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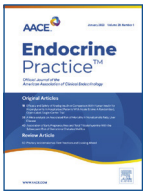

Review Article

Statin Intolerance: A Review and Update

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ABSTRACT

Objective: To review the evidence of existing literature on the management of statin intolerance.
Methods: We searched for literature pertaining to statin intolerance and treatments in PubMed. We reviewed articles published between 2005 and 2022.
Results: Statin-associated myalgia is the most common adverse effect of statin therapy and the most common reason for statin discontinuation. The risk factors for statin intolerance include unexplained muscle pain with other lipid-lowering therapy, unexplained cramps, a history of increased creatine kinase levels, a family history of muscle symptoms, and a family history of muscle symptoms with lipid therapy. Vitamin D repletion and coenzyme Q supplementation may help alleviate the musculoskeletal effects of statins. Trials of different types of statins and different dosing regimens are recommended to improve tolerability. The use of statins in individuals who perform regular exercise requires closer attention to muscular symptoms and creatine kinase levels; however, it does not preclude the use of statins.
Conclusion: Management of the adverse effects of statin therapy and improving statin tolerability are key to achieving optimum cardiovascular benefits. Identifying statin-associated adverse effects and managing them appropriately can reduce unnecessary statin discontinuation and subsequently provide longer cardiovascular protection.

Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. A body of evidence accumulated over several decades has strengthened our understanding of circulating atherogenic lipoproteins, such as low-density lipoprotein (LDL) cholesterol, non–high-density lipoprotein cholesterol, and apolipoprotein B, and their roles in the pathogenesis of CVD. Statin therapy remains the first-line treatment for lowering CVD risk.[1] However, clinicians face a dilemma when managing statin intolerance, having to either discontinue the statin therapy or lower the dosage below the optimum therapeutic dose.[2] In this article, we review the evidence-based management of statin intolerance through 3 real-life cases.

Defining Statin Intolerance

Several definitions have been used for "statin intolerance." The latest one published by the National Lipid Association defines statin intolerance "as one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of a statin or partial intolerance, with inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. To classify a patient as having statin intolerance, a minimum of 2 statins should have been attempted, including at least one at the lowest approved daily dosage. Statin intolerance is a clinical syndrome."[3]

An important concept included in this new definition is *partial intolerance*, which is a clinical dilemma that must be recognized to achieve optimum cardiovascular protection for patients.

Abbreviations: AACE, American Association of Clinical Endocrinology; CK, creatine kinase; CVD, cardiovascular disease; CoQ10, coenzyme Q10; EAS, European Atherosclerosis Society; HR, hazard ratio; LDL, low-density lipoprotein; MCI, mild cognitive impairment; OR, odds ratio; RCT, randomized controlled trial; SAM, statin-associated myalgia; 25(OH)D, 25-hydroxyvitamin D; ULN, upper limit of normal; WMD, weighted mean difference.

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Case 1

A 50-year-old woman with a family history of premature CVD mortality was started on atorvastatin 40 mg to treat a high LDL level of 185 mg/dL. She returned to clinic with new-onset muscle aches and fatigue and described feeling as if she was "wearing a leaded jacket all day since starting the medication." Atorvastatin was discontinued, and symptoms completely resolved. The laboratory results for creatine kinase (CK) levels were not elevated.

Statin-Associated Myalgia

This case presents the most common adverse effect with statin therapy—statin-associated myalgia (SAM). Patients report muscle soreness, muscle aches, cramps, weakness, and fatigue, yet typically have normal CK levels.

The prevalence of SAM has differed in real-world experiences compared with that in randomized controlled trials (RCTs). In a large meta-analysis, the prevalence of SAM was 17% (95% confidence interval [CI], 14%-19%) for 64 observational cohort studies compared with 4.9% (95% CI, 4.0%-6.0%) for 112 RCTs.[4] This difference in prevalence may be because RCTs often exclude patients with prior statin intolerance episodes or predisposing factors (discussed in the next paragraph) and include run-in phases that may self-eliminate such patients. Observational studies do not have these controls, and it is difficult to account for medications taken concurrently with a statin that may impact the incidence of SAM. Nonetheless, the underestimation of prevalence is possible in RCTs.

In the Prediction of Muscular Risk in Observational conditions study, 7924 patients treated with a high dosage statin were surveyed when visiting the outpatient clinic.[5] SAM occurred in 10.5% of patients. Multiple predisposing factors for SAM were reported, with the highest odds ratio (OR) found among patients experiencing unexplained muscle pain with other lipid-lowering therapy (OR, 10.12; 95% CI, 8.23-12.45; $P < .0001$). Other predisposing factors were unexplained cramps (OR, 4.14; 95% CI, 3.46-4.95; $P < .0001$), a history of increased CK levels (OR, 2.04; 95% CI, 1.55-2.68; $P < .0001$), a family history of muscle symptoms (OR, 1.93; 95% CI, 1.10-3.34; $P = .022$), and a family history of muscle symptoms with lipid therapy (OR, 1.89; 95% CI, 1.12-3.17; $P = .017$). In the meta-analysis by Bytyçi et al[4], age, female sex, Asian and Black race, diabetes mellitus, obesity, chronic liver disease, chronic kidney disease, and hypothyroidism were also factors that increased the risk of SAM (Fig. 1).

Nonetheless, discontinuation of statin therapy may lead to detrimental outcomes. The Statin Adverse Treatment Experience survey evaluated reasons for statin discontinuation in 1500 patients.[6] Approximately 332 patients (22.1%) discontinued statin therapy because of side effects, the majority of which were musculoskeletal symptoms. One cohort study evaluated the cardiovascular effects of statin discontinuation in 67418 long-term, elderly statin users.[7] In the group taking statins for the primary prevention of CVD, the risk of major adverse cardiovascular events increased by 32% in those who discontinued statins. In the secondary prevention group, these events increased by 28%. The rates of statin discontinuation were 30% over 5.5 years in the primary prevention group and 25% over 4.2 years in the secondary prevention group. In another cohort study involving elderly participants taking statins for the primary prevention of CVD, statin discontinuation was associated with a 33% increased risk of a cardiovascular event requiring hospital admission.[8] The statin discontinuation rate over 2.4 years was 14.5%.

The mechanism of SAM is poorly understood. However, it is important to consider and appropriately treat modifiable risk factors to maximize the patient's chance of achieving cardiovascular protection from statins.

Highlights

- Statin intolerance is a commonly faced dilemma in clinical practice
- Statin-associated myalgia is the most common adverse effect of statin therapy
- The use of statins with regular exercise requires closer attention to symptoms and creatine kinase levels
- Improving statin tolerance is crucial for optimum cardiovascular protection

Clinical Relevance

The benefits of statin therapy in the prevention of cardiovascular disease are well established. However, statin intolerance resulting in the discontinuation of statin therapy is common and leads to worsening of cardiovascular outcomes. Appropriate management of statin-associated adverse effects to maximize statin tolerability is key to achieving optimum cardiovascular protection.

Are There Treatment Options for SAM?

Vitamin D

Studies have associated vitamin D deficiency with SAM. In a meta-analysis of 9 cohort studies totaling 2906 participants, the total serum 25-hydroxyvitamin D (25(OH)D) levels were significantly lower in the SAM group than in the non-SAM group (weighted mean difference [WMD], −4.17 ng/mL; 95% CI, −7.70 to −0.63; $P = .02$).[9] Four studies from this meta-analysis further assessed SAM after vitamin D supplementation and statin tolerability improved to 89%.

In a prospective study of 150 patients who could not tolerate ≥1 statin and had low serum 25(OH)D levels (< 32 ng/ml), vitamin D supplementation was initiated, and statin therapy was reintroduced at 3 weeks.[10] After a median of 8.1 months on statins, 87% of participants were myalgia-free. The serum 25(OH)D levels were adequately replete in 78% of patients.

Coenzyme Q10

Coenzyme Q10 (CoQ10) deficiency after statin initiation has been associated with SAM. However, whether CoQ10 supplementation alleviates SAM is controversial. One meta-analysis of 9 RCTs[11] reported significant improvement in statin-associated muscle symptoms compared with that using placebo: (1) muscle pain (WMD, −1.60; 95% CI, −1.75 to −1.44; $P < .001$), (2) muscle weakness (WMD, −2.28; 95% CI, −2.79 to −1.77; $P = .006$), (3) muscle cramp (WMD, −1.78; 95% CI, −2.31 to −1.24; $P < .001$), and (4) muscle tiredness (WMD, −1.75; 95% CI, −2.31 to −1.19; $P < .001$). However, the meta-analysis by Kennedy et al[12] that assessed 7 RCTs found no significant improvement in myalgia or statin tolerability in the CoQ10 supplement group compared with that in placebo.

In summary, individuals with vitamin D deficiency on statin therapy and experiencing SAM may benefit from vitamin D supplementation to improve musculoskeletal symptoms and statin tolerability. The evidence demonstrating that CoQ10 supplementation improves SAM is inconclusive. A large RCT is needed to evaluate the effect of CoQ10 supplementation on statin tolerability.

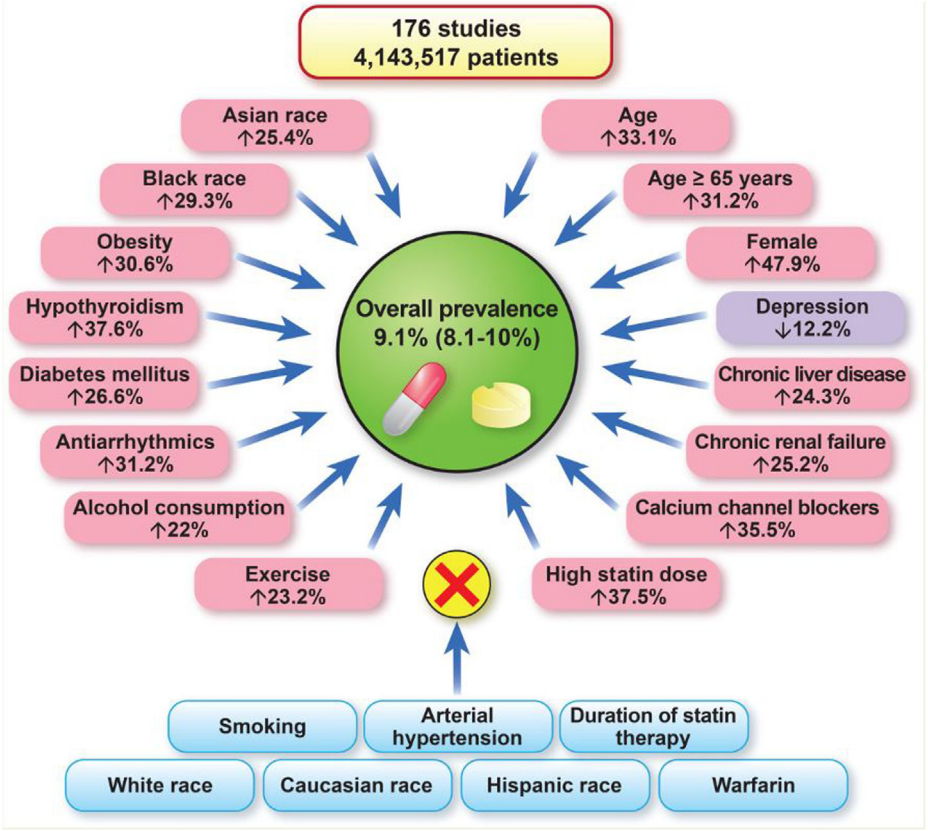

Fig. 1. Worldwide prevalence of statin-induced myalgia (9.1%, CI, 8.1%-10%) and factors that affect (pink/purple) and do not affect (blue) the risk of statin intolerance.[4]

Case 2

The patient was a 61-year-old woman with a history of hypercholesterolemia since menopause, beginning at the age of 50 years. She did not have diabetes, was a nonsmoker, and had no family history of CVD. Her lipid panel showed a high total cholesterol level of 320 mg/dL, triglyceride level of 154 mg/dL, high-density lipoprotein level of 100 mg/dL, and LDL level of 209 mg/dL. Her functional medicine provider had warned her about the potential side effects of statins and she was afraid to initiate therapy.

What Are the Adverse Effects of Statin Therapy?

Myopathy/Rhabdomyolysis

Myalgia is the most common adverse effect, as discussed in case 1. In a systematic review, the overall incidences of rhabdomyolysis were 1.6 per 100 000 person-years for 20 RCTs and 3.4 per 100 000 person-years for 2 cohort studies.[13] The incidences of myopathy, defined as diffuse pain and increased CK levels, were 11 per 100 000 person-years for 1 cohort study in the review and 5 per 100 000 person-years for the 20 RCTs. According to the Food and Drug Administration's Adverse Effects Reporting System, a significantly higher rate of rhabdomyolysis was reported with simvastatin, lovastatin, and atorvastatin monotherapy compared with that with fluvastatin and pravastatin monotherapy (mean rate, 0.73; 95% CI, 0.64-0.82 per 1 million prescriptions [264 cases], vs mean rate, 0.15; 95% CI, 0.09-0.24 per 1 million prescriptions [18 cases]; $P < .001$, respectively).[14] Myalgia is a common adverse effect of statin therapy, whereas myopathy and rhabdomyolysis are both rare.

Liver Dysfunction

Liver disease is also a rare adverse effect of statins and is estimated to occur in 0.1 per 100 000 person-years of use.[13] Even with underreporting taken into account, the incidence of liver failure is estimated to be 0.5 per 100 000 person-years, which is no greater than the incidence observed in the general population not on statin therapy.[15]

Cognitive Impairment

The Food and Drug Administration has received reports of cognitive impairment with statin therapy. However, large observational studies and meta-analyses have not shown an association between statin use and cognitive decline. A post hoc analysis of 18 846 patients from the Aspirin in Reducing Events in the Elderly trial included participants aged ≥65 years without a prior history of CVD or dementia.[16] Statin users versus nonstatin users were assessed for dementia and mild cognitive impairment (MCI) over 4.7 years. Statin use was not associated with a risk of all-cause dementia (hazard ratio [HR], 1.16; 95% CI, 0.97-1.40; $P = .11$), probable Alzheimer disease (HR, 1.33; 95% CI, 1.00-1.77; $P = .05$), or mixed presentation of dementia (HR, 1.06; 95% CI, 0.82-1.35; $P = .67$). Statin use was also not associated with a risk of MCI (HR, 0.97; 95% CI, 0.77-1.22; $P = .81$), MCI consistent with Alzheimer disease (HR, 1.44; 95% CI, 0.90-2.29; $P = .13$), or other MCI (HR, 0.86; 95% CI, 0.66-1.12; $P = .26$).[16] Furthermore, a meta-analysis evaluating statin therapy and cognitive function found that statin therapy was associated with a reduced risk of all-cause dementia (adjusted relative risk, 0.849; 95% CI, 0.787-0.916, $P < .001$) and MCI (adjusted relative risk, 0.737; 95% CI, 0.556-0.976, $P = .033$).[17] Thus, RCTs are needed to better understand the impact of statins on cognitive

function; however, the current evidence suggests that statin therapy does not impair cognition.

New-Onset Diabetes

In a meta-analysis of 5 statin trials totaling 32 752 participants, the incidence of diabetes was compared between the high-dose and moderate-dose groups.[18] The participants did not have a diabetes diagnosis at baseline. A mean of 18.9 cases per 1000 patient-years was observed with high-dose statin therapy compared with 16.9 cases per 1000 patient-years with moderate-dose therapy (OR, 1.12; 95% CI, 1.04-1.22). The number needed to harm was 498 per year. Relative to cardiovascular events, a mean of 44.5 cases per 1000 patient-years was observed in the high-dose group compared with 51.0 cases per 1000 patient-years in the moderate-dose group (OR, 0.84; 95% CI, 0.75-0.94). The number needed to treat was 155 per year.

New-onset diabetes is associated with statin therapy in a dose-dependent manner. One additional case of diabetes was diagnosed for every 498 treated patients per year, whereas 1 less patient experienced a cardiovascular event for every 155 treated patients per year.[18] Thus, the cardiovascular benefit of statin therapy far exceeds the small risk of the incidence of diabetes. Discontinuation of statin therapy increases cardiovascular risk; therefore, statin therapy should be continued when diabetes is diagnosed.[2]

Current Guidelines for Management of Statin Intolerance

The National Lipid Association,[3] American Association of Clinical Endocrinology (AACE),[19] and European Atherosclerosis Society (EAS)[20] recommend that providers assess and treat the modifiable risk factors for statin intolerance, such as hypothyroidism, diabetes mellitus, vitamin D deficiency, alcohol use, strenuous exercise, and drug interactions. On initial assessment, if CK is >10 times the upper limit of normal (ULN), statin therapy should be discontinued because of the risk of developing rhabdomyolysis.[19,20] In addition, the AACE[19] recommends immediate hydration and monitoring of renal function. At this point, future statin use becomes a contraindication. In less severe cases, the guidelines recommend retrial with a lower dose of the same statin, different statin, or less frequent dosing schedule (eg, 1-3 doses per week).[3,19,20] The AACE specifically recommends pitavastatin or extended-release fluvastatin, which are known to cause less myopathy, for patients with risk factors for statin intolerance. Additionally, rosuvastatin and pravastatin are recommended alternatives because their hydrophilic properties lead to less myopathy.[19] The AACE recommends considering a trial of CoQ10 supplementation and/or normalizing serum 25(OH)D levels,[19] whereas the EAS recommends against CoQ10 or vitamin D supplementation.[20] Lastly, nonstatin pharmacotherapy should be considered as an adjunct or alternative therapy if the LDL cholesterol goal is not achieved on the maximum tolerated statin dose or if there is complete statin intolerance. These nonstatin alternatives include ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, bile sequestrants, bempedoic acid, and small interfering ribonucleic acid therapy, such as inclisiran. Fibrates may be considered as an alternative agent.

Case 3

A 22-year-old football player was recently diagnosed with severe hypercholesterolemia (LDL level, 330 mg/dL). His history was consistent with familial hypercholesterolemia. He was otherwise healthy. The initial plan was to start statin therapy; however, his baseline CK level often exceeded 500 U/L (normal range, 44-196 U/L).

Statin Therapy in Individuals Performing Regular Exercise

Currently, there are no guidelines regarding statin therapy for individuals performing regular rigorous exercise. However, because both physical activity and statin therapy can increase CK levels, initiation of statins and monitoring of side effects pose a challenge in this population.

In the Prediction of Muscular Risk in Observational conditions study,[5] 7924 individuals on high-intensity statin therapy were evaluated for muscular side effects. The investigators found a higher incidence of SAM (14.7%) in individuals who performed regular, intense exercise than in those who performed less intense exercise (10.8%). In addition, simvastatin was associated with the highest rate of SAM (18.2%) and lowest rate of fluvastatin (5.1%). In another study involving 22 professional athletes with familial hypercholesterolemia,[21] 6 of 22 athletes tolerated at least 1 type of statin, and 2 of 22 tolerated all attempted statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin). Muscular symptoms, including pain and weakness, were the major reasons for statin intolerance.

Several professional society guidelines recommend regular exercise as part of dyslipidemia treatment because of the demonstrated benefits. For example, the AACE recommends 150 to 300 minutes of moderate-intensity exercise per week.[19] The European Society of Cardiology and EAS recommend at least 30 minutes of moderate-intensity exercise every day.[1] However, “moderate”-intensity exercise is not specifically defined in professional guidelines. According to the Centers for Disease Control and Prevention, examples of moderate-intensity exercise include brisk walking, ballroom dancing, and bicycling slower than 10 miles per hour, and vigorous-intensity exercise includes jogging, running, swimming, and aerobic dancing.[22]

Although statin therapy may increase the risk of SAM in individuals who perform regular, intense exercise, exercise has reduced cardiovascular morbidity and mortality in statin users. In a study involving 6688 patients with hypercholesterolemia on statin therapy, running and walking significantly reduced CVD risk over a 10-year follow-up period.[23] As mentioned previously,[1,19] exercise is also recommended in guidelines to treat dyslipidemia. Therefore, athletes should not be deprived of statin therapy. Instead, statin therapy should be initiated when possible, and individuals should be monitored for side effects.

The International Lipid Expert Panel published a position statement on statin therapy for individuals who exercise regularly.[24] Figure 2 shows their expert opinion on initiating statin therapy, monitoring the CK levels, and rechallenging statin therapy when appropriate.

The risk-benefit ratio for statin therapy of each person must be carefully considered before initiating therapy. If statin therapy is deemed beneficial, the International Lipid Expert Panel recommends initiating a hydrophilic statin (rosuvastatin and pravastatin) at a low-to-moderate-intensity dose in this population. A statin rechallenge can be performed with an alternative statin, lower-dose statin, or once/twice weekly dosing regimen. Rosuvastatin and atorvastatin are well suited for the once/twice weekly dosing regimen because of their long half-lives. If the therapeutic goal is not met with a statin alone, a combination therapy with a nonstatin agent can be considered.[24]

Ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors have not been studied in patients who perform regular, intense exercise. However, both of these agents are known to provide significant LDL reduction and improve cardiovascular outcomes. Ezetimibe has a high safety profile, and alirocumab had less muscle-related adverse effects in patients with statin intolerance compared with atorvastatin in the ODYSSEY ALTERNATIVE

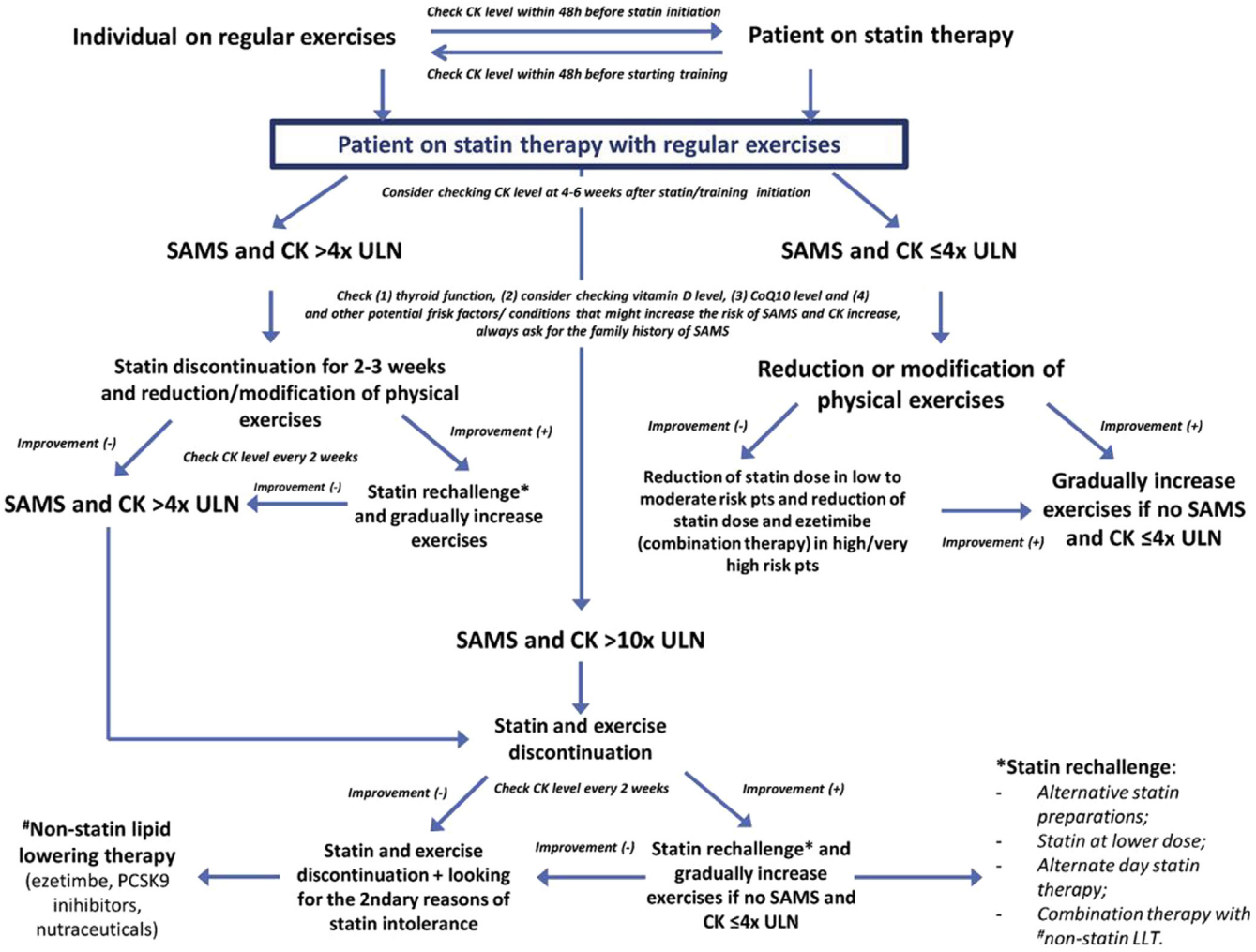

Fig. 2. The International Lipid Expert Panel's recommendations on statin management in individuals with regular exercise.[24] Reprinted with permission from Elsevier. Note: Use of nutraceuticals is based on expert opinion and not professional guidelines. *CK* = creatinine kinase; *CoQ10* = coenzyme Q10; *LLT* = lipid-lowering therapy; *PCSK9* = proprotein convertase subtilisin/kexin type 9; *SAM* = statin-associated myopathy; *ULN* = upper limit of normal.

study.[25] In addition, evolocumab demonstrated less muscle-related adverse effects compared with ezetimibe in the GAUSS-1 through GAUSS-3 trials.[26-28]

Our 22-year-old athlete with familial hypercholesterolemia (case 3) was considered high risk for cardiovascular events, and lipid-lowering therapy was recommended. His baseline CK level increased without statin therapy but was <4 times the ULN. In this case, clinicians should consider initiation of a low- or moderate-intensity hydrophilic statin, such as rosuvastatin or pravastatin, and test the CK levels 4 to 6 weeks after starting the statin. Continuation or reduction of statin therapy and physical activity will depend on the presence or absence of statin-associated muscle symptoms and the CK level. If the CK level is >10 times the ULN with statin-associated muscle symptoms, statin therapy should be discontinued, and the CK levels and symptoms should be reevaluated every 2 weeks. If improvement is not observed, nonstatin therapy should be initiated at this time.

In certain athletes, it may not be feasible to obtain a baseline CK level that is not affected by exercise. The available guidelines do not specifically address the CK level at which statin therapy should not be introduced. In a small study (n = 49) assessing the effect of statin therapy on asymptomatic individuals with baseline CK levels 1 to 5 times the ULN (n = 48) and 5 to 10 times the ULN (n = 1), none of the participants discontinued statin therapy or required dose reductions during the 4-month follow-up period.[29] Further studies are needed to evaluate the safety of statin initiation when the prestatin CK levels are elevated.

Conclusion

The benefits of statin therapy in the prevention of CVD are well established and the first-choice treatment for lowering the LDL levels. However, discontinuation of statin therapy is common and mostly because of muscle-related adverse effects. Statin discontinuation has been associated with an increased risk of cardiovascular events. Therefore, statin-associated adverse effects must be assessed and managed promptly. Careful evaluation and treatment of underlying risk factors as well as trialing different statins and dosing regimens can improve statin tolerability. Statin therapy should not be given up on easily because most individuals tolerate some type or dose of statin therapy. By preventing statin discontinuation, cardiovascular outcomes can be improved.

Disclosure

The authors have no multiplicity of interest to disclose.

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