

REVIEW TOPIC OF THE WEEK

Optimizing Cholesterol Treatment in Patients With Muscle Complaints



Robert S. Rosenson, MD,^a Steven Baker, MSc, MD,^b Maciej Banach, MD, PhD,^{c,d} Kenneth M. Borow, MD,^e Lynne T. Braun, PhD, CNP,^f Eric Bruckert, MD,^g Liam R. Brunham, MD, PhD,^h Alberico L. Catapano, MD, PhD,ⁱ Marshall B. Elam, PhD, MD,^j G.B. John Mancini, MD,^k Patrick M. Moriarty, MD,^l Pamela B. Morris, MD,^m Paul Muntner, PhD,ⁿ Kausik K. Ray, MD, MPH,^o Erik S. Stroes, MD,^p Beth A. Taylor, PhD,^{q,r} Valerie H. Taylor, MD, PhD,^s Gerald F. Watts, DSc, MD, PhD,^t Paul D. Thompson, MD^r

ABSTRACT

Statins are highly effective for preventing cardiovascular events by reducing low-density lipoprotein cholesterol (LDL-C). However, many patients taking statins report muscle-related symptoms that prevent the use of guideline recommended doses. Patients with reported intolerance to statins have a high risk of cardiovascular events. Clinical strategies that optimize cardiovascular risk reduction through LDL-C lowering need to be applied in patients experiencing intolerable side effects that they attribute to statins. In this paper, the authors review definitions of statin intolerance, propose algorithms to better define statin intolerance, and describe approaches to optimize cardiovascular risk reduction among individuals reporting statin-associated muscle symptoms. (J Am Coll Cardiol 2017;70:1290-301)

© 2017 by the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

From the ^aDepartment of Medicine, Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, New York; ^bDepartment of Medicine, Neuromuscular Disease Clinic, McMaster University, Hamilton, Ontario, Canada; ^cDepartment of Hypertension, Medical University of Lodz, Lodz, Poland; ^dCardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland; ^eNational Medication Safety, Outcomes and Adherence Program, MediMergent, Rockville, Maryland; ^fDepartment of Adult Health and Gerontologic Nursing, College of Nursing, Rush University Medical Center, Chicago, Illinois; ^gInstitute of Cardiomatometabolism and Nutrition (ICAN), Endocrinology Department, Hopital Pitié Salpêtrière, Paris, France; ^hDepartment of Medicine, University of Vancouver, British Columbia, Canada; ⁱDepartment of Pharmacological and Biomolecular Sciences, University of Milan, IRCCS Multimedica, Milan, Italy; ^jDepartments of Pharmacology and Medicine, University of Tennessee Health Sciences Center, Memphis, Tennessee; ^kDepartment of Medicine, Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada; ^lDivision of Clinical Pharmacology, Division of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas; ^mDepartment of Medicine, Division of Cardiology, Medical University of South Carolina, Charleston, South Carolina; ⁿDepartment of Epidemiology, University of Alabama Birmingham, Birmingham, Alabama; ^oImperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, London, United Kingdom; ^pDepartment of Vascular Medicine, AMC, Amsterdam, the Netherlands; ^qDepartment of Kinesiology, University of Connecticut, Storrs, Connecticut; ^rDivision of Cardiology, Hartford Hospital, Hartford, Connecticut; ^sDepartment of Psychiatry, University of Toronto, Women's College Hospital, Toronto, Ontario, Canada; and the ^tCardiomatometabolic Service, Department of Cardiology, Royal Perth Hospital, School of Medicine, University of Western Australia, Perth, Western Australia. Dr. Rosenson has served on advisory boards for Amgen, CVS Caremark, Easy Vitals, Eli Lilly, Regeneron, and Sanofi; has received research grants to his institution from Akcea, Amgen, AstraZeneca, Esperion, Medicines Company, and Regeneron; had received honoraria from Akcea and Kowa; and has received royalties from UpToDate. Dr. Banach has served on advisory boards for Abbott Vascular, Amgen, Daichii-Sankyo, Esperion, Eli Lilly, Merck Sharp & Dohme, Resverlogix, and Sanofi; has served on speakers bureaus for Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi, and Valeant; and has received grants from Valeant and Sanofi. Dr. Borow is a consultant for Amarin and MediMergent; has received honoraria from Amarin; and is a stock shareholder in Amarin, Amgen, MediMergent, Merck, Pfizer, Regeneron, and Synergy. Dr. Braun receives royalties from UpToDate. Dr. Bruckert has served on advisory boards for AstraZeneca, AMGEN, Genfit, MSD, Sanofi and Regeneron, Unilever, Institut Benjamin Delessert, Danone, Aegerion, Chiesi, Rottapharm-MEDA, Eli Lilly, and Ionis Pharmaceuticals. Dr. Brunham has served on an advisory board for Sanofi; and has received research grants from Sanofi and Amgen. Dr. Catapano has received grants from Amgen, Merck Sharp & Dohme, Pfizer, Regeneron, and Sanofi; has been a consultant for Akcea, Amgen, AstraZeneca, Esperion, Ionis, Kowa, Meda, Merck Sharp & Dohme, Pfizer, Regeneron, Sanofi, and Takeda; has served on speakers bureaus for Amgen, AstraZeneca, Kowa, Menarini, Meda, Mylan, Regeneron, and Sanofi; and has relationships with SigmaTau, Eli Lilly, Recordati, Mediolanum, Merck, Aegerion, Genzyme, and



Listen to this manuscript's
audio summary by
JACC Editor-in-Chief
Dr. Valentin Fuster.



Treatment with moderate- and high-intensity statins reduces the risk of atherosclerotic cardiovascular disease (ASCVD) in the setting of high-risk primary and secondary prevention (1,2). For every 1 mmol/l reduction in low-density lipoprotein-cholesterol (LDL-C), ASCVD events are reduced by 21% after 1 year of treatment with moderate- or high-intensity statins (3). The reduction in ASCVD increases with long-term statin use (4).

Randomized clinical trials (RCTs) indicate that statins have a side-effect profile almost indistinguishable from placebo or comparator drugs, particularly when used in low dosages (5,6). However, “real world” data obtained from surveys, registries, and insurance claims suggest that side effects of statins are common, especially at higher doses (7,8). Many patients are unwilling to continue with guideline-recommended statin doses after experiencing side effects (9).

This review presents recommendations from a forum of researchers and clinicians convened to discuss strategies for managing statin intolerance and optimizing LDL-C reduction in patients with muscle complaints. Most statin-associated adverse events are not life-threatening, may or may not be asymptomatic, may or may not cause reductions in medication compliance, and may not reoccur upon rechallenge, even with the same statin (10,11). Therefore, a standardized strategy designed to optimize the continued use of statins in patients who perceive that their muscle symptoms are statin induced may substantially reduce ASCVD events.

CLINICAL CONSEQUENCES AND ECONOMIC COSTS OF NONADHERENCE TO STATINS

Discontinuation or down-titration of statin therapy is associated with an increased risk of future ASCVD events (12,13), resulting in higher health care costs (13). Using the algorithm developed in Medicare beneficiaries (14), patients with statin intolerance versus high statin adherence experienced a higher risk for recurrent myocardial infarction (hazard ratio [HR]: 1.50; 95% confidence interval [CI]: 1.30 to 1.73) and coronary heart disease events (HR: 1.51; 95% CI: 1.34 to 1.70), but no difference in mortality (HR: 0.96; 95% CI: 0.87 to 1.06). An analysis that used an algorithm developed in the Henry Ford Health System (15) reported that patients with statin intolerance had higher health care costs (13).

DEFINITIONS OF STATIN INTOLERANCE

Addressing statin intolerance requires a rigorous approach to verify the problem and concerns about quality of life, while optimizing ASCVD risk reduction (16–19). There is no universally accepted definition of statin intolerance (Table 1) but published definitions generally agree on the diagnostic criteria (Table 2) (16–19).

All definitions of statin intolerance require dechallenge and rechallenge phases to assess potential causal associations and multiple statin challenges

ABBREVIATIONS AND ACRONYMS

AHA	= American Heart Association
ACC	= American College of Cardiology
ASCVD	= atherosclerotic cardiovascular disease
CI	= confidence interval
CK	= creatinine kinase
HR	= hazard ratio
LDL-C	= low-density lipoprotein-cholesterol
RCT	= randomized clinical trial
SAMS	= statin-associated muscle symptoms
SAMS-CI	= Statin-Associated Muscle Symptoms Clinical Index

Bayer. Dr. Elam has received research grants to his institution from Amgen, Kowa, and Pfizer. Dr. Mancini has served on advisory boards for Amgen, Sanofi, Boehringer Ingelheim, and Esperion; has received research grants to institution from Amgen and Merck; and has received honoraria from Amgen and Sanofi. Dr. Moriarty has served on advisory boards for Aegerion, Eli Lilly, Eliaz Therapeutics, Duke CRI, Esperion, Genzyme, and Ionis; has received research grants to his institution from Amgen, Arisaph, Catabasis, Ionis, Pfizer, Novartis, Regeneron, Sanofi, and Stage 2 Innovations; and has served on speakers bureaus for Amgen, Kowa, and Regeneron. Dr. Morris has served on advisory boards for Amgen, Sanofi Regeneron, and AstraZeneca; and has received research grants to her institution from Amgen. Dr. Muntner has received grants from Amgen. Dr. Ray has received grants from Pfizer, Amgen, Regeneron, Sanofi, and Merck Sharp and Dohme; has been a consultant for Akcea, Amgen, Regeneron, Sanofi, Pfizer, AstraZeneca, Boehringer Ingelheim, Takeda, Novo Nordisk, Merck Sharp and Dohme, Cerenis, Medicine Company, Kowa, Esperion; and has served on speakers bureaus for Amgen, Sanofi, Regeneron, Takeda, Boehringer Ingelheim, AstraZeneca, Cipla Alorithm, and Kowa. Dr. Stroes has served on advisory boards and speakers bureaus for Amgen, Sanofi, AstraZeneca, and Chiesi. Dr. B.A. Taylor has received research grants to her institution from Regeneron; and has served on an advisory board for Amgen. Dr. V.H. Taylor has received an investigator-initiated grant from Bristol-Myers Squibb; has served on advisory boards for Shire and NovoNordisk; and has received honoraria from Sunovion, Lundbeck, and Shire. Dr. Watts has served on advisory boards for Amgen, Regeneron, Sanofi, and Gemphire; and has received research grants to his institution from Amgen, Regeneron, and Sanofi; and has received honoraria from Amgen, Regeneron, Sanofi, Kowa, and Gemphire. Dr. Thompson has served on advisory boards for Regeneron, Sanofi, and Esperion; has received research support from Sanofi, Regeneron, Esperion, and Amarin; has received honoraria from Amarin, Regeneron, Sanofi, and Amgen; is a stock shareholder in Abbvie, Abbott Laboratories, Johnson & Johnson, General Electric, Serapta, and Medtronic; and has served as a malpractice consultant for statin myopathy and for cardiac complications of exercise. Dr. Baker has reported that he has no relationships relevant to the contents of this paper to disclose. P.K. Shah, MD, served as Guest Editor-in-Chief for this paper. Christie Mitchell Ballantyne, MD, served as Guest Editor for this paper.

TABLE 1 Terms Used to Describe Muscle Effects of Statins

Statin-Associated Adverse Effects: a general term, not limited to any organ system or process that may be symptomatic or asymptomatic
Statin Intolerance: a syndrome that has been verified, confirmed and documented that leads to suboptimal statin dosing, reductions in statin compliance, reductions in patient quality of life and function, statin cessation, and/or suboptimal LDL-C lowering.
Statin-Associated Muscle Effects: statin intolerance pertaining to muscle, not necessarily symptomatic
Statin-Associated Muscle Symptoms: statin intolerance causing muscle symptoms

This table describes the categories and subcategories of statin-associated muscle complaints, which fall into statin-associated adverse events (nonspecific to any organ system, and which may or may not influence statin compliance), statin intolerance (nonspecific to any organ system, has causality with statins and influences statin-related outcomes), statin-associated muscle effects (specific to muscle, influence statin-related outcomes, but may or may not be symptomatic), and statin-associated muscle symptoms (specific to muscle, influence statin-related outcomes, and are symptomatic).

LDL-C = low-density lipoprotein cholesterol.

to support the diagnosis. Additionally, drug-drug interactions and comorbidities may limit statin use and should be evaluated before establishing a diagnosis of statin intolerance.

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guideline does not define statin intolerance, but acknowledges the need for adjunctive or alternative

treatments when there is a “less-than anticipated response” or for patients “who are completely statin intolerant” (1). The inability to tolerate some statins, or some doses, should not be considered statin intolerance, provided it does not prevent achieving treatment thresholds based on the percentage reduction in LDL-C (20). The term “partial intolerance” has been used when the patient can only tolerate less than guideline-recommended statin dose (19).

INCIDENCE OF MUSCLE SYMPTOMS IN RANDOMIZED

TRIALS. The major limitation in the diagnosis and treatment of statin-associated muscle symptoms (SAMS) is the lack of criteria that distinguishes true SAMS from non-statin-related muscle pain (16). A substantial portion of SAMS probably represents nonspecific musculoskeletal pain unrelated to statin use. After pooling data for 56,000 patients from 42 large randomized trials, there were no differences in reported muscle symptoms with statins compared with placebo, with 13% of participants in each group having reported muscle symptoms (21). Similarly, 22% of participants taking statins in the U.S. National Health and Nutrition Examination Survey reported muscle pain compared with 16.7% of non-statin users (22). The STOMP (Effect of Statin on Skeletal Muscle Performance) study used a rigorous dechallenge/rechallenge study protocol designed to validate that self-reported muscle pain attributed to statins was due to this treatment (23). Among 468 participants, muscle symptoms were reported by 9.4% of participants treated with atorvastatin 80 mg versus 4.6% of participants treated with placebo ($p = 0.05$). In the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm), 2.03% of participants randomized to atorvastatin 10 mg daily experienced muscle-related adverse events compared with 2.00% of participants treated with placebo ($p = 0.72$) (6). During the nonblinded, nonrandomized phase, adverse muscle events were reported at a higher rate by participants receiving statins than those who were not (1.26% per year vs. 1.00% per year; HR: 1.41 [1.10 to 1.79]; $p = 0.006$).

Two randomized clinical trials evaluated the tolerability of statins upon rechallenge in patients with prior SAMS on ≥ 2 statins (10,11). The GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin intolerant Subjects 3) trial recruited participants, of whom >80% had experienced intolerable muscle symptoms to at least 3 different statins (11). A placebo/statin double-blind crossover design to document statin myalgia before the participants were enrolled. Over a 12-week period, 42.6% of participants experienced intolerable muscle symptoms only when treated with atorvastatin 20 mg

TABLE 2 Current Consensus Definitions of Statin Intolerance

Guideline, Year (Ref. #)	Definition of Statin Intolerance
NLA, 2014 (16)	<p>Characterized by the inability to tolerate at least 2 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.</p> <p>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</p>
International Lipid Expert Panel, 2015 (18)	<ol style="list-style-type: none"> 1. The inability to tolerate at least 2 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 change 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, 2016 (19)	<p>Goal-inhibiting statin intolerance</p> <ul style="list-style-type: none"> • A clinical syndrome • Characterized by significant symptoms and/or biomarker abnormalities that prevent long-term use of, and adherence to, indicated use of statins • Documented by challenge/de-challenge/rechallenge, when appropriate, using at least 2 statins, including atorvastatin and rosuvastatin • Not due to drug-drug interactions or untreated risk factors for intolerance (e.g. untreated hypothyroidism) • And leading to failure to maintain therapeutic goals as defined by national guidelines

and not when treated with placebo. Conversely, 26.5% experienced muscle symptoms with placebo and not with atorvastatin; 9.8% had symptoms on both placebo and atorvastatin, whereas 17.3% had no symptoms with either treatment. Odyssey Alternative was a randomized, double-blind, double-dummy, active-controlled, parallel-group study of alirocumab versus ezetimibe in patients with statin intolerance, defined as being unable to tolerate ≥ 2 statins, including one at the lowest approved starting dose, due to muscle symptoms (10). Placebo run-in and statin rechallenge arms were included to confirm the diagnosis of intolerance. Participants ($n = 361$) received single-blind subcutaneous and oral placebo for 4 weeks during the placebo run-in phase. During the placebo run-in phase, 13% of participants reported symptoms of whom 8.9% with at least 1 skeletal muscle-related adverse event. The remaining participants were randomized (2:2:1) to double-blind alirocumab 75 mg subcutaneous every 2 weeks plus oral placebo or to ezetimibe 10 mg daily or atorvastatin 20 mg daily plus injected placebo for 24 weeks. Study treatment discontinuation due to skeletal muscle-related adverse events was not different for alirocumab (29.0%) vs. atorvastatin (60.2%) (HR: 0.67; 95% CI: 0.34 to 1.32; $p = 0.24$) or ezetimibe (40.2%) (HR: 0.78; 95% CI: 0.43 to 1.41; $p = 0.41$).

These trials suggest that it is difficult to objectively establish that SAMS exists in all patients who report musculoskeletal symptoms during the course of statin therapy. In Odyssey Alternative, after a blinded placebo run-in designed to exclude patients with muscle complaints while on placebo, different rates of SAMS were found in the occurrence of the first onset of muscle symptoms when comparing treatment with atorvastatin and alirocumab (10). The difference in the incidence of muscle complaints in the treatment groups supports SAMS as a real entity.

EVALUATION OF SAMS

STATIN DISCONTINUATION WITH SYMPTOM IMPROVEMENT. Statin discontinuation and rechallenge is the primary strategy for confirming the presence of statin intolerance in practice and clinical trials (16–19). Reports of statin adverse events in the news and on the Internet have resulted in expectations of harm, or the “nocebo” effect (24) that complicate efforts to reintroduce the same or alternative statin. Placebo-controlled assessments of patient responses have been proposed to diagnose true statin intolerance in individual patients, but are not practical in routine practice (25).

Characteristics of muscle symptoms, temporal onset and resolution of symptoms are important in evaluating myalgia. Features that make the diagnosis of statin intolerance less likely include: 1) symptoms that occur immediately after statin initiation or disappear within minutes to hours upon cessation (19,23); 2) symptoms that do not improve or disappear within 12 weeks after statin discontinuation (23); 3) symptom onset that is present after protracted use (>12 weeks) without changes in any other apparent patient status (19); and 4) symptoms that occur with other classes of lipid-lowering agents or with other classes of pharmacotherapies (19).

CLINICAL TOOLS

Questionnaires have been designed to facilitate the clinical diagnosis of SAMS. However, these questionnaires require additional validation. The National Lipid Association Statin Muscle Safety Task Force proposed a Statin Myalgia Clinical Index that classifies the likelihood of true SAMS into probable, possible, or unlikely categories (16). This scoring index and its recent modification (SAMS Clinical Index [SAMS-CI]) (26) was based on the type, location, and pattern of muscle symptoms and the response to drug discontinuation and rechallenge (Figure 1). The Canadian Cardiology Working Group proposed modifications to the Statin Myalgia Clinical Index, including whether muscle symptoms appear with other nonstatin cholesterol-lowering drugs and resolve within a day of drug cessation (19). A validation study conducted using data obtained in a randomized double-blind crossover trial with coenzyme Q10 in SAMS patients (27). A SAMS-CI score ≤ 4 had a negative predictive value of 91% in identifying patients who were unlikely to have “true” myalgia (28).

Noninvasive assessments of muscle function have not proven useful in distinguishing between myalgia related to statin therapy and nonspecific muscle symptoms (Table 3) (16). New technology, particularly metabolic imaging, may prove useful in the assessment of muscle mitochondrial function (29). Genetic variants have been identified that are associated with SAMS, most notably the *rs4149056* variant in *SLCO1B1* (30–32), but none of these techniques have sufficient sensitivity or specificity to aid in the diagnosis of SAMS. Rarely, individuals with large increases in creatinine kinase (CK) may have autoimmune myopathy characterized by muscle weakness, muscle necrosis and markedly elevated CK levels (33). Detection of HMG-CoA reductase autoantibodies may lead to the development of better clinical tools in this area.

FIGURE 1 Statin-Associated Muscle Symptoms Clinical Index

Statin-Associated Muscle Symptom Clinical Index (SAMS)

Instructions:

- Use with patients who have had muscle symptoms that were **new or increased** after starting a statin regimen.
- A **statin regimen** includes any statin at any dose or frequency, including a statin the patient has used previously, at the same or a different dose.
- Muscle symptoms** may include aches, cramps, heaviness, discomfort, weakness, or stiffness.
- Interpret overall score in light of **other possible causes** of the muscle symptoms, such as:
 - Recent physical exertion Hypothyroidism Concurrent illness
 - Changes in exercise patterns Drug interaction with statin Underlying muscle disease
- See [reverse](#) for Frequently Asked Questions

How many statin regimens has the patient had that involved new or increased muscle symptoms?

One
Complete the question on the left side of this page.

Two or more
Complete the questions on the right side of this page.

Regarding this statin regimen:

A. Location and pattern of muscle symptoms
(If more than one category applies, record the highest number.) **Enter score:**

Symmetric, hip flexors or thighs	3	<div style="border: 1px solid #007bff; width: 30px; height: 30px; margin: 0 auto;"></div>
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent, or not specific to any area	1	

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3	<div style="border: 1px solid #007bff; width: 30px; height: 30px; margin: 0 auto;"></div>
4-12 weeks	2	
>12 weeks	1	

C. Timing of muscle symptom improvement after withdrawal of statin
(If patient is still taking statin, stop regimen and monitor symptoms.)

<2 weeks	2	<div style="border: 1px solid #007bff; width: 30px; height: 30px; margin: 0 auto;"></div>
2-4 weeks	1	
No improvement after 4 weeks	0	

Rechallenge the patient with a statin regimen, (even if same statin compound or regimen as above) then complete final question:

D. Timing of recurrence of similar muscle symptoms in relation to starting second regimen

<4 weeks	3	<div style="border: 1px solid #007bff; width: 30px; height: 30px; margin: 0 auto;"></div>
4-12 weeks	1	
>12 weeks or similar symptoms did not reoccur	0	

Total:
All four scores above must be entered before totaling

Regarding this statin regimen *before* the most recent regimen:

A. Location and pattern of muscle symptoms
(If more than one category applies, record the highest number.) **Enter score:**

Symmetric, hip flexors or thighs	3	<div style="border: 1px solid #dc3545; width: 30px; height: 30px; margin: 0 auto;"></div>
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent, or not specific to any area	1	

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3	<div style="border: 1px solid #dc3545; width: 30px; height: 30px; margin: 0 auto;"></div>
4-12 weeks	2	
>12 weeks	1	

C. Timing of muscle symptom improvement after withdrawal of statin

<2 weeks	2	<div style="border: 1px solid #dc3545; width: 30px; height: 30px; margin: 0 auto;"></div>
2-4 weeks	1	
No improvement after 4 weeks	0	

Regarding the *most recent* statin regimen: (even if same statin compound as above)

D. Timing of recurrence of similar muscle symptoms in relation to starting regimen

<4 weeks	3	<div style="border: 1px solid #dc3545; width: 30px; height: 30px; margin: 0 auto;"></div>
4-12 weeks	1	
>12 weeks or similar symptoms did not reoccur	0	

Total:
All four scores above must be entered before totaling

	Total score:	2-6	7-8	9-11
Interpretation	Likelihood that the patient's muscle symptoms are due to statin use:	Unlikely	Possible	Probable

This index evaluates muscle symptoms using several domains that encompass the statin regimen (location and pattern of muscle symptoms, timing of muscle symptom onset in relation to starting statin regimen, timing of muscle symptom improvement after withdrawal of statin); timing of recurrence after rechallenge with the statin regimen; and previous symptoms on statin regimen prior to the current exposure. A score is selected on the basis of the patterns in the different domains. A total score is used to assess the likelihood of the patient's muscle symptoms from statin use. A score ≤ 4 is "unlikely, 5 to 8 is "possible," and 9 to 11 is "probable." Adapted with permission from Rosenson *et al.* (26).

TABLE 3 Noninvasive Tests That May Be Used to Assess SAMS

	Rationale	Strengths	Weaknesses
Serial measurements of resting CK	Small elevations in CK may occur with statin therapy	Inexpensive; CK is a noninvasive marker of muscle damage; easily accessible biomarker for clinicians	CK elevations can occur in the absence of SAMS; CK varies according to age, gender, ethnicity, recent exercise and medication use; resting CK data typically not reported in clinical trials to validate methodology
Post-exercise elevations in CK	Exercise-associated elevations in CK may be greater in asymptomatic patients on statins than those not on statins	Exercise-associated elevations in CK may be more sensitive than resting CK	Not validated in patients with SAMS; exercise model is less practical for clinical utilization
Muscle strength testing (isometric or isokinetic arm or leg)	Established technique for detecting muscle weakness, a common complaint in SAMS	May quantify muscle symptoms; observational reports in patients with self-reported SAMS or older asymptomatic adults on statins established decrements in muscle strength of 10% to 40%	Muscle strength equipment is expensive and not readily accessible to clinicians; application of standardized muscle strength testing in clinical practice has not confirmed decrements in patients with SAMS
Aerobic testing with inspired/expired gases (maximal oxygen uptake, lactate threshold, respiratory exchange ratio)	Established technique for detecting aerobic capacity changes associated with energy utilization and mitochondrial dysfunction, a potential mechanism underlying SAMS	Potential noninvasive assessment of aerobic capacity and glycolytic/oxidative substrate metabolism, may quantify symptoms associated with fatigue	Testing aerobic parameters requires substantial equipment, cost and personnel; equivocal findings to date in statin studies
³¹ P magnetic resonance spectroscopy for phosphocreatine recovery kinetics following exercise	Slower time course of recovery indicates impaired mitochondrial oxidative function, a potential mechanism underlying SAMS	Potential noninvasive assessment of mitochondrial function; small study showed decrements in statin-treated patients	Technique needs to be replicated in a larger clinical trial; high equipment cost and technical expertise necessary to conduct MR imaging
Kinetics of pulmonary oxygen uptake from rest to exercise	Can effectively distinguish between patients with and without mitochondrial myopathies	Potential noninvasive assessment of mitochondrial function	Methodology has not been tested in patients with SAMS; costly, difficult and time-consuming to use clinically

CK = creatine kinase; MR = magnetic resonance; SAMS = statin-associated muscle symptoms.

MANAGING SAMS

RECHALLENGE AND SWITCHING STATINS. The initial step in evaluating SAMS is discontinuation and rechallenge with the same or other statin (Figure 1). After evaluating the response to statin discontinuation and reinitiation, changing statin type and dose reduction are the next steps. As established by both RCTs and clinical practice, it is recommended that before rechallenge, a washout period may be useful to allow symptom resolution, which varies among individuals (16–18). However, whereas switching statins and dose reduction are commonplace, rechallenge with the same statin at the same dose is unusual except perhaps among specialists (34,35). Even when providers are comfortable with recommending this approach (36), patients may be unwilling to retry a statin that they perceive has induced intolerable side effects (37). Consequently, lower doses or less intense regimens are often prescribed when treating these patients.

MINIMAL NUMBER OF STATINS TESTED FOR DEFINING SAMS.

The pharmacokinetic profile and plasma concentrations differ among statins and among patients treated with the same statin (38,39). Thus, patients may tolerate an alternative statin with different pharmacokinetic characteristics (Table 4). Twelve of 19 clinical studies of SAMS (40) documented the number of statins tried. SAMS was defined as intolerable muscle symptoms to 2 statins (10,41–44), ≥ 2 statins (11) or 1 statin (45). Consequently, ≥ 2 statins should be tried before diagnosing statin intolerance (10,11,16–19).

We support prescribing an alternative statin as recommended by several consensus documents (16–19). This approach is supported by the distinct pharmacokinetics and drug disposition properties of different statins; for instance, pravastatin is not metabolized by cytochrome enzymes, and pitavastatin is marginally metabolized by the cytochrome enzymes (CYP8/9). Thus, these agents have low rates of drug-drug interactions (38,39).

TABLE 4 Clinical Pharmacokinetics of HMG-CoA Reductase Inhibitors

	Atorvastatin	Fluvastatin	Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Fraction absorbed, %	30	50	98	98	80	30	34	60-80
Bioavailability, %	12	19-29			>60	18	20	5
Lipophilicity	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Protein binding, %	80-90	>99	>99	>95	99	55	88	94-98
Metabolism	Hydroxylation oxidation, CYP3A4	CYP2C9 (CYP2C8-3A4) (minor)	CYP2C9 (CYP2C8-3A4) (minor)	CYP3A4	Glucuronidation (UGT1A3-2B7) CYP2C8/9 (minor)	Sulfation, hydroxylation, oxidation	Biliary Excretion (CYP2C9-2C19) (minor)	CYP3A4
Metabolites	Active	Inactive	Inactive	Active	Inactive	Inactive	Active (minor)	Active
OAT1B1 transporter substrate	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
T _{1/2} , h	15-30	0.5-2.3	4.7	2.9	12	1.3-2.8	19	2-3
Urinary excretion, %	2		6	10	15	20	10	13
Fecal excretion, %	70	90	90	83	79	71	90	58

LOWER THAN INDICATED INTENSITY OF STATIN THERAPY. Incorporating specific doses into a universal definition of statin intolerance is problematic. Few clinical trials have used explicit definitions of statin doses to define intolerance (46). This relates to the high number of available statins, individual variability in the LDL-C response to a given statin regimen, and variation in tolerance to type and dose of different statins (“partial statin intolerance”) (19,47,48). Some studies require that the definition of statin intolerance include at least one of the two drugs be tried at the lowest approved daily dose (10,11,41).

Intermittent dosing with the longer acting statins including rosuvastatin and atorvastatin may be required for some patients who experience SAMS on daily statin dosing, which is consistent with the GAUSS-3 trial design (11). When implementing intermittent dosing, the Canadian Cardiology Working Group recommended atorvastatin and rosuvastatin (19), both of which have half-lives long enough for intermittent dosing (47,48). A meta-analysis of 13 RCTs with 1,023 patients comparing alternate-day dosing versus daily dosing of statins also demonstrated that intermittent dosing, especially of atorvastatin and rosuvastatin, is as efficacious as daily dosing in reducing LDL-C (49). However, the efficacy of intermittent statin dosing on ASCVD outcomes has not been established.

LIFESTYLE. Lifestyle should be considered first-line therapy for lowering LDL-C and reducing cardiovascular disease risk. Several nonpharmacological approaches are effective in lowering LDL-C and cardiovascular disease risk, including consumption of a heart healthy diet, maintaining a normal weight, avoidance of tobacco products, and regular exercise. The use of these therapeutic lifestyle changes are particularly important for patients with SAMS who cannot tolerate statin therapy. Beyond statin

rechallenge, working with patients to help them achieve a healthy lifestyle is an essential component of treating those with SAMS.

ROLE OF NONSTATIN PHARMACOTHERAPIES. Among patients unable to tolerate statin therapy or able to tolerate only low doses or intermittent dosing, consideration should be given to adding non-statin agents to prevent ASCVD events (20). The 2016 ACC Expert Consensus document recommended ezetimibe before a PCSK9 inhibitor to lower LDL-C in those with less than a 50% reduction in LDL-C on maximal tolerated statin therapy, and consideration of ezetimibe before a PCSK9 inhibitor to lower LDL-C in those with LDL-C ≥ 70 mg/dl.

Bile acid sequestrants are not absorbed and these agents would not be expected to have adverse muscle complaints even though some patients report SAMS with bile acid sequestrants (50). Studies in patients with statin intolerance have shown that the majority of patients are able to tolerate ezetimibe (50-55). The IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) evaluated the effect of ezetimibe combined with simvastatin compared with simvastatin alone in stable patients following acute coronary syndrome (55). There were no statistically significant differences in the incidence of myopathy, rhabdomyolysis, or myalgia with CK elevations ≥ 5 times upper limit of normal with ezetimibe-simvastatin combination therapy compared with simvastatin monotherapy. The incidence of myalgia without CK elevations was not reported. The GAUSS-3 trial compared the PCSK9 inhibitor, evolocumab, and ezetimibe in patients with statin intolerance (11). There was a greater incidence of myalgias in patients randomized to ezetimibe (28.8% vs. 20.7%). Nevertheless, most evidence indicates that ezetimibe does not increase muscle-related symptoms either as monotherapy or in combination with moderate-intensity statin therapy (10,11,55).

TABLE 5 Effects of Nutraceuticals on LDL-C in Patients With SAMS

Study Population	Sample Size	Study Design	Nutraceutical	LDL-C Reduction	Discontinuation due to SAMS	Ref. #
SAMS patients treated with ezetimibe 10 mg	57	Retrospective	Red yeast rice (monacolin) 3 mg daily and berberine 500 mg twice daily	19%	2%	(66)
SAMS patients treated with ezetimibe 10 mg	53	Retrospective	Berberine 500 mg twice daily	17%	0%	(66)
SAMS patients treated with ezetimibe 10 mg	32	Retrospective	Phytosterols 900 mg and psyllium fiber	10%	0%	(66)
SAMS	62	Case-control	Red yeast rice 1.8 g twice daily	21.3%	7%	(67)
SAMS	43	Randomized, controlled trial vs. pravastatin 20 mg twice daily	Red yeast rice 2.4 g twice daily	30.2	5% vs. 9% with pravastatin	(68)

LDL-C = low-density lipoprotein cholesterol; SAMS = statin-associated muscle symptoms.

Fenofibrate lowers LDL-C by 20% in patients with hypercholesterolemia (56), but this agent has failed to reduce ASCVD events in multiple RCTs (57) including 1 trial in statin-treated patients (58). Niacin did reduce ASCVD events in hypercholesterolemia patients with myocardial infarction in the Coronary Drug Project (59), so it is occasionally prescribed for selected patients with refractory hypercholesterolemia, particularly due to lipoprotein (a) excess (60). However, in statin-treated patients with an average LDL-C of 64 mg/dl (61) and 73 mg/dl (62), niacin did not reduce ASCVD events.

The role of monoclonal antibody PCSK9 inhibitors in patients with SAMS has been evaluated in several recent studies (10,11,41). The GAUSS-2 study enrolled 307 patients who had experienced intolerable statin-attributed muscle symptoms to at least 2 statins (41). None of the participants discontinued evolocumab due to muscle-related adverse events. The GAUSS-2 study confirmed that evolocumab reduced LDL-C by 53% to 56% with few muscle complaints, but the study duration was only 12 weeks. In the GAUSS-3 trial, active therapy was discontinued for SAMS in 6.8% in ezetimibe-treated patients and 0.7% in evolocumab-treated patients. In Odyssey Alternative, SAMS occurred less frequently with alirocumab (32.5%) versus atorvastatin (46.0%) (HR: 0.61; 95% CI: 0.38 to 0.99; $p = 0.042$), but the difference in SAMS between alirocumab versus ezetimibe (41.1%) was not statistically significant (HR: 0.71; 95% CI: 0.47 to 1.06; $p = 0.096$) (10). Study treatment discontinuation due to SAMS was nonsignificantly different for alirocumab (15.9%) versus atorvastatin (22.2%) (HR: 0.67; 95% CI: 0.34 to 1.32; $p = 0.24$) or ezetimibe (20.2%) (HR: 0.78; 95% CI: 0.43 to 1.41; $p = 0.41$).

The investigational agent bempedoic acid is an inhibitor of citrate lyase, an enzyme in the mevalonate pathway that converts citrate to acetyl-Co A (63).

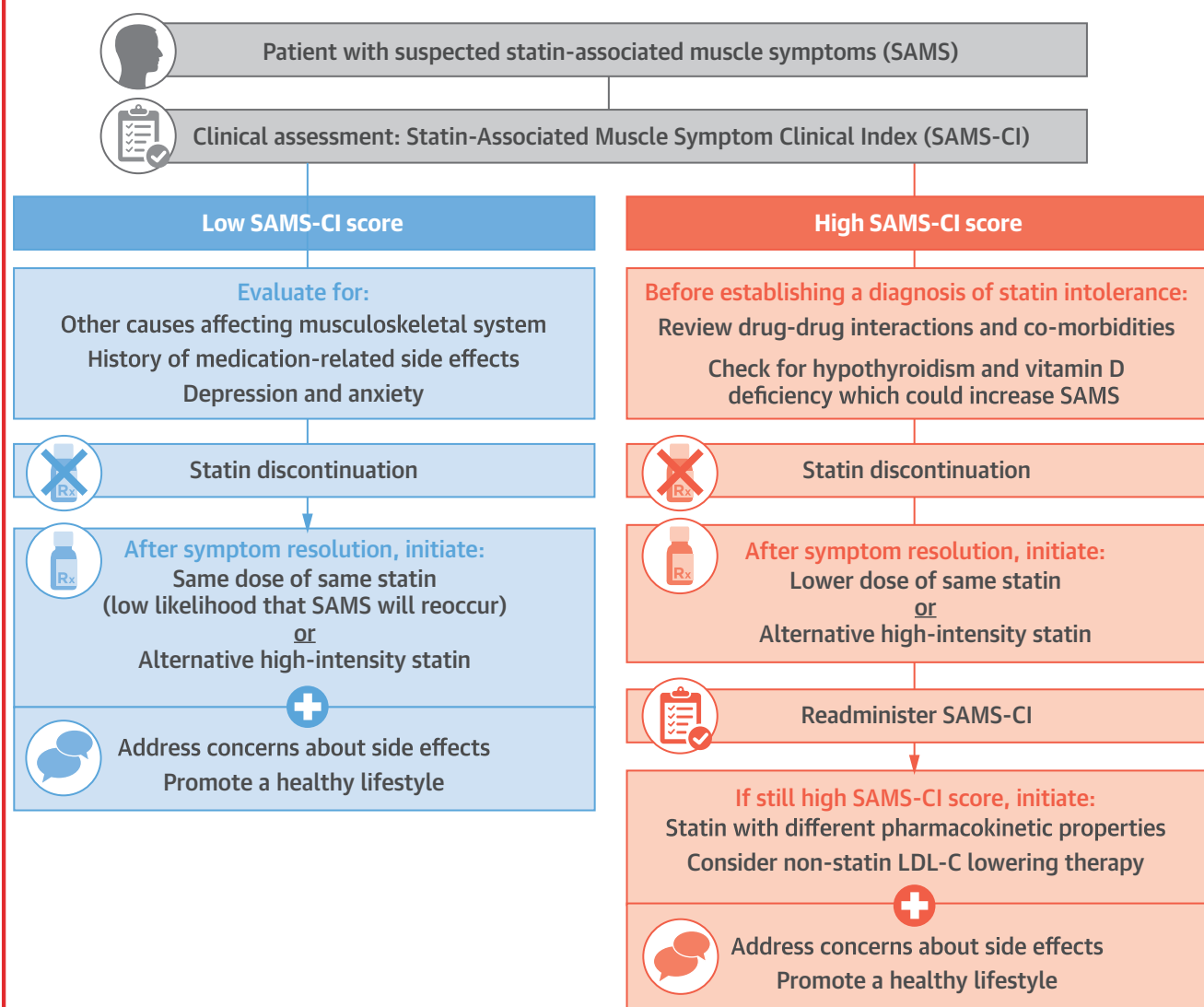
It is administered as an inactive prodrug that is activated by a very long chain acyl CoA synthetase-1 (ACSVL1). ACSVL1 appears to be expressed only in liver and kidney microsomes, and has been studied in individuals with a history of statin intolerance (64,65). Among 56 patients randomized 2:1 to bempedoic acid 240 mg or placebo, LDL-C was reduced by a mean 29% (65). Muscle-related adverse events were comparable between placebo and bempedoic acid.

NUTRACEUTICALS

Nutraceuticals can lower LDL-C in patients with SAMS (Table 5) (66–68). These agents may appeal to individuals with aversion to statins and other drugs. Nutraceuticals have also been proposed for treating SAMS (69). Coenzyme Q10 synthesis is impaired by statins, suggesting that CoQ10 supplementation could counteract SAMS, but a beneficial effect on SAMS has not been demonstrated in a randomized, double-blind, crossover trial (28). Vitamin D (25-hydroxycholecalciferol) deficiency can produce myopathy and could increase SAMS, but no RCTs have demonstrated a beneficial effect in reducing SAMS through vitamin D supplementation (44,70,71). Curcuminoids, polyphenolics found in turmeric, have anti-inflammatory and antioxidant properties, and can improve pain in patients with diverse musculoskeletal conditions (72). They can also reduce plasma lipids and improve mitochondrial function and skeletal muscle fiber regeneration, but have also not yet been demonstrated to reduce SAMS.

Additional trials are needed to evaluate nutraceutical therapies, using a rigorous double-blind, crossover design (28). Moreover, as is the case with suboptimal dosing of statins, outcome trials with these interventions are not available. Until rigorously conducted trials with nutraceuticals have

CENTRAL ILLUSTRATION Clinical Approach to Patient With SAMS



Rosenson, R.S. *et al.* J Am Coll Cardiol. 2017;70(10):1290-301.

Evaluation of statin-associated muscle symptoms (SAMS) includes clinical assessment of muscle symptoms and the likelihood that they are statin associated vs non-statin related. A high score warrants evaluation for secondary causes of muscle symptoms. Rechallenge with an alternative statin may include a change to a different high-intensity statin, lower dosage of the same statin, or moderate-intensity statin with different pharmacokinetic properties. In patients who fail a minimum of 2 statins, nonstatin LDL-C-lowering therapy should be considered. LDL-C = low-density lipoprotein cholesterol; SAMS-CI = Statin-Associated Muscle Symptoms Clinical Index.

demonstrated ASCVD reduction, they should be used in SAMS only after other strategies have failed (19,73).

CLINICAL STRATEGIES. A proposed strategy for the assessment of SAMS begins with evaluation by the SAMS-CI (16,26). Patients with low likelihood of SAMS (Central Illustration) should be evaluated for other

diseases affecting the musculoskeletal system, a history of medication-related side effects, and psychological factors affecting statin use given that a recent study showed that weekly to daily occurrence of somatic symptoms of anxiety was associated with a 33% increase in the risk of statin nonadherence (74). Fear of side effects can also play a role, and among patients who have discontinued their statin therapy,

perceived harmful effects from statins or fear of them are the most commonly reported reasons for discontinuing therapy (75). This highlights the need for screening and patient education. For patients with a high SAMS-CI score, reducing the dose of the same statin (**Central Illustration**) may be prudent with a subsequent rechallenge at a higher dosage after the muscle symptoms have resolved or a change to a different statin. In high-risk patients who cannot tolerate a moderate- or high-intensity statin, it may be necessary to use a low-intensity statin or intermittent statin dosing and/or add a second-line agent. A low SAMS-CI score indicates a low likelihood that muscle symptoms will reoccur upon repeat challenge. Thus, we particularly advocate rechallenging with a different high potency statin in patients with a low SAMS-CI score.

CONCLUSIONS

SAMS are the most common cause for statin discontinuation or dose reduction. Most patients with muscle symptoms can continue statin therapy and clinicians should avoid statin discontinuation, which results in increased ASCVD risk, especially in high-risk patients. Clinicians are often hesitant to prescribe an alternative statin because of a perceived

class effect, and patients are often unwilling to take a second or third statin due to concerns about adverse effects. Efforts are needed to develop practical approaches to identify patients who will develop SAMS upon repeat challenge. It is important to communicate to patients that the majority of individuals who were “intolerant” to 2 or more statins in randomized, controlled, crossover trials were able to tolerate statin therapy upon rechallenge. An essential component of addressing patient concerns about medication safety and adverse events is engaging the patient to overcome their concerns.

Statin intolerance leads to higher ASCVD risk. When a patient presents with SAMS, healthcare providers should verify that the patient truly cannot tolerate statin therapy. These efforts involve evaluation of symptoms after drug withdrawal and assessment of symptoms upon reinitiation with an alternative statin or lower doses of the same or a different statin.

ADDRESS FOR CORRESPONDENCE: Dr. Robert S. Rosenson, Icahn School of Medicine at Mount Sinai, Cardiovascular Institute, One Gustave L. Levy Place, Box 1030, New York, New York 10029. E-mail: robert.rosenson@mssm.edu.

REFERENCES

- Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63 Pt B:2889–934.
- Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Atherosclerosis* 2016;253:281–344.
- Baigent C, Keech A, Kearney PM, et al., Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–78.
- McConnachie A, Walker A, Robertson M, et al. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. *Eur Heart J* 2014;35:290–8.
- Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;388:2532–61.
- Gupta A, Thompson D, Whitehouse A, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet* 2017;389:2473–81.
- 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;19:403–14.
- Patel J, Marin SS, Banach M. Expert opinion: the therapeutic challenges faced by statin intolerance. *Exp Opin Pharmacother* 2016;17:1497–507.
- Colantonio LD, Huang L, Monda KL, et al. Adherence to high intensity statins following a myocardial infarction hospitalization among Medicare beneficiaries. *JAMA Cardiol* 2017 Apr 19 [E-pub ahead of print].
- Moriarty PM, Jacobson TA, Bruckert E, et al. Efficacy and safety of alirocicab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. *J Clin Lipidol* 2014;8:554–61.
- 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;315:1580–90.
- Serban MC, Colantonio LD, Manthripragada A, et al. Statin intolerance and risk for recurrent myocardial infarction, coronary heart disease events and all-cause mortality following hospital discharge after myocardial infarction among Medicare beneficiaries. *J Am Coll Cardiol* 2017;69:1386–95.
- Graham JH, Sanches RJ, Sassen JJ, Mallya UG, Panaccio MP, Evans MA. Clinical and economic consequences of statin intolerance in the United States: results from an integrated health system. *J Clin Lipidol* 2017;11:70–9.
- Colantonio LD, Kent ST, Huang L, et al. Algorithms to identify statin intolerance in Medicare administrative claim data. *Cardiovasc Drugs Ther* 2016;30:525–33.
- Schulman KL, Lamerato LE, Dalal MR, et al. Development and validation of algorithms to identify statin intolerance in a US administrative database. *Value Health* 2016;19:852–60.
- Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol* 2014;8 Suppl:S58–71.
- Stroes ES, Thompson PD, Corsini A, et al., European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment,

- Aetiology and Management. *Eur Heart J* 2015;36:1012-22.
18. 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* 2015;11:1-23.
 19. 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 Suppl:S35-65.
 20. 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.
 21. Stulc T, Ceska R, Gotto AM Jr. Statin intolerance: the clinician's perspective. *Curr Atheroscler Rep* 2015;17:69.
 22. Buettner C, Davis RB, Leveille SG, Mittleman MA, Mukamal KJ. Prevalence of musculoskeletal pain and statin use. *J Gen Intern Med* 2008;23:1182-6.
 23. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. *Circulation* 2013;127:96-103.
 24. Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. *J Clin Lipidol* 2016;10:739-47.
 25. Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. *Ann Intern Med* 2014;160:301-10.
 26. Rosenson RS, Miller K, Bayliss M, et al. The Statin Myalgia Clinical Index (SMCI): Revision for clinical use, content validation, and inter-rater reliability. *Cardiovasc Drugs Ther* 2017;31:179-86.
 27. Taylor BA, Lorson L, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. *Atherosclerosis* 2015;238:329-35.
 28. Taylor BA, Sanchez RJ, Jacobson TA, et al. Application of the Statin Associated Muscle Symptoms Clinical Index (SAMS-CI) to a randomized controlled trial on statin myopathy. *J Am Coll Cardiol* 2017. In press.
 29. Wu JS, Buettner C, Smithline H, Ngo LH, Greenman RL. Evaluation of skeletal muscle during calf exercise by 31-phosphorus magnetic resonance spectroscopy in patients on statin medications. *Muscle Nerve* 2011;43:76-81.
 30. Link E, Parish S, Armitage J, et al., SEARCH Collaborative Group. SLC01B1 variants and statin-induced myopathy—a genomewide study. *N Engl J Med* 2008;359:789-99.
 31. Voora D, Shah SH, Spasojevic I, et al. The SLC01B1*5 genetic variant is associated with statin-induced side effects. *J Am Coll Cardiol* 2009;54:1609-16.
 32. Donnelly LA, Doney AS, Tavendale R, et al. Common nonsynonymous substitutions in SLC01B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. *Clin Pharmacol Ther* 2011;89:210-6.
 33. Mammen AL. Statin-associated autoimmune myopathy. *N Engl J Med* 2016;374:664-9.
 34. Hovingh GK, Gandra SR, McKendrick J, et al. Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey. *Atherosclerosis* 2016;245:111-7.
 35. Rosenson RS, Gandra SR, McKendrick J, et al. Identification and management of statin-associated symptoms in clinical practice: extension of a clinical survey to 12 further countries. *Cardiovasc Drugs Ther* 2017;31:185-95.
 36. Tanner RM, Safford MM, Monda KL, et al. Primary care physician perspectives on barriers to statin treatment. *Cardiovasc Drugs Ther* 2017 Jul 14 [E-pub ahead of print].
 37. Tanner R, Colantonio L, Safford L, et al. Prevalence and correlates of statin side effects and willingness to be rechallenged on a statin: data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Paper presented at: ACC.17, March 17, 2017; Washington, DC.
 38. Schachter M. Clinical and pharmacokinetic properties of statins. *Fundam Clin Pharmacol* 2005;19:117-25.
 39. Wiggins BS, Saseen JJ, Page RL 2nd, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2016;134:e468-95.
 40. Algharably EA, Filler I, Rosenfeld S, Grabowski K, Kreutz R. Statin intolerance: a question of definition. *Exp Opin Drug Saf* 2017;16:55-63.
 41. Stros E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014;63:2541-8.
 42. Visser ME, Wagener G, Baker BF, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. *Eur Heart J* 2012;33:1142-9.
 43. Glueck CJ, Abuchai C, Wang P. Symptomatic myositis-myalgia in hypercholesterolemic statin-treated patients with concurrent vitamin D deficiency leading to statin intolerance may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle. *Med Hypotheses* 2011;77:658-61.
 44. Khayznikov M, Hemachandra K, Pandit R, Kumar A, Wang P, Glueck CJ. Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. *N Am J Med Sci* 2015;7:86-93.
 45. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA* 2012;308:2497-506.
 46. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart J* 2014;168:6-15.
 47. 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.
 48. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med* 2013;158:526-34.
 49. 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 Jul 24 [E-pub ahead of print].
 50. Rivers SM, Kane MP, Busch RS, Bakst G, Hamilton RA. Colesevelam hydrochloride-ezetimibe combination lipid-lowering therapy in patients with diabetes or metabolic syndrome and a history of statin intolerance. *Endocr Pract* 2007;13:11-6.
 51. Marazzi G, Pelliccia F, Campolongo G, et al. Usefulness of nutraceuticals (Armolidip Plus) versus ezetimibe and combination in statin-intolerant patients with dyslipidemia with coronary heart disease. *Am J Cardiol* 2015;116:1798-801.
 52. Wierzbicki AS, Doherty E, Lumb PJ, Chik G, Crook MA. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipidaemias. *Curr Med Res Opin* 2005;21:333-8.
 53. Stein EA, Ballantyne CM, Windler E, et al. Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. *Am J Cardiol* 2008;101:490-6.
 54. Athyros VG, Tziomalos K, Kakafika AI, Koumaras H, Karagiannis A, Mikhailidis DP. Effectiveness of ezetimibe alone or in combination with twice a week Atorvastatin (10 mg) for statin intolerant high-risk patients. *Am J Cardiol* 2008;101:483-5.
 55. Cannon CP, Blazing MA, Giugliano RP, et al., IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387-97.
 56. Farnier M, Bonnefous F, Debbas N, Irvine A. Comparative efficacy and safety of micronized fenofibrate and simvastatin in patients with primary type IIa or IIb hyperlipidemia. *Arch Intern Med* 1994;154:441-9.
 57. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med* 2010;363:692-4.
 58. Ginsberg HN, Elam MB, Lovato LC, et al., ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;36:1563-74.
 59. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project

patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986;1245–55.

60. Stein EA, Raal F. Future directions to establish lipoprotein(a) as a treatment for atherosclerotic cardiovascular disease. *Cardiovasc Drugs Ther* 2016;30:101–8.

61. Boden WE, Probstfield T, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255–67.

62. HPS-2 THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;371:203–12.

63. Pinkosky SL, Newton RS, Day EA, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun* 2016;7:13457.

64. Thompson PD, Rubino J, Janik MJ, et al. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. *J Clin Lipidol* 2015;9:295–304.

65. Thompson PD, MacDougall DE, Newton RS, et al. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL-C in hypercholesterolemic patients with or without statin intolerance. *J Clin Lipidol* 2016;10:556–67.

66. Cicero AF, Morbini M, Bove M, et al. Additional therapy for cholesterol lowering in ezetimibe-treated, statin-intolerant patients in clinical practice: results from an internal audit of a university lipid clinic. *Curr Med Res Opin* 2016;8:1–6.

67. Becker DJ, Gordon RY, Halbert SC, French B, Morris PB, Rader DJ. Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial. *Ann Intern Med* 2009;150:830–9.

68. Halbert SC, French B, Gordon RY, et al. Tolerability of red yeast rice (2,400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. *Am J Cardiol* 2010;105:198–204.

69. Banach M, Serban C, Ursoniu S, et al., Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Statin therapy and plasma coenzyme Q10 concentrations—a systematic review and meta-analysis of placebo-controlled trials. *Pharmacol Res* 2015;99:329–36.

70. Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, et al., Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Analysis of vitamin D levels in patients with and without statin-associated myalgia: a systematic review and meta-analysis of 7 studies with 2420 patients. *Int J Cardiol* 2015;178:111–6.

71. Kang JH, Nguyen Q-N, Mutka J, Le QA. Rechallenging statin therapy in veterans with statin-induced myopathy post vitamin D replenishment. *J Pharm Pract* 2016 Oct 24 [E-pub ahead of print].

72. Sahebkar A, Saboni N, Pirro M, Banach M. Curcumin: an effective adjunct in patients with statin-associated muscle symptoms? *J Cachexia Sarcopenia Muscle* 2017;8:19–24.

73. Arca M, Pigna G. Treating statin-intolerant patients. *Diabetes Metab Syndr Obes* 2011;4:155–66.

74. Korhonen MJ, Pentti J, Hartikainen J, Kivimäki M, Vahtera J. Somatic symptoms of anxiety and nonadherence to statin therapy. *Int J Cardiol* 2016;214:493–9.

75. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (US-AGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol* 2012;6:208–15.

KEY WORDS cardiovascular disease, low-density lipoprotein, myalgia, myopathy, statin intolerance