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Original Contribution

An assessment by the Statin Muscle Safety Task Force: 2014 update

Robert S. Rosenson, MD, FNLA*, Steven K. Baker, MSc, MD, FRCP(C), Terry A. Jacobson, MD, FNLA, Stephen L. Kopecky, MD, Beth A. Parker, PhD

Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, New York, NY 10029, USA (Dr Rosenson); McMaster University, Hamilton, ON, Canada (Dr Baker); Emory University, Atlanta, GA, USA (Dr Jacobson); Mayo Clinic, Rochester, MN, USA (Dr Kopecky); and Department of Cardiology, Henry Low Heart Center, Hartford Hospital, Hartford, CT, USA (Dr Parker)

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Statin intolerance;
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Abstract: The National Lipid Association's Muscle Safety Expert Panel was charged with the duty of examining the definitions for statin-associated muscle adverse events, development of a clinical index to assess myalgia, and the use of diagnostic neuromuscular studies to investigate muscle adverse events. We provide guidance as to when a patient should be considered for referral to neuromuscular specialists and indications for the performance of a skeletal muscle biopsy. Based on this review of evidence, we developed an algorithm for the evaluation and treatment of patients who may be intolerant to statins as the result of adverse muscle events. The panel was composed of clinical cardiologists, clinical lipidologists, an exercise physiologist, and a neuromuscular specialist.

Muscle complaints represent the most frequent adverse reports among patients treated with statins. These complaints occur in a population that often has musculoskeletal pain and dysfunction in the absence of statins; therefore, the careful assessment of such adverse reports is essential to provide the most efficacious cardiovascular risk management. The spectrum of statin-associated muscle toxicity, often termed "statin-associated myopathy," is considered to include several distinct entities that may overlap in clinical presentation (Table 1); however, there is no evidence that the constellation of muscle adverse reports is a continuum that begins with myalgia and progress to more severe manifestations of myopathy. Thus, each statin-associated muscle event must be categorized with the use of standard definitions to minimize misinterpretation of the etiology and misclassification of muscle adverse reports in those using statins for prevention of cardiovascular diseases. These associations are usually temporal, and causality is often very hard to prove. It should also be noted that statins are not the only chemical entity that can induce myopathic changes. Other common drugs include substances of abuse (alcohol, cocaine, opioids), neuroleptics and psychotropic agents (haloperidol, risperidone), immunosuppressants (cyclosporine A, azathioprine), antiviral agents (zidovudine, ritonavir, didanosine), analgesics and anti-inflammatory drugs (salicylates, nonsteroidal anti-inflammatory drugs, glucocorticoids), fibrates (gemfibrozil, fenofibrate), anesthetics and neuromuscular blocking agents (propofol, ketamine, succinylcholine). Furthermore, genetic, infectious, and immune disorders can present with muscle signs and symptoms. Misdiagnosis may preclude

* Corresponding author.
E-mail address: robert.rosenson@mssm.edu
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Evidence grading: strength of recommendation*

Grade	Strength of recommendation
A	**Strong Recommendation** There is high certainty based on the evidence that the net benefit† is substantial
B	**Moderate Recommendation** There is moderate certainty based on the evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate
C	**Weak Recommendation** There is at least moderate certainty based on the evidence that there is a small net benefit
D	**Recommend Against** There is at least moderate certainty based on the evidence that it has no net benefit or that the risks/harms outweigh benefits
E	**Expert Opinion** There is insufficient evidence or evidence is unclear or conflicting, but this is what the expert panel recommends
N	**No Recommendation for or against** There is insufficient evidence or evidence is unclear or conflicting

*The system was adapted as a hybrid of the National Heart Lung and Blood Institutes (NHLBI) rating system (NHLBI cardiovascular-based methodology) used in the new American Heart Association/American College of Cardiology cholesterol guidelines[1] and adapted from the original Grading of Recommendations Assessment, Development, and Evaluation system of evidence rating.[2]

†Net benefit is defined as benefit minus risks/harms of the service/intervention.

unnecessarily the future use of this class of efficacious agents in a given patient and delay appropriate treatment of other unrelated myopathic disorders.

Statin-associated adverse muscle symptoms may present from the patient at any time after beginning therapy with these drugs. They need to be evaluated by history, physical examination and laboratory testing when appropriate. These findings may include muscle discomfort (myalgia), muscle weakness (myopathy), tenderness to palpation, with or without muscle inflammation (myositis) and/or

Evidence grading—quality of evidence

Type of evidence	Quality rating*
Well-designed, well-executed RCTs is that adequately represent populations to which the results are applied and directly assess effects on health outcomes Well-conducted meta-analyses of such studies Highly certain about the estimate of effect; more research is unlikely to change our confidence in the estimate of effect	High
RCTs with minor limitations affecting confidence in, or applicability of, the results Well-designed, well-executed nonrandomized controlled studies and well-designed. Well-executed observational studies Well-conducted -meta-analysis of such studies Moderately certain about the estimate of effect; additional research may have an impact on our confidence n the estimate of effect and may change the estimate	Moderate
RCTs with major limitations Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports) Physiological studies in humans Meta-analyses of such studies Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.	Low

RCT, randomized controlled trial.

This was the system used in the new American Heart Association/American College of Cardiology cholesterol guidelines[1] that were published in the 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report from the Panel members appointed to the Eighth Joint National Committee (JNC 8).[3]

From James PA, Oparil S, Carter BL, et al.[3]

*The evidence quality rating system used in this guideline was developed by the Nations Heart, Lung, and Blood Institute's (NHLBI's) Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI cardiovascular disease guideline panels and work groups during this project. As a result, it includes the evidence quality rating for many types of studies, including studies that were not used in this guideline. Additional details regarding the evidence quality rating system are available in the online Supplement.