

NLA scientific statement on statin intolerance: a new definition and key considerations for ASCVD risk reduction in the statin intolerant patient

Mary Katherine Cheeley, PharmD, CLS, FNLA, Joseph J. Saseen, PharmD, FNLA, CLS, Anandita Agarwala, MD, Sudha Ravilla, MD, FNLA, Nicole Ciffone, MSN, ANP-C, CLS, FNLA, Terry A. Jacobson, MD, FNLA, Dave L. Dixon, PharmD, FNLA, CLS, Kevin C. Maki, PhD, CLS, FNLA*

Grady Health System, Atlanta, GA, United States (Dr Cheeley); Departments of Clinical Pharmacy and Family Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, United States (Dr Saseen); Center for Cardiovascular Disease Prevention, Cardiovascular Division, Baylor Scott and White Health Heart Hospital Baylor Plano, Plano, TX, United States (Dr Agarwala); Tallahassee Memorial Healthcare Lipid Center, Tallahassee, FL, United States (Dr Ravilla); Arizona Center for Advanced Lipidology, Tucson, AZ, United States (Dr Ciffone); Department of Medicine, Lipid Clinic and CVD Risk Reduction Program, Emory University School of Medicine, Atlanta, GA, United States (Dr Jacobson); Department of Pharmacotherapy & Outcomes Science, Virginia Commonwealth University School of Pharmacy, Richmond, VA, United States (Dr Dixon); Department of Applied Health Science, School of Public Health, Indiana University, Bloomington, IN and Midwest Biomedical Research, 211 E. Lake St., Ste 3, Addison, IL 60101, United States (Dr Maki)

KEYWORDS

Statin intolerance;
Statin;
Adherence;
Persistence;
Nocebo;
Non-statin;
Non-statin therapy;
Atherogenic lipoproteins

Abstract: Although statins are generally well tolerated, statin intolerance is reported in 5-30% of patients and contributes to reduced statin adherence and persistence, as well as higher risk for adverse cardiovascular outcomes. This Scientific Statement from the National Lipid Association was developed to provide an updated definition of statin intolerance and to inform clinicians and researchers about its identification and management. Statin intolerance is defined as one or more adverse effects associated with statin therapy which resolves or improves with dose reduction or discontinuation and can be classified as a 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 two statins should have been attempted, including at least one at the lowest approved daily dosage. This Statement acknowledges the importance of identifying modifiable risk factors for statin intolerance and recognizes the possibility of a “nocebo” effect (patient expectation of harm resulting in perceived side effects). To identify a tolerable statin regimen it is recommended that clinicians consider using several different strategies (e.g., different statin, dose, and/or dosing frequency).

* Corresponding author.

E-mail address: kmaki@mbclinicalresearch.com (K.C. Maki).

Submitted May 25, 2022. Accepted for publication May 26, 2022.

Non-statin therapy may be required for patients who cannot reach therapeutic objectives with lifestyle and maximal tolerated statin therapy. If so, therapies with outcomes data from randomized trials showing reduced cardiovascular events are favored. In high and very high risk patients who are statin intolerant, clinicians should consider initiating non-statin therapy while additional attempts are made to identify a tolerable statin in order to limit the time of exposure to elevated levels of atherogenic lipoproteins.

© 2022 National Lipid Association. Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality in the United States and around the world. Robust evidence demonstrates that statin therapy produces substantial reductions in circulating levels of atherogenic lipoproteins, as indicated by effects on low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein (Apo) B. Several types of evidence support the view that reducing concentrations of atherogenic lipoproteins lowers risk for clinical ASCVD events and statin therapy is the treatment modality for which the strongest evidence base exists.¹⁻³ Results from randomized controlled trials (RCTs) of non-statin therapies, and from Mendelian randomization studies have provided additional evidence to support the use of non-statin modalities for reducing ASCVD risk, if sufficient lowering of atherogenic lipoproteins cannot be achieved with lifestyle plus maximal tolerated statin therapy.^{1,2,4-6}

Although statins are generally well tolerated, statin intolerance (or perceived intolerance) is common in clinical practice and is frequently cited as a reason for discontinuation or modification of statin therapy.^{7,8} This has important clinical implications since lack of persistence and poor adherence to statin therapy have been associated with higher risk for adverse cardiovascular outcomes.⁹⁻¹² Identification of intolerance may help to facilitate the discussions and interventions necessary to limit disruptions in therapy, and/or alert the clinician to the need for non-statin treatment to achieve therapeutic objectives. In 2014, the National Lipid Association (NLA) was the first major organization to propose a working definition of statin intolerance.¹³ Since then, multiple organizations have proposed their own definitions of statin intolerance and some are summarized in Table 1.^{7,13-15}

The purpose of this NLA Scientific Statement is to provide an updated statin intolerance definition, with accompanying rationale, to inform clinicians and researchers in the identification, management, and investigation of the syndrome of statin intolerance. This statement encompasses perspectives from multiple disciplines, including pharmacy, medicine, nursing, and epidemiology, consistent with the NLA's commitment to a team-based approach for clinical ASCVD risk management, and support for public health and healthcare system initiatives to promote optimal cardiometabolic health.

Question 1: what is the new National Lipid Association definition of statin intolerance?

Statin intolerance is defined 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 two statins should have been attempted, including at least one at the lowest approved daily dosage.

Statin intolerance is a clinical syndrome that encompasses various symptoms and signs pertaining to multiple organ systems. The most frequently reported complaints with statin therapy are skeletal muscle-related symptoms (myalgias) that can be reported variously by patients as muscle soreness, aches, cramps, fatigue, and/or weakness. In most cases, statin-associated muscle symptoms occur without creatine kinase (CK) elevation.⁷ Less commonly, statin therapy has been associated with myopathy (defined as “unexplained muscle pain or weakness, accompanied by creatine kinase [CK] concentration > 10 times the upper limit of normal”),⁸ occurring in ~1/10,000 patients per year.⁷ A rare muscle related side effect is rhabdomyolysis (which is characterized by “CK typically > 40 times the upper limit of normal, which can cause myoglobinuria and acute renal failure”),⁸ occurring in ~1/100,000 patients per year of treatment.⁷ It is potentially life-threatening but is generally reversible when detected early. Other signs or symptoms that have been associated with statin therapy include transaminase elevation, worsening glycemia, and, in rare cases, confusion and memory loss.⁸

The new NLA definition differs from the other definitions in Table 2 in that it classifies clinical intolerance as complete or partial and refers to the patient's inability to tolerate a sufficient dose of statin to achieve therapeutic objectives. Patients unable to tolerate any statin dose or regimen are classified as completely intolerant. Patients able to tolerate a lower statin dose, different statin, or an unconventional dosing regimen (e.g., every other day or twice weekly) are classified as partially intolerant if the tolerated dose and regimen are insufficient to achieve desired levels of atherogenic lipoproteins or the desired intensity of statin therapy, e.g., the therapeutic objective. The therapeutic objective is a shared decision between provider and patient that should consider individual

Table 1 Definitions of statin intolerance from select organizations.

Society	Definition
NLA Expert Panel on Statin Intolerance 2014 ¹³	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, but reproducible by rechallenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise and underlying muscle disease). Specifically, the lowest starting statin daily dose is defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg and pitavastatin 2 mg.
Unified Definition from an International Lipid Expert Panel ¹⁴	1. The inability to tolerate at least two different statins - one statin at the lowest starting average daily dose and the other statin at any dose, 2. Intolerance associated with confirmed intolerable statin-related adverse effect(s) or significant biomarker abnormalities. 3. Symptom or biomarker changes resolution or significant improvement upon dose decrease or discontinuation, 4. Symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance.
Canadian Consensus Working Group ¹⁵	A clinical syndrome, not caused by drug interactions or risk factors for untreated intolerance and characterized by significant symptoms and/or biomarker abnormalities that prevent the long-term use and adherence to statins documented by challenges/dechallenge/re-challenge where appropriate using at least two statins, including atorvastatin and rosuvastatin, and that leads to failure of maintenance of therapeutic goals as defined by national guidelines
Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management ⁷	Assessment of the probability of SAMS being due to a statin take account of the nature of the muscle symptoms, the elevation in CK levels and their temporal association with statin initiation, discontinuation, and re-challenge. Note that this is a clinical definition, which may not be appropriate for regulatory purposes.
Abbreviations: CK, creatine kinase; NLA, National Lipid Association; SAMS, statin-associated muscle symptoms	

Table 2 Clinical definition of statin intolerance.

Definition	Characteristics
Statin intolerance is defined 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 two statins should have been attempted, including at least one at the lowest approved daily dosage.	
Complete	Inability to tolerate any dose or regimen of a statin
Partial	Ability to tolerate a lower dose of statin than is required to achieve the desired therapeutic objective

ASCVD risk, the potential costs, risks, and benefits of proposed therapies, as well as patient preferences. The consensus was that to classify a patient as having statin intolerance, at least two statins should be attempted, one of which should be the lowest approved daily dosage.

When a statin is prescribed and/or when an intolerance is identified, it is important to evaluate for modifiable risk factors. These may predispose a patient to experience an intolerance, and correction of the risk factor may mitigate adverse effects. A list of commonly encountered modifiable risk factors is included in Table 3.

Controversy exists regarding the causality of the associations between statin therapy and adverse experiences that produce intolerance. Results from placebo-controlled studies suggest that the incidence of muscle-related complaints with statin therapy may be at least partly attributable to the “nocebo” effect, in which the expectation of harm results in perceived side effects that may be unrelated to the pharmacological effects of the drug.¹⁶ In this document, the terminology that adverse experiences are “associated with statin therapy” is used to acknowledge that causality is sometimes uncertain.

Table 3 Modifiable factors associated with statin intolerance^{27,77,78}.

- Hypothyroidism
- Other therapies with potential drug to drug interactions (e.g., gemfibrozil, protease inhibitors, amiodarone, calcium channel blockers, azole antifungals, macrolides, immunosuppressants, colchicine)
- Alcohol use
- Strenuous exercise
- Vitamin D deficiency
- Obesity
- Diabetes

In the evaluation of a patient with statin-associated adverse effects, a retreat to confirm the symptom(s) after an appropriate washout can be helpful. However, even when a reported adverse experience is not causally related to the reported symptom(s), the result can still be failure to achieve therapeutic objectives if it contributes to poor adherence, or lack of persistence, with statin therapy.⁹⁻¹¹

The consensus is that the body of evidence supporting the efficacy of statin therapy to reduce ASCVD risk is compelling, and therefore it is recommended that multiple strategies should be attempted to achieve statin tolerance whenever feasible. However, not all strategies must be exhausted prior to initiating non-statin therapies, since reducing exposure to atherogenic lipoproteins as quickly as possible is essential for reducing risk for adverse cardiovascular events in high- and very-high-risk patients.^{1,2,17,18} Furthermore, once a patient starts one or more non-statin lipid lowering medications, the effort to identify a tolerable statin treatment regimen should not be abandoned. Results from randomized trials and clinical experience have shown that most patients with reported statin intolerance can tolerate some degree of statin therapy.^{7,19-21} Finding an acceptable regimen may require modification of the agent, dosage, and/or dosing regimen.

The recommendations from this NLA Scientific Statement regarding the NLA's new definition of statin intolerance are presented in Table 4.

Key points

- Statin intolerance is a clinical syndrome that can manifest on a continuum. Some patients experience partial intolerance while others are completely intolerant.
- Modifiable risk factors may contribute to statin intolerance symptoms and addressing the risk factor may improve statin tolerance in some instances.
- Multiple strategies should be employed, where feasible, in an attempt to identify a tolerable statin regimen which may involve changes in agent and/or dose and/or dosing regimen, because complete statin intolerance is uncommon (<5% of patients).
- In high-risk or very-high-risk patients, clinicians need not necessarily employ various unconventional dosing strategies before initiating non-statin therapy to limit the time

of exposure to elevated levels of atherogenic lipoproteins. Likewise, it is equally important that they do not abandon attempts to identify a tolerable statin regimen after a non-statin therapy is initiated.

Question #2: what is the prevalence of statin intolerance?

Statin-associated muscle symptoms are an important contributor to statin non-adherence and discontinuation. The Statin Adverse Treatment Experience (STATE) survey assessed statin usage and reasons for discontinuation in 1500 patients with high cholesterol who had taken a statin within the past two years and experienced at least one statin-associated symptom within the prior six months.²² Of the survey participants, a total of 332 individuals (22.1%) reported having discontinued statin therapy; the main reasons given for discontinuation were due to being bothered by, or intolerant of, side effects. Those who had discontinued statin therapy also reported experiencing more severe symptoms, which were predominantly musculoskeletal in nature, than those who continued to take a statin. The STATE survey was designed to assess patient experiences with statin therapy and did not account for whether the symptoms that led to discontinuation were truly related to the pharmacologic effects of statin therapy or only perceived to be so. Also, data from the STATE survey cannot be used to estimate the prevalence of statin intolerance in clinical practice but do support the view that the presence of statin-associated adverse effects can hinder persistence with statin therapy.

The Understanding Statin Use in America and Gaps in Education (USAGE) survey assessed the attitudes, beliefs, practices, and behavior of current and former statin users.^{23,24} This survey evaluated 10,138 respondents who were current (n=8918) or former (n=1220) statin users. Muscle-related side effects were reported by 60% of former statin users and 35% of current statin users. Side effects were cited as the reason for stopping statin therapy among 62% of former users (756 of the 1220 patients). If these results are extrapolated to the entire USAGE participant population, discontinuation due to statin-associated side effects was 7.5% (756 of 10,138). This survey provides important information about the prevalence of statin intolerance in a large sample, but the cross-sectional design, and recruitment of a convenience sample of individuals who had participated in other online

Table 4 Statin Intolerance – NLA Definition and Recommendations for ASCVD Risk Management.

Recommendation	Class of Recommendation (Strength)	Level of Evidence
<i>Statin intolerance is defined 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 two statins should have been attempted, including at least one at the lowest approved daily dosage.</i>		
For patients demonstrating non-adherence, or lack of persistence with statin therapy, statin intolerance should be evaluated as a potential contributing factor.	I	B-R
For patients with suspected statin intolerance, clinicians should attempt multiple strategies to identify a tolerable statin regimen (e.g., lower dose, switching statins, non-daily dosing), because complete statin intolerance is uncommon (<5% of patients).	I	B-R
When non-statin therapies are used, those with data from randomized trials showing reduced cardiovascular event risk should be favored.	I	A
For patients with known or suspected statin intolerance who are at high- or very-high ASCVD risk, non-statin therapy should be considered while additional attempts are made to identify a tolerable statin regimen to avoid excessive delay in lowering atherogenic lipoproteins.	IIa	B-R
For patients with statin intolerance, it is reasonable to consider the nocebo effect as a possible cause; however, this does not make such symptoms less clinically relevant and ASCVD risk related to elevated atherogenic lipoproteins should be addressed.	IIa	A
For patients with complete or partial statin intolerance, it is reasonable to consider non-statin therapy to assist in lowering atherogenic lipoproteins.	IIa	A

Abbreviation: ASCVD, atherosclerotic cardiovascular disease

panels raise questions about how representative this sample is of the population encountered in clinical practice.²³

The Effects of Statins on Muscle Performance (STOMP) study was designed to specifically assess the musculoskeletal side effects of statin therapy (Table 5).²⁵ In this randomized, double-blind, placebo-controlled study, 420 healthy, statin-naïve patients were randomized to atorvastatin 80 mg once daily vs. placebo for 6 months. Participants were selected across three clinical sites and completed a baseline muscle symptom questionnaire, laboratory testing, and baseline exercise strength testing. Participants who were treated with lipid-lowering medications at the time of recruitment, or previously, were excluded, as were those on medications known to affect skeletal muscle function or alter statin metabolism. Additionally, those with laboratory abnormalities such as an elevation in serum CK level >10 times the upper limit of normal, or alanine aminotransferase level >3 times the upper limit of normal on two occasions were excluded. Participants were monitored using telephone contact and visits for laboratory testing, strength and handgrip testing, knee endurance testing, and assessment of maximal oxygen consumption.

Treatment with atorvastatin did not affect muscle strength or exercise performance during the study. Twenty-three atorvastatin (11.3% of the analysis sample) and 14 placebo subjects (6.5% of the analysis sample) reported new, unexplained muscle pain. The definition of myalgia was prede-

defined and required resolution of muscle symptoms shortly after stopping study medication and reappearance on restarting the medication. Nineteen atorvastatin (9.4% of the analysis sample) and 10 placebo subjects (4.6% of the analysis sample) met the study definition for myalgia ($p=0.05$). The authors note that the incidence of 9.4% is similar to that reported in a survey of 7924 French patients taking high dosage statin therapy of 10.5%, as was the time to onset of ~1 month (35 ± 31 days in STOMP).²⁶ The findings from STOMP illustrate the importance of a blinded placebo group for attributing causality because unexplained muscle symptoms are relatively common in the absence of statin therapy.

The prevalence of statin-associated muscle symptoms varies widely across registry and observational datasets.^{7,22,23,26} Reported statin intolerance is less prevalent in RCTs than in observational studies. The Lipid and Blood Pressure Meta-Analysis Group and the International Lipid Expert Panel (ILEP) conducted a meta-analysis of 176 studies (4,143,517 patients) to estimate the prevalence of statin intolerance.²⁷ Three definitions of statin intolerance from the NLA, European Atherosclerosis Society (EAS), and ILEP were utilized; these most closely align with the NLA's new definition of complete statin intolerance.^{7,13,14} The prevalence (or cumulative incidence) of statin intolerance was 4.9% (95% confidence interval [CI] 4.0%-6.0%) in the 112 RCTs included. However, the prevalence (or

Table 5 Prevalence or incidence of muscle-related side effects in clinical trials.

Study name	Population	Study Design	Key Findings
STOMP ²⁵	Healthy, statin-naïve subjects	Randomized double-blind parallel trial Subjects randomized to atorvastatin 80 mg/d or placebo for 6 months	n=420 subjects randomized Unexplained new muscle pain: reported by 23/203 (11.3%) atorvastatin and 14/217 (6.5%) placebo subjects Myalgia: 19/203 (9.4%) atorvastatin subjects and 10/217 (4.6%) placebo subjects (p=0.05)
GAUSS-3 ³⁰	Patients with elevated LDL-C who were unable to tolerate an effective dose of a statin because of muscle-related adverse effects -Inability to tolerate atorvastatin 10 mg and any other statin at any dose or, alternatively, 3 more statins, with 1 at the lowest average daily starting dose and 2 other statins at any dose because of muscle-related adverse effects	Phase A: double-blind, placebo-controlled crossover to rechallenge patients with atorvastatin 20 mg/d Phase B: patients who experienced intolerable muscle symptoms during the first period entered a double-blind randomization to ezetimibe or evolocumab in a double-dummy design	n=472 subjects completed both conditions during Phase A Intolerable muscle symptoms reported in: 44.3% with atorvastatin but not placebo, 27.5% with placebo but not atorvastatin, 18.0% with neither treatment, and 10.2% with both treatments Active study drug was stopped for muscle symptoms in 6.8% of ezetimibe-treated patients and 0.7% of evolocumab-treated patients
ODYSSEY ALTERNATIVE ²¹	Patients with primary hypercholesterolemia at moderate or high cardiovascular risk and with statin intolerance defined as the inability to tolerate 2 or more statins because of unexplained skeletal muscle-related symptoms, other than those due to strain or trauma that began or increased during statin treatment and resolved with statin discontinuation. One of the 2 statins had to have been discontinued while at or below the lowest approved daily starting dose	Randomized, double-blind, double-dummy, active-controlled, parallel group study Patients with no skeletal-muscle related AE on placebo were randomized to alirocumab, ezetimibe or atorvastatin 10 mg/d (statin rechallenge arm) for 24 weeks	n=314 subjects randomized Myalgia most common AE in all groups Of the 63 randomized to atorvastatin, 14% discontinued treatment due to statin-associated muscle symptoms Skeletal muscle-related events were less frequent with alirocumab vs. atorvastatin (HR 0.61, 95% CI 0.38-0.88, p=0.042) Rate of study treatment discontinuation due to skeletal muscle-related AEs was not different for alirocumab vs. atorvastatin or vs. ezetimibe
SAMSON ³¹	Patients who had abandoned statins clinically with no intention of restarting, because of intolerable symptoms of any type arising within 2 weeks of starting	Multiple-crossover, 3-condition n-of-1, double-blind, placebo controlled trial Subjects received 12 one-month bottles of medication (4 atorvastatin 20 mg, 4 placebo, and 4 empty) that they took in random order	n=60 subjects randomized No difference in mean symptom intensity in patients taking placebo vs. statin during the study: mean symptom score of 8.0 during no-tablet months, 16.3 in statin months, and 15.4 in placebo months Nocebo ratio was 0.90
StatinWISE ³²	Patients who were considering stopping their statin (complained of symptoms during consultation) or had stopped taking a statin in the last 3 years because of muscle symptoms	Series of randomized, double-blind, placebo-controlled n-of-1 trials Patients were randomized to a series of 6 treatment periods of either placebo or atorvastatin 20 mg/d	n=200 subjects randomized n=151 subjects provided muscle symptom scores for at least 1 statin period and 1 placebo period No difference in mean muscle symptom scores between statin periods (1.68) and placebo periods (1.85)

Abbreviations: AE, adverse event; CI, confidence interval; GAUSS, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; SAMSON, Self-assessment Method for Statin Side-effects; StatinWISE, Statin Web-based Investigation of Side Effects; STOMP, Effects of Statins on Muscle Performance

cumulative incidence) was 17% (95% CI 14%-19%) in the 64 observational cohort studies included.

The primary objectives of the RCTs included in this meta-analysis were generally to assess clinical outcomes other than adverse effects and tolerability. Self-selection of those who volunteer for clinical trials of statin therapy, coupled with design elements such as exclusion of patients with prior statin intolerance or co-morbid conditions that may predispose to statin intolerance and run-in phases on statin therapy for some trials, suggest that results from clinical trials may produce an underestimation of the true incidence of statin intolerance in the population. Therefore, estimates of prevalence from observational cohort data may more accurately reflect the real-world clinical experience. Meta-regression analysis identified 10 risk factors that were significantly associated with statin intolerance: statin dose, diabetes mellitus, obesity, hypothyroidism, chronic liver disease, chronic kidney disease, excessive use of alcohol, strenuous exercise, use of antiarrhythmic medications, and use of calcium channel blocker medications.²⁷ These ten risk factors should be interpreted with caution because they were often collected with limited detail. For example, the quantity and frequency of alcohol use and the frequency, intensity, and duration of exercise were often not fully described.

Results from other clinical trials suggest that some degree of statin intolerance may have relatively high prevalence in those with ASCVD. In two large, randomized, placebo-controlled cardiovascular outcome trials, each evaluating the addition of a proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibody to statin therapy in patients with documented ASCVD, 30.7% and 11.2% of patients were unable to be titrated to high-intensity statin therapy in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) (n=27,564) and ODYSSEY Outcomes studies (n=18,924), respectively.^{28,29} Although insufficient information is available to estimate the prevalence of statin intolerance according to the new NLA definition, it is likely that a large proportion of these patients would be categorized as having at least partial statin intolerance since high-intensity statin therapy is recommended for high- and very high-risk patients.¹

The ODYSSEY ALTERNATIVE trial included patients with self-reported prior statin intolerance, defined as the inability to tolerate two or more statins, including one at the lowest approved daily starting dose (Table 5).²¹ After a placebo run-in period, 314 patients were randomized to alirocumab, ezetimibe 10 mg/d, or atorvastatin 20 mg/d. Of the 63 patients randomized to atorvastatin, 14 (22.2%) discontinued therapy due to statin-associated muscle symptoms, indicating that almost 80% of patients with reported statin intolerance could tolerate this regimen of atorvastatin therapy.

The Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS)-3 trial (n=491) was a randomized clinical trial that included patients with a history of statin intolerance (Table 5).³⁰ The definitions of statin intolerance were the inability to toler-

ate atorvastatin at 10 mg and any other statin at any dose, or an inability to tolerate three or more statins, with one at the lowest average daily starting dose and two other statins at any dose. The study included two phases. The first phase had a crossover design in which patients were randomized to atorvastatin 20 mg daily or placebo for two 10-week periods, separated by a 2-week washout. Patients who experienced muscle-related adverse effects while taking atorvastatin, but not placebo, were eligible for the second phase in which patients were randomized to receive evolocumab or ezetimibe. Of those that completed both the placebo and atorvastatin conditions during the first phase of the study (n=472), 44.3% experienced intolerable muscle symptoms with atorvastatin but not placebo, compared to 27.5% that experienced intolerable muscle symptoms with placebo but not atorvastatin. An additional 28.2% of patients experienced no symptoms on either atorvastatin or placebo (18.0%) or experienced symptoms on both atorvastatin and placebo (10.2%). Since the frequency of symptoms on atorvastatin was higher than that with placebo, these results support the existence of symptoms that are attributable to the pharmacologic effects of statin therapy. However, since less than half of this sample with a history of statin intolerance reported symptoms while taking atorvastatin, but not while taking placebo, the results also support the view that the nocebo effect is also a substantial contributor to reported statin intolerance.

Results from two n-of-1 studies, Self-Assessment Method for Statin Side-effects or Nocebo (SAMSON) and Statin Web-based Investigation of Side Effects (StatinWISE), suggest that up to 90% of the reported statin intolerance among statin users may be attributed to the nocebo effect.^{31,32} In SAMSON, 60 patients who had previously discontinued statin therapy within two weeks of initiation were enrolled in a double-blind, three-condition n-of-1 trial to assess whether symptoms were elicited by a statin vs. placebo. Each patient received four bottles of atorvastatin 20 mg, four bottles of placebo, and four empty bottles, and were instructed to use each bottle for a one-month period according to a random sequence. Symptoms were reported daily during this period. The primary endpoint was the ratio of symptom intensity induced by taking the placebo compared to the symptom intensity induced by taking a statin. No difference was noted in mean symptom intensity in patients taking the placebo vs. statin during the study. Furthermore, in patients who had discontinued statin therapy due to side effects, 90% of the symptom burden (the nocebo ratio) that was elicited by statins was also elicited by the placebo.

StatinWISE was an n-of-1 trial in 200 participants who had recently stopped, or were considering stopping, statin therapy because of muscle symptoms. Participants were randomized to a series of six double-blind treatments of either placebo or atorvastatin 20 mg daily. Among the 151 participants who provided muscle symptom scores, there were no significant differences in statin-associated muscle symptoms between statin therapy and placebo. Discontinuation due to intolerable muscle symptoms was 9% during the atorvastatin periods and 7% during the placebo periods.

When taking the above evidence into account, it appears that the incidence of statin intolerance (partial or complete) ranges between approximately 5% and 30%, and likely varies according to the characteristics of the population studied. Statin-associated side effects, whether related to the pharmacologic effects of statin therapy or not, have an impact on patient quality of life and day-to-day functioning, and should not be dismissed. The focus of therapy should be on achieving the patient-specific therapeutic objective, while also maximizing quality of life and minimizing side effects. The recommendations from this NLA Scientific Statement regarding the incidence and prevalence of statin intolerance in clinical practice are presented in [Table 4](#).

Key points

- Some degree of statin intolerance is reported in as many as 5% to 30% of patients, although incidence and prevalence vary by population studied and setting.
- It is reasonable to attribute some proportion of statin-associated symptoms to the placebo effect; however, this does not make such symptoms less clinically relevant.
- ASCVD risk related to elevated levels of atherogenic lipoproteins should be addressed in patients with statin-associated adverse effects, regardless of causality (i.e., pharmacologic or placebo effects).

Question #3: what is the evidence for use of non-statin therapies to lower atherogenic lipoproteins as a means of reducing adverse cardiovascular event risk?

Results from prospective cohort studies, Mendelian randomization studies, and randomized intervention trials have consistently demonstrated a log-linear relationship between the magnitude of exposure of the vasculature to an elevated circulating level of atherogenic lipoprotein particles and adverse cardiovascular event risk.^{2,33,34} The strength of this relationship increases with greater duration of exposure.^{2,35} Adverse cardiovascular event risk is lowered by reduction of the plasma atherogenic lipoprotein level, and this benefit is proportionate to both the degree of reduction and the length of time that a lower level is maintained.^{2,36,37} The benefit of atherogenic lipoprotein reduction appears to be independent of the mechanism through which the reduction is induced, provided that there are no deleterious off-target effects of the intervention employed.^{2,28,29,36-39}

LDL-C is the most frequently used surrogate for atherogenic lipoprotein concentration, although non-HDL-C and Apo B have been found to be stronger and more consistent indicators of ASCVD risk.^{1,40} Non-HDL-C reflects the concentration of cholesterol carried by all Apo B-containing lipoprotein particles, while Apo B concentration is a direct measure of the burden of atherogenic lipoproteins, because each non-HDL lipoprotein particle contains a single molecule of Apo B. The levels of both major compo-

nents of non-HDL-C (LDL-C and very low-density lipoprotein cholesterol [VLDL-C]) show similar relationships to adverse cardiovascular event risk.^{2,41} However, adjustment for the Apo B concentration reduces the associations of both LDL-C and VLDL-C to non-significance, consistent with the view that lowering the concentration of all Apo B-containing lipoproteins should be the main focus of therapeutic strategies.^{2,42,43}

The main modalities available in the US for lowering atherogenic lipoprotein concentration include:

1. Lifestyle therapies
2. Statins
3. Ezetimibe (cholesterol absorption inhibitor)
4. PCSK9 inhibitors (monoclonal antibody and small interfering RNA [siRNA])
5. Bile acid sequestrants
6. Bempedoic acid (ATP citrate lyase inhibitor)
7. Fibrates
8. Icosapent ethyl

Clinical effects and safety of interventions for modification of lipoprotein and lipoprotein lipid concentrations has been reviewed in detail elsewhere.^{1,44} Lifestyle modification, including a healthy dietary pattern, dietary adjuncts, regular activity, weight loss if overweight or obese, and smoking cessation, and statin therapy are considered cornerstones in the management of dyslipidemia for adverse cardiovascular event risk reduction.^{1,3} The former because of low risk and expense, as well as the ability to institute changes early in life that are maintained for decades, and the latter because it is the class of medications for which the most evidence is available from RCTs to demonstrate reduced adverse cardiovascular event risk.¹

For patients with statin intolerance, non-statin pharmacologic therapies are often needed as an adjunct to statin therapy, or as an alternative to statin therapy, to achieve therapeutic objectives. Clinicians should be aware that most patients with statin intolerance are able to tolerate some statin therapy.^{7,19,20} Finding a regimen that is acceptable to the patient may require switching agents, dosages, or use of alternative regimens such as dosing on alternate days.^{13,45,46} However, some patients will demonstrate an inability to tolerate, or unwillingness to use, any statin. Below, the evidence for the effects of non-statin pharmacotherapies is briefly reviewed ([Table 6](#)).

Ezetimibe. Ezetimibe is the only currently available cholesterol absorption inhibitor in the US. When employed as monotherapy (10 mg/d), it generally reduces LDL-C by 15-20% and produces additional LDL-C lowering of 20-25% when added to statin therapy. The efficacy of ezetimibe for reducing ASCVD risk has been evaluated in several trials, most often in combination with statin therapy.^{38,39,47,48} The results of these trials indicate reductions in adverse cardiovascular event risk consistent with expectations based on the degree of additional LDL-C reduction.³⁶ The largest of these trials, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated ezetimibe

Table 6 Key studies in the evidence base for non-statin therapies available in the US that lower atherogenic lipoproteins for reducing adverse cardiovascular event risk.

Class/Agent	RCT	Population Studied	Treatment Arms	Median Duration, y	LDL-C, Diff. Between Groups, mg/dL*	TG, Diff. Between Groups, mg/dL*	CV Event RRR, HR (95% CI) [†]	CV Event ARR, %
Cholesterol Absorption Inhibitor								
Ezetimibe	IMPROVE-IT ³⁹	N=18,144 subjects hospitalized with ACS within 10 days prior to enrollment and LDL-C 50-100 mg/dL**	Simvastatin 40 mg/d plus ezetimibe 10 mg/d vs. simvastatin 40 mg/d plus placebo	6	-16.7	-14.0	0.94 (0.89-0.99)	2.0
Ezetimibe	SHARP ³⁸	N=9438 subjects with CKD on dialysis with no known history of MI or coronary revascularization	Simvastatin 20 mg/d plus ezetimibe 10 mg/d vs. placebo [‡]	4.9	-43.0	NA	0.83 (0.74-0.94)	2.1
Ezetimibe	EWTOPIA 75 ⁴⁸	N=3796 subjects ≥75 y with elevated LDL-C without history of CAD	Ezetimibe 10 mg/d vs. usual care (dietary counseling)	4.1	-19.0	-4.0	0.66 (0.50-0.86)	2.6
PCSK9 Inhibitor								
Alirocumab	ODYSSEY Outcomes ²⁹	N=18,924 subjects with ACS in prior 1-12 months with LDL-C ≥70 mg/dL, non-HDL-C ≥100 mg/dL or Apo B ≥80 mg/dL	Alirocumab (dose-adjusted to target LDL-C 25-50 mg/dL) vs placebo on background high-intensity statin	2.8	-48.0	NA	0.85 (0.78-0.93)	1.6
Evolocumab	FOURIER ²⁸	N=27,564 subjects with ASCVD and LDL-C ≥70 mg/dL	Evolocumab (140 mg every 2 weeks or 420 mg/month) vs. placebo on background optimized lipid-lowering therapy [¶]	2.2	-56.0	-15.5	0.85 (0.79-0.92)	1.5
Fibrate								
Fenofibrate	FIELD ⁶²	N=9795 subjects 50-75 y of age with T2D and not taking statin at study entry	Fenofibrate 200 mg/d vs. placebo	5	-14.7	-51.3	0.89 (0.75-1.05)	1.0
Fenofibrate	ACCORD Lipid ⁶³	N=5518 subjects with T2D and HbA1c ≥7.5%, with LDL-C 60-180 mg/dL, HDL-C <50 mg/dL and TG <750 mg/dL [§]	Fenofibrate vs. placebo on background simvastatin	4.7	+2.1	-26	0.92 (0.79-1.08)	0.2

(continued on next page)

Table 6 (continued)

Class/Agent	RCT	Population Studied	Treatment Arms	Median Duration, y	LDL-C, Diff. Between Groups, mg/dL*	TG, Diff. Between Groups, mg/dL*	CV Event RRR, HR (95% CI) [†]	CV Event ARR, %
Gemfibrozil	HHS ⁵⁸	N=4081 subjects with non-HDL-C ≥ 200 mg/dL without symptomatic CHD	Gemfibrozil 1200 mg/d vs. placebo	5	-21.8	-62.5	0.66 (0.47, 0.92)	1.4
Gemfibrozil	VA-HIT ⁵⁹	N=2531 subjects with CHD, with HDL-C ≤ 40 mg/dL and LDL-C ≤ 140 mg/dL	Gemfibrozil 1200 mg/d vs. placebo	5.1	0.0	-52.0	0.78 (0.65-0.93)	4.4
Prescription omega-3 fatty acids								
Icosapent Ethyl	REDUCE-IT ⁶⁹	N=8179 subjects with CVD or diabetes + other risk factors, with TG 135-499 mg/dL and LDL-C 41-100 mg/dL	Icosapent ethyl 4 g/d vs. placebo on background statin	4.9	-5.0	-44.5	0.75 (0.68, 0.83)	4.8
Bile Acid Sequestrant								
Cholestyramine	LRC-CPPT ⁵³	N=3806 male subjects, 35-59 y of age with total-C ≥ 265 mg/dL and LDL-C ≥ 190 mg/dL	Cholestyramine vs. placebo	7.4	-40.2	+7.1	0.81 (0.68, 0.97)	1.7
ATP Citrate Lyase Inhibitor								
Bempedoic Acid	CLEAR OUTCOMES ⁵⁷	N=14,014 subjects with all of the following: ASCVD or at high risk of ASCVD, documented statin intolerance, and LDL-C ≥ 100 mg/dL	Bempedoic acid 180 mg/d vs. placebo on background guideline-directed medical therapy	3.5 (planned)	NA	NA	NA	NA
Small Interfering RNA Targeting PCSK9								
Inclisiran	ORION 4 ⁵¹	N=15,000 subjects ≥ 55 y of age with pre-existing ASCVD	Inclisiran sodium 300 mg vs. placebo	5 (planned)	NA	NA	NA	NA
Fibrate/Selective PPAR-alpha Modulator								

(continued on next page)

Table 6 (continued)

Class/Agent	RCT	Population Studied	Treatment Arms	Median Duration, y	LDL-C, Diff. Between Groups, mg/dL*	TG, Diff. Between Groups, mg/dL*	CV Event RRR, HR (95% CI) [†]	CV Event ARR, %
Pemafibrate	PROMINENT ⁶⁸	N=10,000 subjects with T2D, TG 200-499 mg/dL and HDL-C ≤40 mg/dL	Pemafibrate 0.4 mg/d vs. placebo on background statin therapy or met LDL-C criteria [‡]	3.75 (planned) [#]	NA	NA	NA	NA

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACS, acute coronary syndrome; Apo, apolipoprotein; ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CLEAR, Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen; CV, cardiovascular; Diff., difference; EWTOPIA 75, Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; HR, hazard ratio; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; NA, not available; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin kexin type 9; PPAR, peroxisome proliferator-activated receptor; PROMINENT, Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients; RCT, randomized controlled trial; RRR, relative risk reduction; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; SHARP, Study of Heart and Renal Protection; T2D, type 2 diabetes; total-C, total cholesterol; VA-HIT, Veterans Affairs HDL Intervention Trial; TG, triglycerides; w, weeks; y, year(s)

*Difference in the change between on-treatment group and placebo group.

[†]Results are for the primary outcome variable as defined in each trial: IMPROVE-IT, composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, or nonfatal stroke; SHARP, first major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure); ODYSSEY Outcomes, composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization; FOURIER, composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; ACCORD Lipid, first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes; LRC-CPPT, combination of definite coronary heart disease death and/or definite nonfatal myocardial infarction; EWTOPIA 75, composite of sudden cardiac death, myocardial infarction, coronary revascularization or stroke; HHS, total cardiac endpoints (fatal or nonfatal myocardial infarction and cardiac death); VA-HIT, nonfatal myocardial infarction or death from coronary causes; FIELD, coronary events (coronary heart disease death or non-fatal myocardial infarction); REDUCE-IT, composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina

^{**}The LDL-C range listed was for patients taking lipid-lowering therapy; for patients not receiving lipid-lowering therapy the LDL-C entry criterion was 50-125 mg/dL.

[‡]Patients were initially randomized 3 ways between simvastatin 20 mg/d plus ezetimibe 10 mg/d, simvastatin 20 mg/d, and placebo; those initially allocated to simvastatin alone were re-randomized to simvastatin 20 mg/d plus ezetimibe 10 mg/d vs. placebo after 1 year.

[§]Optimized regimen of lipid-lowering therapy was defined as preferably a high-intensity statin but must have been at least atorvastatin at a dose of 20 mg/d or its equivalent, with or without ezetimibe.

[§]The HDL-C criterion was <55 mg/dL for women and blacks; the TG level listed was for patients not receiving lipid therapy, for those receiving lipid therapy the TG criterion was <400 mg/dL.

[¶]Subjects were either on moderate to high-intensity statin therapy or had LDL-C ≤70 mg/dL within the prior 12 months. Statin intolerant patients were also eligible if they had LDL-C ≤100 mg/dL.

[#]In April 2022 PROMINENT was stopped because of low likelihood of demonstrating benefit for the primary outcome, additional results are pending.

10 mg/d added to simvastatin 40 mg/d vs. placebo plus simvastatin 40 mg/d in 18,144 patients who had been hospitalized with an acute coronary syndrome within the preceding 10 days and had LDL-C levels of 50-100 mg/dL (on lipid therapy) or 50-125 mg/dL (not taking lipid therapy). When added to statin, ezetimibe reduced the event rate for the primary endpoint at 7 years by ~6% (hazard ratio 0.936, 95% CI 0.89-0.99, $p=0.016$).³⁹

A trial in Japan (Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older [EWTOPIA 75]) assessed the efficacy of ezetimibe without statin therapy for lowering ASCVD event risk in patients who were at least 75 years of age at baseline with no history of coronary artery disease.⁴⁸ All patients received di-

etary counseling and were randomized to receive usual care alone or usual care plus 10 mg/d of ezetimibe. The sample included 3796 patients with median follow-up of 4.1 years. Ezetimibe reduced the incidence of the primary composite outcome by 34% (hazard ratio 0.66, 95% CI 0.50-0.86, $p=0.002$).

PCSK9 inhibitors. Three agents that target PCSK9 are available in the US, two monoclonal antibodies (evolocumab and alirocumab) and one siRNA agent (inclisiran). Each lowers LDL-C by 50-60% when added to statin therapy.^{28,29,49} These agents also lower lipoprotein (a) by 20-25%.⁵⁰ Cardiovascular outcomes trial data are available for the two monoclonal antibodies and a cardiovascular outcomes trial is underway for the siRNA agent.^{28,29,51} The trials with the mono-

clonal antibodies were conducted in patients with established ASCVD on background statin therapy and both showed 15% reductions ($p < 0.001$) in composite major adverse cardiovascular events outcomes over relatively short median follow-up periods of 2.2 to 2.8 years. No data on the effects of PCSK9i monotherapy on cardiovascular outcomes are available as of this writing.

Bile acid sequestrants. Bile acid sequestrants available in the US include cholestyramine, colestipol, and colesevelam. At the maximal daily dosages, these reduce LDL-C by ~13-25%, although this may also be accompanied by increases of ~5-20% in triglycerides (TG), particularly in patients with hypertriglyceridemia at baseline.¹ As a result, the reduction in non-HDL-C is typically less than that for LDL-C, most often in the range of 8-15%. Notably, colesevelam also lowers fasting glucose and glycated hemoglobin, and thus has an additional approved indication for management of glycemia in type 2 diabetes mellitus.⁵²

Minimal data are available from cardiovascular outcomes trials of bile acid sequestrant therapies. The main trial supporting efficacy is the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), the initial results of which were published in 1984, prior to the availability of statin therapy.⁵³ In this trial, 3806 men with primary hypercholesterolemia were randomized to placebo or cholestyramine (24 g/d). After mean follow-up of 7.4 years, the cholestyramine group showed a 19% reduction in the primary outcome of definite fatal coronary heart disease or non-fatal myocardial infarction.

Bempedoic acid. Bempedoic acid (180 mg/d) is an ATP citrate lyase inhibitor that is available as a single agent and in combination with ezetimibe. Its effects on LDL-C are additive to those of statins and ezetimibe, with LDL-C lowering ranging from 13-25% in phase 3 randomized trials.^{54,55} The combination of bempedoic acid (180 mg/d) and ezetimibe (10 mg/d) lowers LDL-C by ~38%, with results consistent across subgroups, including those with and without statin therapy.⁵⁵ Because bempedoic acid is a pro-drug that is converted to its active form in the liver and is not in its active form in skeletal muscle, reduced risk of muscle symptoms is expected with its use.⁵⁶

No results are available at present from cardiovascular outcomes trials of bempedoic acid, although such a trial is underway in subjects at high- and very-high risk for ASCVD who have documented statin intolerance and LDL-C ≥ 100 mg/dL.⁵⁷ Subjects have been randomized in a 1:1 ratio to placebo or bempedoic acid 180 mg/d. Enrollment has been completed (N=14,014) and the trial will continue until 1620 participants have experienced the primary endpoint of a major adverse cardiovascular event. Results are expected in 2023.

Fibrates. Agents in the fibrate class of peroxisome proliferator activated receptor (PPAR)-alpha modulators available in the US include fenofibric acid, fenofibrate, and gemfibrozil. The effects of fibrates on the lipid profile vary markedly by phenotype. In patients with isolated hyper-

cholesterolemia, the LDL-C level may be reduced by up to 20%. For those with mixed dyslipidemia (elevated TG and LDL-C), the LDL-C level is generally reduced modestly (5-15%), with a larger effect on the TG concentration (25-35% reduction). For patients with more severe hypertriglyceridemia (≥ 300 mg/dL), the TG level may be reduced by as much as 45-55%, while the LDL-C concentration in such patients may rise. Typically, the net effect of fibrate therapy is to lower non-HDL-C, although the contributions of LDL-C and VLDL-C reductions vary by phenotype.

The effects of fibrate therapy on ASCVD risk have been assessed in several large-scale RCTs which have produced mixed results.⁵⁸⁻⁶³ Two trials of monotherapy with gemfibrozil were completed: the Helsinki Heart Study (HHS), a primary prevention trial, and the Veterans Affairs-HDL Intervention Trial [VA-HIT], a secondary prevention trial. Both showed benefits for reducing coronary heart disease events compared with placebo. However, in two trials with fenofibrate (Fenofibrate Intervention and Event Lowering in Diabetes [FIELD] and Action to Control Cardiovascular Risk in Diabetes [ACCORD] Lipid), in which patients with type 2 diabetes mellitus were studied, no significant overall benefit for composite endpoints of major adverse coronary or cardiovascular events were observed.

Results from meta-analyses of subgroups suggested a potential benefit of fibrate therapies in those with elevated TG, particularly when accompanied by reduced HDL-C.⁶⁴⁻⁶⁷ However, such analyses are primarily useful for hypothesis generation and require prospective verification.

A new selective PPAR-alpha modulator (pemafibrate) was studied in the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial.⁶⁸ This trial was evaluating the efficacy of pemafibrate in high-risk patients with type 2 diabetes mellitus plus high TG and low HDL-C levels but was stopped after a planned interim analysis when it was concluded that the primary endpoint (composite of nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization and cardiovascular death) was unlikely to be met. Further details are not available at the time of this writing.

Icosapent ethyl. Two formulations of prescription omega-3 fatty acids are currently available in the US: omega-3-acid ethyl esters (eicosapentaenoic + docosahexaenoic acid ethyl esters) and icosapent ethyl (IPE), which is an eicosapentaenoic acid-only ethyl ester. Both are used to treat severe hypertriglyceridemia (TG ≥ 500 mg/dL), but only icosapent ethyl has an approved indication for secondary prevention of ASCVD. The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) evaluated 8179 patients with established ASCVD, or with diabetes and other risk factors, who had been receiving statin therapy and had a fasting TG level of 135-499 mg/dL and LDL-C of 41-100 mg/dL.⁶⁹ Patients received 4 g/d IPE or placebo. After one year of treatment, TG were reduced by 19.7% with IPE vs. placebo and LDL-C was increased significantly less with IPE than placebo (6.6% less, 3.1% with IPE vs. 10.2%

with placebo). The risk of the primary major adverse cardiovascular composite outcome during median follow-up of 4.9 years was significantly reduced with IPE (hazard ratio 0.75, 95% CI 0.68-0.83, $p < 0.001$). While icosapent ethyl lowers atherogenic lipoproteins (10-13% differences in non-HDL-C and Apo B), it appears likely that other mechanisms contributed to its observed effects in REDUCE-IT to lower adverse cardiovascular event risk.⁷⁰

Nicotinic acid. Nicotinic acid and other forms of niacin are sometimes used as lipid-altering agents to reduce elevated LDL-C, non-HDL-C, Apo B and TG levels in patients with primary hyperlipidemia and mixed dyslipidemia. Nicotinic acid can effectively reduce LDL-C by 5-25%, and triglycerides by 20-50% and also raise HDL-C by 15-35% and reduce lipoprotein (a) by 25-40%.⁷¹⁻⁷³ Two large, randomized trials, one with extended-release niacin and one with niacin plus laropiprant, failed to demonstrate benefits on adverse cardiovascular events when added to statin therapy.^{74,75} Compared to placebo, niacin $\pm$ laropiprant use was associated with increased frequencies of adverse effects. Accordingly, nicotinic acid is not considered one of the main modalities for modification of atherogenic lipoproteins, although its use may be appropriate in some circumstances, generally under the direction of a Clinical Lipid Specialist.^{13,76}

The recommendations from this NLA Scientific Statement regarding the use of non-statin therapies are presented in Table 4.

Key points

- An acceptable statin treatment regimen can be identified for most patients with statin intolerance which may require a different dose, statin, or dosing schedule.
- Non-statin therapy may be required for patients who cannot reach therapeutic objectives with lifestyle and maximal tolerated statin therapy. Clinicians should favor non-statin therapies with data from outcomes trials showing a reduction in adverse cardiovascular events.
- The evidence base for non-statin interventions for dyslipidemia management to lower adverse cardiovascular event risk is not as well-developed as that for statin therapy but has been growing in recent years and is bolstered by results from observational data, particularly Mendelian randomization studies. Taken together, these results support the view that adverse cardiovascular event risk is lowered by reduction of the plasma atherogenic lipoprotein level, and this benefit is proportionate to both the degree of reduction and the length of time that a lower level is maintained.
- Ongoing and planned RCTs are expected to provide additional information regarding the risks and potential benefits of non-statin therapies for reducing adverse cardiovascular event risk.

Conflict of interest

Disclosures for KCM during the prior 24 months include consulting fees from 89Bio, Beren Therapeutics, Matinas BioPharma, New Amsterdam Pharma and research grant support from Matinas BioPharma. NAC received consulting fees from Amarin, Amgen, Astra Zeneca, Esperion, Point of Care Network and Regeneron during the past 24 months. MKC, JJS, AA, SR, TAJ, and DLD have nothing to disclose.

CRediT authorship contribution statement

All authors contributed to the conception, design, final revision, and approval of the article. MKC, JJS, AA, SR, NC, and KCM drafted the statement.

Acknowledgments

The authors wish to thank Mary R. Dicklin, PhD of Midwest Biomedical Research, Addison, IL for assistance with editing and formatting.

References

1. 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*. 2019;139:e1082-e1143.
2. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459-2472.
3. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111-188.
4. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol*. 2016;68:92-125.
5. Beshir SA, Hussain N, Elnor AA, Said ASA. Umbrella review on non-statin lipid-lowering therapy. *J Cardiovasc Pharmacol Ther*. 2021;26:437-452.
6. Masana L, Ibarretxe D, Plana N. Reasons why combination therapy should be the new standard of care to achieve the LDL-cholesterol targets: lipid-lowering combination therapy. *Curr Cardiol Rep*. 2020;22:66.
7. 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. *Eur Heart J*. 2015;36:1012-1022.
8. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39:e38-e81.
9. Gomez Sandoval YH, Braganza MV, Daskalopoulou SS. Statin discontinuation in high-risk patients: a systematic review of the evidence. *Curr Pharm Des*. 2011;17:3669-3689.

10. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78:684–698.
11. Banach M, Stulc T, Dent R, Toth PP. Statin non-adherence and residual cardiovascular risk: there is need for substantial improvement. *Int J Cardiol*. 2016;225:184–196.
12. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J*. 2016;37:908–916.
13. Guyton JR, Bays HE, Grundy SM, Jacobson TA. The National Lipid Association Statin Intolerance Panel. An assessment by the statin intolerance panel: 2014 update. *J Clin Lipidol*. 2014;8(3 suppl):S72–S81.
14. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci: AMS*. 2015;11:1–23.
15. Mancini GB, Baker S, Bergeron J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian consensus working group update (2016). *Can J Cardiol*. 2016;32:S35–S65.
16. Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. *J Clin Lipidol*. 2016;10:739–747.
17. Wilson PWF, Polonsky TS, Miedema MD, Khera A, Kosinski AS, Kuvvin JT. Systematic review for the 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. *J Am Coll Cardiol*. 2019;73:3210–3227.
18. Ray KK, Reeskamp LF, Laufs U, et al. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. *Eur Heart J*. 2022;43:830–833.
19. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. *Am Heart J*. 2013;166:597–603.
20. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med*. 2013;158:526–534.
21. 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. *J Clin Lipidol*. 2015;9:758–769.
22. Jacobson TA, Cheeley MK, Jones PH, et al. The statin adverse treatment experience survey: experience of patients reporting side effects of statin therapy. *J Clin Lipidol*. 2019;13:415–424.
23. 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. *J Clin Lipidol*. 2012;6:208–215.
24. Jacobson TA, Khan A, Maki KC, Brinton EA, Cohen JD. Provider recommendations for patient-reported muscle symptoms on statin therapy: insights from the understanding statin use in America and gaps in patient education survey. *J Clin Lipidol*. 2018;12:78–88.
25. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. *Circulation*. 2013;127:96–103.
26. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19:403–414.
27. Bytççi I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis. *Eur Heart J*. 2022.
28. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
29. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107.
30. 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*. 2016;315:1580–1590.
31. Howard JP, Wood FA, Finegold JA, et al. Side effect patterns in a crossover trial of statin, placebo, and no treatment. *J Am Coll Cardiol*. 2021;78:1210–1222.
32. 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.
33. Di Angelantonio E, Gao P, Pennells L, et al. Lipid-related markers and cardiovascular disease prediction. *JAMA*. 2012;307:2499–2506.
34. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60:2631–2639.
35. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol*. 2016;67:2578–2589.
36. 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 (London, England)*. 2010;376:1670–1681.
37. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;316:1289–1297.
38. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet (London, England)*. 2011;377:2181–2192.
39. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
40. Johannesen CDL, Mortensen MB, Langsted A, Nordestgaard BG. Apolipoprotein B and Non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients. *J Am Coll Cardiol*. 2021;77:1439–1450.
41. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol*. 2006;98:1363–1368.
42. Richardson TG, Sanderson E, Palmer TM, et al. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: a multivariable Mendelian randomization analysis. *PLoS Med*. 2020;17:e1003062.
43. Marston NA, Giugliano RP, Melloni GEM, et al. Association of apolipoprotein B-containing lipoproteins and risk of myocardial infarction in individuals with and without atherosclerosis: distinguishing between particle concentration, type, and content. *JAMA Cardiol*. 2022;7:250–256.
44. Davidson MH, Toth PP, Maki KC. *Therapeutic Lipidology*. Therapeutic Lipidology. Switzerland, AG: Springer Nature; 2021. 2nd ed.
45. Alonso R, Cuevas A, Cafferata A. Diagnosis and management of statin intolerance. *J Atheroscler Thromb*. 2019;26:207–215.
46. Awad K, Mikhailidis DP, Toth PP, et al. Efficacy and safety of alternate-day versus daily dosing of statins: a systematic review and meta-analysis. *Cardiovasc Drugs Ther*. 2017;31:419–431.
47. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–1356.
48. Ouchi Y, Sasaki J, Arai H, et al. Ezetimibe lipid-lowering trial on prevention of atherosclerotic cardiovascular disease in 75 or older (EWTOPIA 75): a randomized, controlled trial. *Circulation*. 2019;140:992–1003.
49. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382:1507–1519.
50. Ruscica M, Greco MF, Ferri N, Corsini A. Lipoprotein(a) and PCSK9 inhibition: clinical evidence. *Eur Heart J Suppl*. 2020;22:L53–L56.
51. Henney NC, Banach M, Penson PE. RNA Silencing in the Management of Dyslipidemias. *Curr Atheroscler Rep*. 2021;23:69.

52. Fonseca VA, Handelsman Y, Staels B. Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. *Diabetes Obes Metab*. 2010;12:384–392.
53. The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251:351–364.
54. Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med*. 2019;380:1022–1032.
55. 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. *Eur J Prevent Cardiol*. 2020;27:593–603.
56. Susekov AV, Korol LA, Watts GF. Bempedoic acid in the treatment of patients with dyslipidemias and statin intolerance. *Cardiovasc Drugs Ther*. 2021;35:841–852.
57. Nicholls S, Lincoff AM, Bays HE, et al. Rationale and design of the CLEAR-outcomes trial: evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. *Am Heart J*. 2021;235:104–112.
58. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237–1245.
59. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans affairs high-density lipoprotein cholesterol intervention trial study group. *N Engl J Med*. 1999;341:410–418.
60. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. *Circulation*. 2000;102:21–27.
61. Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ*. 2002;325:1139.
62. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet (London, England)*. 2005;366:1849–1861.
63. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563–1574.
64. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*. 2010;375:1875–1884.
65. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med*. 2010;363:694–695.
66. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis*. 2011;217:492–498.
67. Maki KC, Guyton JR, Orringer CE, Hamilton-Craig I, Alexander DD, Davidson MH. Triglyceride-lowering therapies reduce cardiovascular disease event risk in subjects with hypertriglyceridemia. *J Clin Lipidol*. 2016;10:905–914.
68. Pradhan AD, Paynter NP, Everett BM, et al. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes (PROMINENT) study. *Am Heart J*. 2018;206:80–93.
69. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22.
70. Mason RP, Eckel RH. Mechanistic insights from REDUCE-IT strengthen the case against triglyceride lowering as a strategy for cardiovascular disease risk reduction. *Am J Med*. 2021;134:1085–1090.
71. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. 2001;285:2486–2497.
72. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31:2844–2853.
73. Handhe A, Viljoen A, Wierzbicki AS. Elevated lipoprotein(a): background, current insights and future potential therapies. *Vasc Health Risk Manag*. 2021;17:527–542.
74. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
75. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropirant in high-risk patients. *N Engl J Med*. 2014;371:203–212.
76. Superko HR, Zhao XQ, Hodis HN, Guyton JR. Niacin and heart disease prevention: Engraving its tombstone is a mistake. *J Clin Lipidol*. 2017;11:1309–1317.
77. Glueck CJ, Budhani SB, Masineni SS, et al. Vitamin D deficiency, myositis-myalgia, and reversible statin intolerance. *Curr Med Res Opin*. 2011;27:1683–1690.
78. Ward NC, Watts GF, Eckel RH. Statin toxicity. *Circ Res*. 2019;124:328–350.