. Arthritis & Rheumatology Dec 2012;64(12):4087–93. doi:10.1002/art.34673

30. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet Nov 19 2016;388(10059):2532–2561. doi:10.1016/s0140-6736(16)31357-5 [PubMed: 27616593]
31. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-Associated Side Effects. Journal of the American College of Cardiology. 05 24 2016;67(20):2395–2410. doi:10.1016/j.jacc.2016.02.071
32. Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. Journal of Clinical Lipidology Jul-Aug 2016;10(4):739–747. doi:10.1016/j.jacl.2016.05.002 [PubMed: 27578103]
33. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. Jama Apr 19 2016;315(15):1580–90. doi:10.1001/jama.2016.3608 [PubMed: 27039291]
34. Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. Annals of Internal Medicine 2014;160(5):301–310. doi:10.7326/M13-1921 [PubMed: 24737272]
35. Wood FA, Howard JP, Finegold JA, et al. N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects. New England Journal of Medicine Nov 26 2020;383(22):2182–2184. doi:10.1056/NEJMc2031173 [PubMed: 33196154]
36. Herrett E, Williamson E, Brack K, et al. Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. BMJ 2021;372:n135. Published 2021 Feb 24. doi:10.1136/bmj.n135 [PubMed: 33627334]
37. Wiggins BS, Saseen JJ, Page RL, 2nd, et al. Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation Nov 22 2016;134(21):e468–e495. doi:10.1161/cir.0000000000000456 [PubMed: 27754879]
38. Shaik AN, Bohnert T, Williams DA, Gan LL, LeDuc BW. Mechanism of Drug-Drug Interactions Between Warfarin and Statins. Journal of Pharmaceutical Sciences Jun 2016;105(6):1976–1986. doi:10.1016/j.xphs.2016.03.011 [PubMed: 27103011]
39. Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Current Controlled Trials in Cardiovascular Medicine 2001;2(5):205–207. doi:10.1186/cvm-2-5-205 [PubMed: 11806796]
40. Ballantyne CM, Bays H, Catapano AL, Goldberg A, Ray KK, Saseen JJ. Role of Bempedoic Acid in Clinical Practice. Cardiovascular Drugs and Therapy 08 2021;35(4):853–864. doi:10.1007/s10557-021-07147-5 [PubMed: 33818688]
41. Kee PS, Chin PKL, Kennedy MA, Maggo SDS. Pharmacogenetics of Statin-Induced Myotoxicity. Frontiers in Genetics 2020;11:575678. doi:10.3389/fgene.2020.575678 [PubMed: 33193687]
42. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. New England Journal of Medicine Aug 21 2008;359(8):789–99. doi:10.1056/NEJMoa0801936 [PubMed: 18650507]
43. Lloyd SM, Stott DJ, de Craen AJ, et al. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS One 2013;8(9):e72642. doi:10.1371/journal.pone.0072642 [PubMed: 24023757]
44. Neil HA, DeMicco DA, Luo D, et al. Analysis of efficacy and safety in patients aged 65–75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care Nov 2006;29(11):2378–84. doi:10.2337/dc06-0872 [PubMed: 17065671]
45. 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. Annals of Internal Medicine 2010;152(8):488–W174. doi:10.7326/0003-4819-152-8-201004200-00005 [PubMed: 20404379]
46. Birmingham BK, Bujac SR, Elsby R, et al. Impact of ABCG2 and SLCO1B1 polymorphisms on pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid in Caucasian and Asian subjects: a class effect?. European Journal of Clinical Pharmacology 2015;71(3):341–355. doi:10.1007/s00228-014-1801-z [PubMed: 25673568]
47. Lee HK, Hu M, Lui SSh, Ho CS, Wong CK, Tomlinson B. Effects of polymorphisms in ABCG2, SLCO1B1, SLC10A1 and CYP2C9/19 on plasma concentrations of rosuvastatin and lipid

response in Chinese patients. Pharmacogenomics 2013;14(11):1283–1294. doi:10.2217/pgs.13.115 [PubMed: 23930675]

48. Crestor package insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021366s033lbl.pdf. Accessed 2022/04/17
49. Khan S, Holbrook A, Shah BR. Does Googling lead to statin intolerance? International Journal of Cardiology Jul 1 2018;262:25–27. doi:10.1016/j.ijcard.2018.02.085 [PubMed: 29706390]
50. Nissen SE. Statin Denial: An Internet-Driven Cult With Deadly Consequences. Annals of Internal Medicine 2017:281–282. vol. 4.
51. Backes JM, Ruisinger JF, Gibson CA, Moriarty PM. Statin-associated muscle symptoms-Managing the highly intolerant. Journal of Clinical Lipidology Jan-Feb 2017;11(1):24–33. doi:10.1016/j.jacl.2017.01.006 [PubMed: 28391891]
52. Ward NC, Watts GF, Eckel RH. Statin Toxicity. Circulation Research 2019;124(2):328–350. doi:10.1161/CIRCRESAHA.118.312782 [PubMed: 30653440]
53. Backes JM, Venero CV, Gibson CA, et al. Effectiveness and tolerability of every-other-day rosuvastatin dosing in patients with prior statin intolerance. Annals of Pharmacotherapy Mar 2008;42(3):341–6. doi:10.1345/aph.1K604 [PubMed: 18285559]
54. https://www.goodrx.com. Accessed 2022/04/17
55. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. New England Journal of Medicine Jun 18 2015;372(25):2387–97. doi:10.1056/NEJMoa1410489 [PubMed: 26039521]
56. Roth EM, Davidson MH. PCSK9 Inhibitors: Mechanism of Action, Efficacy, and Safety. Reviews in Cardiovascular Medicine2018;19(S1):S31–s46. doi:10.3909/ricm19S1S0002 [PubMed: 30207556]
57. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. New England Journal of Medicine Apr 16 2015;372(16):1489–99. doi:10.1056/NEJMoa1501031 [PubMed: 25773378]
58. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. New England Journal of Medicine Apr 16 2015;372(16):1500–9. doi:10.1056/NEJMoa1500858 [PubMed: 25773607]
59. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. Journal of Clinical Lipidology Nov-Dec 2015;9(6):758–769. doi:10.1016/j.jacl.2015.08.006 [PubMed: 26687696]
60. FDA Approves Bempedoic Acid for Treatment of Adults With HeFH or Established ASCVD. American College of Cardiology https://www.acc.org/latest-in-cardiology/articles/2020/02/24/10/09/fda-approves-bempedoic-acid-for-treatment-of-adults-with-hefh-or-established-ascvd. Accessed 2022/02/06
61. Nexletol package insert https://pi.esperion.com/nexletol/nexletol-pi.pdf. Accessed 2022/03/28
62. Ray KK, Bays HE, Catapano AL, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. New England Journal of Medicine Mar 14 2019;380(11):1022–1032. doi:10.1056/NEJMoa1803917 [PubMed: 30865796]
63. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. Jama Nov 12 2019;322(18):1780–1788. doi:10.1001/jama.2019.16585 [PubMed: 31714986]
64. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. Journal of the American Heart Association Apr 2 2019;8(7):e011662. doi:10.1161/jaha.118.011662 [PubMed: 30922146]
65. Esperion Therapeutics I. A Randomized, Double-blind, Placebo-controlled Study to Assess the Effects of Bempedoic Acid (ETC-1002) on the Occurrence of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant. Clinical trial registration 2021. NCT02993406. 2021/09/07/. Accessed 2022/03/28/. https://clinicaltrials.gov/ct2/show/NCT02993406

66. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. European Journal of Preventive Cardiology Apr 2020;27(6):593–603. doi:10.1177/2047487319864671 [PubMed: 31357887]

67. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. Atherosclerosis Oct 2018;277:195–203. doi:10.1016/j.atherosclerosis.2018.06.002 [PubMed: 29910030]

68. Laufs U, Ballantyne CM, Banach M, et al. Efficacy and safety of bempedoic acid in patients not receiving statins in phase 3 clinical trials. Journal of Clinical Lipidology 2022;16(3):286–297. doi:10.1016/j.jacl.2022.03.001 [PubMed: 35346603]

69. FDA approves add-on therapy to lower cholesterol among certain high-risk adults. FDA Published online December 27, 2021. Accessed February 7, 2022. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-add-therapy-lower-cholesterol-among-certain-high-risk-adults

70. Ray KK, Wright RS, Kallend D, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. New England Journal of Medicine 2020;382(16):1507–1519. doi:10.1056/NEJMoa1912387 [PubMed: 32187462]

71. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. European Heart Journal 2015;36(17):1012–1022. doi:10.1093/eurheartj/ehv043 [PubMed: 25694464]

72. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel. An assessment by the Statin Muscle Safety Task Force: 2014 update. Journal of Clinical Lipidology 2014;8(3 Suppl):S58–S71. doi:10.1016/j.jacl.2014.03.004 [PubMed: 24793443]

73. Feingold KR. Cholesterol Lowering Drugs. In: Feingold KR, Anawalt B, Boyce A, et al., eds. Endotext South Dartmouth (MA): MDText.com, Inc.; March 30, 2021.

Practice Points

- Statins are first line medications for lowering LDL-C levels in patients at risk of ASCVD, and they are usually well tolerated. Premature statin discontinuation is associated with an increased risk of ASCVD events. Efforts should be made to continue the statin or switch to alternative lipid-lowering therapies.
- Statin intolerance is defined as a clinical syndrome characterized by the inability to tolerate at least two statins: one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, reproducible by re-challenge with other known determinants being excluded.
- Before attributing myalgias, myopathy, or rhabdomyolysis to a statin, other causes of muscle symptoms should be excluded.
- The nocebo effect is the subjective perception that a drug or other intervention will cause harm, and it can play a strong role in whether a patient is “intolerant” of a statin.
- Drug-drug interactions can increase the risk of adverse effects from statins. Careful review of all medications is important.
- If a patient reports intolerance to a statin, other approaches to continuing statin therapy should be made including dose reduction, intermittent dosing, or switching to a different statin.
- In patients who are unable to achieve their LDL-C targets with maximally tolerated statin therapy, addition of other lipid-lowering therapies including ezetimibe, PCSK9 inhibitors, and bempedoic acid should be considered.
- The practice of shared decision-making is an invaluable tool in helping patients and their providers achieve therapy goals.

Research Agenda

- Studies into the long-term clinical outcomes of novel lipid-lowering agents are needed.
- More research in elucidating pharmacogenetic causes of SAMS is needed.
- Studies of methods for increasing adherence to medications are needed.

Table 1:

Terminology of Muscle Adverse Events

Adverse Event Term	American Heart Association 2019	European Atherosclerosis Society 2015	National Lipid Association 2014
SAMS	Muscle symptoms reported during statin therapy but not necessarily caused by the statin	Muscle symptoms and/or elevations in CK levels observed with statin use	
Myalgia	Muscle pain or aches	Muscle symptoms present. Normal CK May be related to statin therapy, but causality is uncertain.	Unexplained muscle discomfort often described as “flu-like” symptoms with normal CK level. The spectrum of myalgia complaints includes: muscle aches, muscle soreness, muscle stiffness, muscle tenderness, and muscle cramps with or shortly after exercise (not nocturnal cramping)
Myositis		Muscle symptoms present. CK >10 times ULN Also called “myopathy” by regulatory agencies and other groups. Pain typically generalized and proximal; may be muscle tenderness and weakness. May be associated with underlying muscle disease.	Muscle inflammation
Myopathy	Unexplained muscle pain or weakness accompanied by CK concentration >10 times ULN	Muscle symptoms present. CK >10 times ULN Also called “myositis” by regulatory agencies and other groups. Pain typically generalized and proximal; may be muscle tenderness and weakness. May be associated with underlying muscle disease.	Muscle weakness (not attributed to pain and not necessarily associated with elevated CK).
Rhabdomyolysis	Severe myopathy, with CK typically >40 times ULN, which can cause myoglobinuria and acute renal failure	Muscle symptoms present. CK >40 times ULN Associated with renal impairment and/or myoglobulinuria.	Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine ≥ 0.5 mg/dL)
HyperCKemia: Mild		Muscle symptoms absent. CK >ULN <4 times ULN Raised CK found incidentally, may be related to statin therapy. Consider checking thyroid function; may be exercise-related.	Myonecrosis- muscle enzyme elevations or hyperCKemia CK >3 times untreated baseline CK level or ULN that are adjusted for age, race, and sex.
HyperCKemia: Moderate		Muscle symptoms absent. CK >4 times ULN Needs repeating; if persistent, clinical significance is unclear.	Myonecrosis- muscle enzyme elevations or hyperCKemia CK ≥ 10 times untreated baseline CK level or ULN that are adjusted for age, race, and sex.
HyperCKemia: Severe			Myonecrosis- muscle enzyme elevations or hyperCKemia CK ≥ 50 times baseline CK level or ULN that are adjusted for age, race, and sex.

There is significant heterogeneity in definitions between organizations, so this table was adapted in a way to present the definitions as uniformly as possible. Abbreviations: CK= creatine kinase, SAMS= statin-associated muscle symptoms, ULN= upper limit of normal

Table 2:

Risk Factors for Adverse Muscle Effects with Statins

Medications that alter statin metabolism
Advanced age
Female gender
Asian ethnicity
Hypothyroidism
Vitamin D deficiency
Excess alcohol
Neuromuscular disorders
Renal disease
Liver disease
Physical exertion
Personal or family history of statin intolerance
Low body mass index
Polymorphism in SLCO1B1 gene
High dose statin

Modified from Feingold ([1]), with permission.

Table 3:

Common Statin Drug-Drug Interactions

Enzyme	Statin Substrates	Significant Drug-Drug Interactions
CYP3A4	Atorvastatin, lovastatin, simvastatin	Amiodarone, clarithromycin, cyclosporine, erythromycin, grapefruit juice, azole antifungals, imatinib, protease inhibitors, tacrolimus
CYP2C9	Fluvastatin, rosuvastatin	Amiodarone, azole antifungals
P-gp	Atorvastatin, lovastatin, pitavastatin, simvastatin	Amiodarone, clarithromycin, colchicine, cyclosporine, grapefruit juice, azole antifungals, protease inhibitors, tacrolimus
OATP1B1	Atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	Clarithromycin, cyclosporine, erythromycin, gemfibrozil, protease inhibitors
OAT1B3	Fluvastatin, pravastatin, rosuvastatin	Clarithromycin, cyclosporine, erythromycin

CYP= cytochrome P, OATP= organic anion-transporting polyprotein, P-gp= permeability glycoprotein