Overcoming patient reluctance to statin intolerance

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ABSTRACT

Statin therapy is a cornerstone in the management of dyslipidemia, both in primary and secondary prevention of cardiovascular events. Despite strong guidelines supporting statin use, concerns regarding side effects, particularly musculoskeletal symptoms, contribute to statin intolerance and patient reluctance. While statin intolerance is reported in 5% to 30% of patients, its true prevalence may be overestimated due to the influence of the nocebo effect. Factors associated with higher incidence of statin intolerance include older age, female sex, comorbidities such as diabetes and chronic kidney disease, and concurrent use of medications such as antiarrhythmic agents or calcium channel blockers. Clinical characterization of statin intolerance requires thorough evaluation and exclusion of alternative causes of musculoskeletal symptoms. Strategies to address statin intolerance include reassessing cardiovascular risk, engaging in shared decision-making, statin rechallenge after appropriate washout periods, dosage titration for tolerability, and consideration of alternative therapies when low-density lipoprotein goals cannot be achieved with statins. This review provides an overview of the spectrum of statin intolerance, its clinical assessment, and a systematic approach to caring for a patient with statin intolerance.

Key words: cholesterol, dyslipidemia, statins

The American College of Cardiology (ACC) 2022 guidelines recommend statin therapy as the primary prevention for patients diagnosed with familial hypercholesterolemia (FH), patients aged 20 to 39 years with a family history or premature atherosclerotic cardiovascular disease (ASCVD) and low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dl, patients aged 40 to 75 years with diabetes mellitus regardless of LDL-C level, and patients of any age with an LDL-C ≥190 mg/dl [1]. Statins are also the standard of care for secondary prevention in patients with clinical ASCVD, including acute coronary syndrome, stable angina, arterial calcification, stroke, transient ischemic attack, and peripheral arterial disease [1]. Recommended LDL-C targets are 70–100 mg/dl for primary prevention and 55–70 mg/dl for secondary prevention [1]. European guidelines for lipid-lowering therapy recommend a comprehensive risk assessment utilizing the SCORE2 tool [2, 3]. This tool estimates the 10-year cardiovascular risk of developing fatal and non-fatal cardiovascular diseases by factoring in variables such as age, sex, smoking status, lipid levels, diabetes, and blood pressure [2, 3]. Patients are classified into low risk (SCORE2 risk <1%), moderate (SCORE2 risk 1%–5%), high (SCORE2 risk 5%–10%), and very high risk (SCORE2 risk ≥10%) [3]. The European Society of Cardiology (ESC) recommends statin therapy for individuals classified as high-risk (goal LDL-C <70 mg/dl and ≥50% baseline reduction) or very high-risk (goal LDL-C <55 mg/dl ≥50% baseline reduction) in the SCORE-2 model in addition to all patients with post-acute myocardial infarction [2, 3]. They also recommend statin therapy for patients with moderate risk on the SCORE2 model if lifestyle strategies do not reduce LDL-C <100 mg/dl [2, 3]. In addition, the Polish Cardiac Society and the International

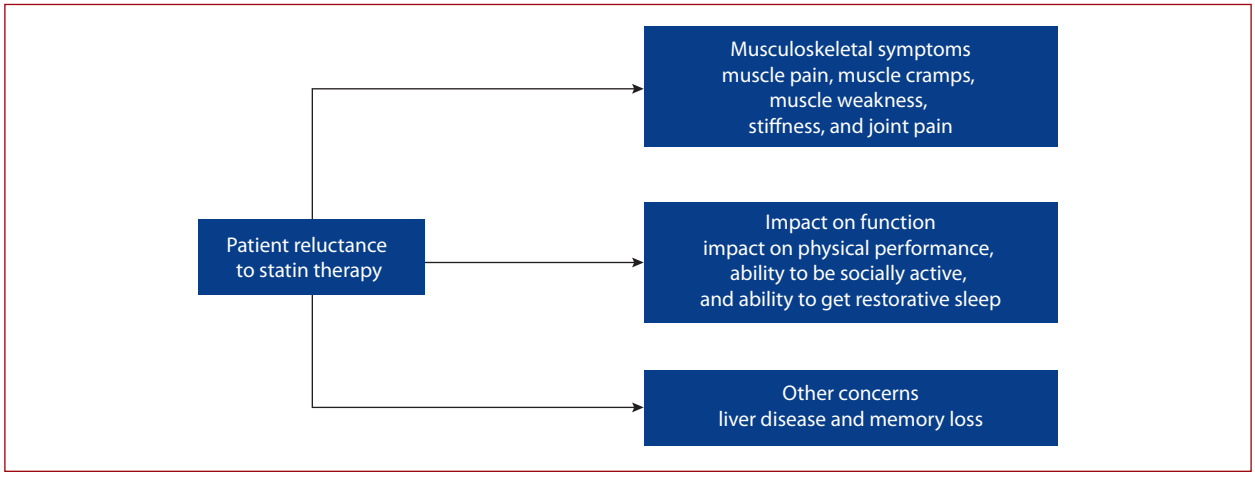

Figure 1. Reasons for patient reluctance to statin therapy

Lipid Expert Panel have defined criteria for patients with extremely high-risk ASCVD and recommend a lower LDL-C target of <40 mg/dl for this patient group [4, 5]. Extremely high-risk patients include those with multivessel coronary artery disease, polyvascular disease, heterozygous FH, and diabetes mellitus [4, 5]. This category also takes into account other risk factors such as high-sensitivity C-reactive protein ≥3 mg/l, chronic kidney disease with estimated glomerular filtration rate <60 ml/min/1.73 m^2, lipoprotein a >50 mg/dl, and patients with a history of vascular events within the last 2 years who did not achieve a target LDL-C <55 mg/dl [4, 5]. Statins may also benefit patients with atherosclerotic vascular aneurysms [6]. Despite all of these recommendations, some patients are unwilling to consider statin therapy.

The literature cites multiple reasons why patients are reluctant to consider statin therapy (Figure 1). In a survey study conducted on an online health forum posted by over 2000 patients utilizing statins, 90% reported discontinuing statins due to musculoskeletal side effects [7]. Similarly, in a lipid managing registry evaluating lipid management practices, 55% of patients reported discontinuing statins due to musculoskeletal side effects [8]. Among patients who were reluctant to consider statins (10%), the most common reason was worry regarding side effects, concerns for liver disease, memory loss, and musculoskeletal issues [8]. Other reasons included patients wanting to try diet or exercise, the belief that statins were unnecessary, not wanting to take medications, preferring natural remedies, and cost/insurance reasons [8]. In another survey study, the Statin Adverse Treatment Experience survey, reporting the experience of 1500 statin patients, 22.1% of patients reported musculoskeletal symptoms of muscle pain, muscle cramps, stiffness, joint pain, muscle weakness, and other symptoms such as easy fatigability [9]. Additionally, the impact of symptoms on performance, productivity, ability to be physically and socially active, and getting restorative sleep were important patient concerns [9]. Patient-reported symptoms do not necessarily correlate with the dosage of statins. This was demonstrated in an observational study of 1000 statin users, 78% of whom were on low-intensity statins (5 mg rosuvastatin, 10 mg atorvastatin, or 20 mg simvastatin) [10]. In this study, approximately 10% of patients reported musculoskeletal symptoms, demonstrating the occurrence of symptoms even with low-intensity statin therapy [10].

Statin intolerance, reported in 5% to 30% of patients, is defined by the National Lipid Association as adverse symptoms that occur with statin pharmacotherapy and resolve either with discontinuation, dose reduction, or spacing of statin dosage [11–13]. The most common adverse symptoms are musculoskeletal symptoms; others include liver toxicity and dysglycemia [14]. Statin intolerance may be partial or complete; partial intolerance is intolerance at specific doses, while patients with complete intolerance cannot tolerate any dose [11]. Patients with partial intolerance can typically tolerate smaller statin doses or alternative statins, but such treatments are usually insufficient for achieving the desired LDL-C reduction [11]. According to the National Lipid Association, a patient must be trialed on a minimum of two statins with at least one at the lowest approved daily dose before a diagnosis of statin intolerance can be established. There are several factors reported to be associated with a higher incidence of statin intolerance. These include older age, female sex, Asian or Black ethnicity, alcohol use, obesity, diabetes mellitus, hypothyroidism, chronic liver disease, kidney disease, and use of certain medications (e.g., antiarrhythmic agents or calcium channel blockers) [15]. Since the presentation of statin intolerance can mimic symptom presentation in other conditions such as vitamin D deficiency, polymyalgia rheumatica, polymyositis, hypothyroidism, and medication interactions, it is important to exclude these conditions before establishing the presence of statin intolerance [16]. Statin intolerance has also been reported as part of the spectrum in patients with multiple drug intolerances [17]. Although the etiology

of multiple drug intolerance is unknown, factors reported to be associated with this phenomenon included female sex, long-standing hypertension, comorbidities involving respiratory, gastrointestinal, rheumatological, and endocrine systems, and chronic use of medications such as analgesics and beta-blockers [17].

The true number of patients with statin intolerance may be overestimated by clinicians as patient-reported symptoms can be factually true or perceived to be true (nocebo effect) [15]. In a meta-analysis of over 4 million patients, Bytyci et al. [15] evaluated statin intolerance across 176 cohort studies and randomized controlled trials. Using statin intolerance research criteria established by international lipid societies, the authors estimated that the prevalence of statin intolerance in randomized blinded controlled trials was significantly lower when compared to cohort studies (4.9% vs. 17%), supporting the concept of overestimation [15]. These estimates which are lower than those reported in observational studies suggest that a fraction of patient-reported symptoms may reflect the nocebo effect [18, 19]. Nocebo effects reported by patients varied from exaggeration of existing symptoms to reporting new symptoms, or exaggerated fear of medication side effects, all of which may result in patients losing trust in their healthcare providers or intentionally non-adhering or discontinuing treatment [20, 21]. Factors that influence nocebo effects include female gender, cultural and contextual elements, misinformation from friends, family members, and media, and patient expectations influenced by information from healthcare providers, pharmacists, and medication package inserts [22–24].

Clinical characterization of statin intolerance in practice can be a challenge. In the absence of abnormalities in biomarkers related to muscle function, clinicians must rely on patient reports supplemented with a thorough workup to rule out other causes of musculoskeletal symptoms. Details regarding all prior statin use including statin type, dosage at which adverse effects occurred, resolution of adverse effects with discontinuation of statins, alternative statin used, and length of washout period before statin retrial will help establish a diagnosis. Although a good history may be sufficient to establish the presence of statin intolerance, there are tools that clinicians can avail to assess statin intolerance and guide medication choices. One such tool is the ACC Statin Intolerance Tool [25]. The tool has 3 components: 1) evaluation, 2) follow-up, and 3) drug comparison. The first component aids in evaluating the patient's likelihood of statin intolerance taking into account the prescribed statin and specific dosage, secondary factors, and medical comorbidities that may contribute to musculoskeletal symptoms. It also evaluates whether medication interactions may be playing a role in musculoskeletal symptoms. The second component, follow-up, guides appropriate laboratory workup, washout period, and provides options for rechallenging with statins. Additionally, it includes an algorithm to guide evaluation of musculoskeletal symptoms that may occur with a rechallenge. The third component offers dosage guidelines for statins and evaluates potential medication interactions [25]. A second tool, Statin Choice Decision Aid, although not specific to statin intolerance, can be used for shared decision-making with the patient regarding atherosclerotic cardiovascular risk, need for statin therapy, and the pros and cons of standard dose versus high dose versus no statin [26].

Several strategies have been recommended to address statin intolerance and patient concerns related to intolerance. A systematic review by Meza-Contreras et al. [16] identified 26 articles that described clinical strategies to address statin intolerance. Most of the studies recommended early exclusion of other causes of musculoskeletal symptoms such as vitamin D deficiency, polymyositis, hypothyroidism, or drug-drug interactions. Almost all studies recommended stopping the current statin and recalculating ASCVD risk, and all studies recommended rechallenging with a statin after a washout period of 2–6 weeks. Regarding the selection of type and dosage of statin, recommendations included re-assessing the current statin dose, using a lower dose, switching to another statin, altering the statin dosing schedule, adding a non-statin drug to the best-tolerated statin therapy, or switching to non-statin. Ezetimibe, while lacking pleiotropic benefits, was the most recommended first-line non-statin therapy and the most frequently used when transitioning patients from statins [27–29]. Other non-statin therapies included proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, nutraceuticals, bempedoic acid, and ion exchange resins [16].

Based on recommendations in the literature and our clinical experience in the cardiovascular lipid clinic, we suggest the following approaches to address statin intolerance and patient reluctance toward statins:

EVALUATE FOR STATIN INTOLERANCE AND ADDRESS OTHER ETIOLOGIES FOR MUSCULOSKELETAL SYMPTOMS

Evaluate statin intolerance using a detailed history of current or previous statin use, symptoms and their chronological association with statin initiation, biomarker abnormalities at the time of undesirable effects, and details regarding symptom resolution once statin was discontinued. As part of this evaluation, a thorough workup to assess for other causes of musculoskeletal symptoms such as myopathies and polymyositis, exclusion of conditions such as vitamin D deficiency, hypothyroidism, and medication interactions should be considered [16]. In rare instances, if indicated, workup could include testing for gene variants and antibodies (solute carrier organic anion transporter family member 1B1 [SLCO1B1] and human menopausal gonadotropin CoA reductase antibodies) in patients who may be genetic carriers and therefore at higher risk of statin myopathy [30–32].

REASSESS ASCVD RISK AND BENEFITS AND RISKS OF STATIN THERAPY THROUGH SHARED DECISION-MAKING

- Once the existence of statin-associated symptoms has been verified, we recommend reassessing ASCVD risk and re-establishing the need for statin therapy.
- This can occur in shared decision-making in a clinical encounter and if needed can be assisted by electronic clinical decision aids [33].
- ASCVD risk can be calculated by online tools such as the ASCVD [34], MESA [35], or the Astro-CHARM ASCVD risk calculator [36] in the United States, and SCORE2-based online tool in Europe [3].
- Another tool that incorporates both ASCVD risks and benefits and risks of statin therapy for individual patients is the Statin Choice Decision Aid developed by the Knowledge and Evaluation Research Unit of the Mayo Clinic [26]. This tool is currently embedded in electronic medical records and systems such as EPIC [37] and can help assess the patient's present and future risk of coronary disease using either the ACC and American Heart Association ASCVD, Framingham risk score, or Reynolds risk score calculators depending on the type of patient data available [26]. Using this tool, clinicians can input patient data, calculate current risk, and predict future risk scenarios in various conditions (without a statin, with a low dose, or with a high-dose statin) to determine the most appropriate statin dose based on the patient's current risk [26].
- During shared decision-making, other considerations that may assist with enhancing compliance to therapy include inquiries into patient preferences regarding therapy, education regarding possible side effects, their management, the potential for nocebo effect, and options to navigate this.
- Additionally, discussion regarding additional lipid-lowering benefits of cardiovascular lifestyle activities (healthy diet, moderate exercise, weight loss, and cessation of smoking) may be encouraged. Discussion regarding the use of dietary supplements such as CoQ10 to mitigate muscle symptoms may be considered [38–41]. Although occasionally patients may gravitate to natural products such as fermented red yeast rice, fish oil, cinnamon, garlic, and turmeric, there is insufficient credibility and/or evidence to justify using these products as lipid-lowering therapies [42, 43].

CONSIDER ALTERNATIVE DOSING STRATEGIES AND WASHOUT PERIODS BEFORE RETRIALS

Once a choice of statin has been narrowed, we recommend initiation of a statin starting with a low dose and gradually titrating it to obtain the optimal dosage. In a patient with a history of statin-associated symptoms and currently not on a statin, we recommend using a lower dose of a previously used statin or an alternative statin after an appropriate washout period of a minimum of 4 weeks. Considerations include starting the patient on a lower statin than recommended i.e., 25%-50% of the lowest strength of that statin either daily or on alternate days or two times a week, and dosage or frequency can be titrated. If, at any time during this titration, patients report symptoms, dosage or frequency can be decreased to previously tolerable doses/frequency. Consider a short washout period before retrials. If the patient is currently on a statin and is experiencing symptoms, we recommend a minimum of a 4-week washout period before retrying the statin. In such cases, the previously mentioned considerations should be implemented [16].

ESTABLISH STATIN INTOLERANCE

To meet the criteria for statin intolerance, patients should have failed trials with a minimum of two different statins, at least one of which is trialed at the lowest approved daily dose. Statin intolerance may be either a complete inability to tolerate any statin or partial intolerance with higher doses necessitating adjunctive treatments [11, 44, 45].

APPROACHES FOR PATIENTS WITH STATIN INTOLERANCE

- If target LDL-C cannot be achieved by low-dose statins, then non-statins such as ezetimibe, bempedoic acid alone or in combination can be utilized for modest LDL-C reduction, or PCSK9 monoclonal antibodies (evolocumab and alirocumab) can be considered for more aggressive LDL-C reduction [1, 46–48]. These medications have lower reported musculoskeletal side effects, however, they may require insurance justification to rationalize the need for nonstatin; this could be a high ASCVD score, imaging evidence of ASCVD, and/or documentation of statin intolerance [49].
- In patients with complete statin intolerance, non-statin therapies can be utilized as alternative therapy. The choice of non-stains in these situations depends on clinical scenarios including ASCVD risk, presence of established coronary artery disease, and other medical comorbidities such as diabetes and chronic kidney disease. Inclisiran, which acts through PCSK9 inhibition and is FDA-approved for clinical ASCVD or familial hyperlipidemia, is another consideration [11]. An overview of these treatment options is presented in Table 1.

SPECIAL SCENARIOS

Statins are the mainstay treatment for FH patients [50]. For patients who are intolerant to statins or do not achieve target LDL-C reduction, the ESC recommends adding ezetimibe [50, 51]. The ESC considers statins combined with ezetimibe as the cornerstone for treatment of FH patients [50]. If patients do not achieve the target LDL-C level with the maximally tolerated statin dose and ezetimibe, guidelines recommend adding PCSK9 inhibitors to therapy [50].

Table 1. Comparative overview of statin and non-statin therapies

Medication	Dose and route	Mean LDL-C reduction	Side effects	Monitoring
Atorvastatin Rosuvastatin Simvastatin Pravastatin	10–80 mg/day, once orally 5–40 mg/day, once orally 5–40 mg/day, once orally, 10–80 mg/day, once orally	Up to 50% Less than 30%	• Musculoskeletal side effects • Elevation in transaminases	• Lipid monitoring within 2–4 weeks of initiation/titration • Liver enzymes monitoring with dosage initiation/titration
Bempedoic acid	180 mg/day, once orally, may be combined with 10 mg ezetimibe	17%–18%	• Upper respiratory tract infection • Muscle spasm • Hyperuricemia • Back pain • Abdominal pain • Bronchitis • Pain in extremity • Anemia • Elevated liver enzyme	• Uric acid • Liver enzymes
Ezetimibe	10 mg/day, orally	18% (alone) 25% (combined with statin)	Monotherapy: • Upper respiratory tract infection • Diarrhea • Arthralgia • Sinusitis • Pain in extremity Combined with statins: • Nasopharyngitis • Myalgia • Upper respiratory tract infection • Arthralgia • Diarrhea	• Aspartate transaminase • Alanine transaminase
PCSK9 mAb	Alirocumab: • 75 mg, *s.c.* every 2 weeks, may increase to 150 mg every two weeks (ASCVD, or primary hyperlipidemia) • 300 mg, *s.c.* every 4 weeks (ASCVD, or primary hyperlipidemia) • 150 mg, *s.c.* every 2 weeks (HeFH undergoing LDL apheresis, or HoFH) Evolocumab: • 140 mg, *s.c.* every 2 weeks (ASCVD, or HeFH) • 420 mg, *s.c.* once monthly, if needed can be increased to every 2 weeks (HoFH) • 420 mg, *s.c.* every 2 weeks (HoFH on LDL apheresis)	Alirocumab: 45%–58% Evolocumab: 58%–64%	Primary hyperlipidemia: • Nasopharyngitis • Injection site reaction • Influenza • Urinary tract infection • Back pain ASCVD: • Non -cardiac chest pain • Nasopharyngitis • Myalgia • Diabetes • Urinary tract infection	Repeat lipid panel before 5th dose and annually
Inclisiran	284 mg *s.c.* on day 1, 90, then every 6 months in an Infusion Center	48%–52%	• Injection site reaction • Arthralgia • Urinary tract infection • Bronchitis • Diarrhea • Pain in extremity • Dyspnea	Recheck before the 2nd dose and annually

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; PCSK9 mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibody; *s.c.*, subcutaneous

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