

2014 Statin Safety Task Force

Terry A. Jacobson, MD, FACP, FNLA, Chair

2014 Statin Safety Task Force

- A group of experts in the fields of clinical lipidology, diabetes, neurology, hepatology and myology participated in the NLA Statin Safety Task Force meeting held in October 2013.
- Goals of the 2014 Statin Safety Task Force
 - To update the 2006 Statin Safety Task Force report, providing expert panel opinion on issues discussed in that report, as well as new issues raised in the interim.
 - To address specific questions of clinical relevance and grade the evidence using a hybrid of the NHLBI rating system, adapted from the original Grading of Recommendations Assessment, Development and Evaluation system of evidence rating and the quality of evidence grading from the new AHA/ACC cholesterol guidelines.



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An Assessment by the Statin Intolerance Panel: 2014 Update

John R. Guyton, MD, FNLA

Harold E. Bays, MD, FNLA

Scott M. Grundy, MD, PhD, FNLA

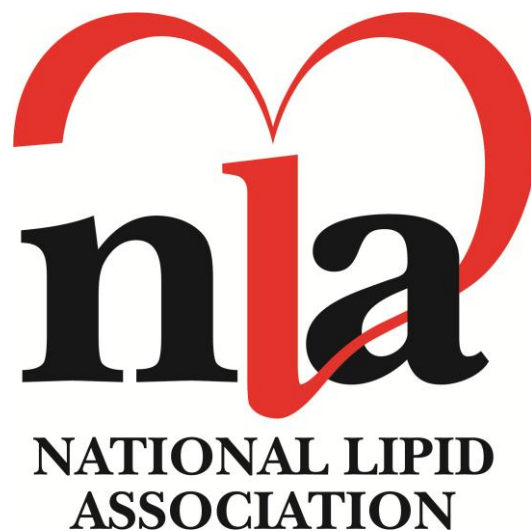
Terry A. Jacobson, MD, FACP, FNLA

Statin Intolerance Highlights

- Statin intolerance is a real phenomenon that manifests mostly as an array of muscle-related symptoms (aching, stiffness, proximal motor weakness, fatigue, and back pain)
- Statin intolerance might occur in 10% of patients (based on the fraction of patients reporting muscle symptoms with high-dose statins), but the true frequency is unknown.
- Cognitive difficulties, elevated serum hepatic transaminase levels, and increased risk for new-onset diabetes mellitus are also reported with statin use.
- Specific recommendations for the issues associated with muscle, liver, cognition, and diabetes can be found in the reports of the Statin Safety Task Force panels addressing these topics.

Statin Intolerance Highlights (continued)

- Statin intolerance requires a patient-centered approach in practice, based on the patient's subjective feelings, preferences, and judgment.
- Statin intolerance usually does not involve substantial risk for mortality or permanent disability. Thus, the clinician should assist the patient in distinguishing statin intolerance from a true “drug allergy” which could imply significant risk with rechallenge.
- Attempts to maintain statin treatment in some form (i.e., lower doses, alternative statins) is recommended in almost every case of statin intolerance.
- Innovative approaches to research on statin intolerance are needed, including development of a validated index of statin muscle intolerance.



An Assessment by the Statin Cognitive Safety Task Force: 2014 Update

Carlos H. Rojas-Fernandez, BSc(Pharm), PharmD

Larry B. Goldstein, MD

Allan I. Levey, MD, PhD

Beth A. Taylor, PhD

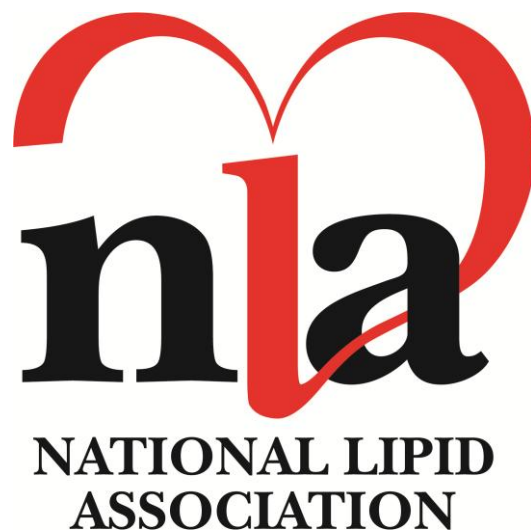
Vera Bittner, MD, MSPH, FNLA

Statin Cognition Safety Highlights

- Statins have been associated with spontaneous reports of adverse cognitive effects such as amnesia, concentration difficulties, confusion, and other complaints.
- Spontaneous reports from the FDA's Adverse Event Reporting System form the basis for the FDA statin label change request regarding cognitive side effects. These data do not allow for appropriate causality assessment.
- To date, the weight of the evidence (albeit of low to moderate quality) does not support the contention that statins have a clear propensity to meaningfully or commonly contribute to adverse cognitive effects.

Statin Cognition Safety Highlights (continued)

- If patients report adverse cognitive effects that they attribute to initiation of statin therapy, clinicians should not dismiss these reports. A thorough assessment should be conducted to rule out other potential causes. If no other causes of cognitive function are identified, discontinuation of the medication should be considered after a careful review of the benefit:risk ratio.
- Baseline assessment of cognition prior to initiating a statin drug is not recommended. It is unlikely that conducting the available cognitive tests would be useful, owing to the clinical and practical issues associated with their administration.



An Assessment by the Statin Diabetes Safety Task Force: 2014 Update

Kevin C. Maki, PhD, FNLA

Paul M Ridker, MD, MPH

W. Virgil Brown, MD, FNLA

Scott M. Grundy, MD, PhD, FNLA

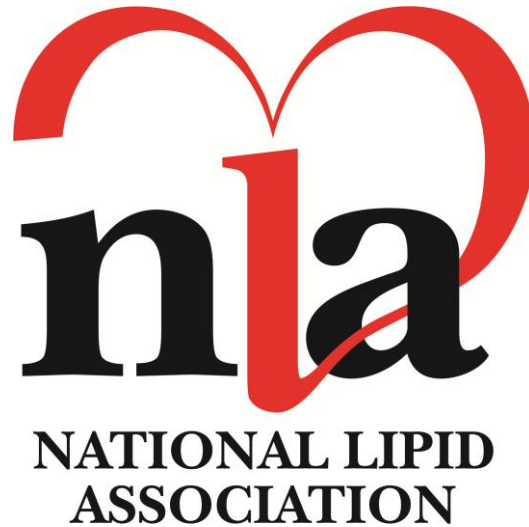
Naveed Sattar, MD, PhD

Statin Diabetes Safety Highlights

- Statin use is associated with a modest, yet statistically significant, increase in risk for new-onset type 2 diabetes mellitus (diabetes) of ~10%, compared with placebo or usual care.
- Intensive statin therapy appears to increase diabetes risk beyond that of moderate-dose statin therapy.
- Excess risk for diabetes with statin use is most clearly evident in those with major risk factors for diabetes.
- The cardiovascular benefits of statin therapy far outweigh the potential risk for diabetes development, with several cardiovascular events prevented for each excess case of diabetes.

Statin Diabetes Safety Highlights (continued)

- Statin therapy should continue to be recommended where appropriate for the reduction of cardiovascular disease event risk.
- Lifestyle modification should be emphasized to all patients for whom statin therapy is recommended to reduce cardiovascular risk, as well as attenuate any slight increase in diabetes risk.
- Patients with risk factors for diabetes should be screened with fasting glucose or glycated hemoglobin (HbA_{1c}), ideally prior to starting statin therapy, within 1 year of initiation, and at intervals no longer than 3 years thereafter.



An Assessment by the Statin Liver Safety Task Force: 2014 Update

Harold Bays, MD, FNLA

David E. Cohen, MD, PhD

Naga Chalasani, MBBS

Stephen A. Harrison, MD, COL, MC

Statin Liver Safety Highlights

- Data since the 2012 FDA statin safety label change continue to support a favorable benefit:risk ratio with the strategy of obtaining liver enzymes at baseline and then as clinically indicated afterwards.
- In statin-treated patients, an increase in liver enzymes may be due to different etiologies which the clinician should consider before assuming the increase is due to the statin.
- Mild to modest increases in liver enzymes are not necessarily a contraindication to either initiation or continued use of statins, especially if the clinical presentation and subsequent assessment suggests non-alcoholic fatty liver disease as the reason for the liver enzyme elevation.

Statin Liver Safety Highlights (continued)

- Statins have drug interactions with medications used to treat infections such as hepatitis B, C, etc. If a drug interaction is possible, then consideration should be given to change the statin to one without a potential drug interaction or limit the statin to lower doses.
- Patients with elevated liver enzymes, whether found before initiation of statin therapy, or discovered while treated with statin therapy, are best evaluated using an organized, systematic approach.



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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

Statin Muscle Safety Highlights

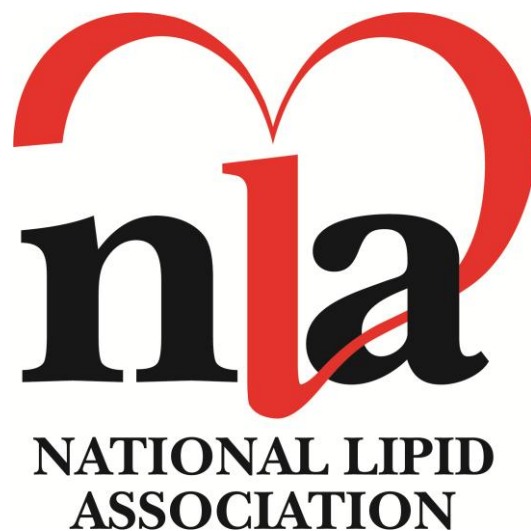
- Creation of new terminology for muscle-related disorders
 - Statin-associated muscle adverse events: entire spectrum of muscle-related disorders in statin-treated patients (muscle aches, soreness, stiffness, tenderness and cramps with or shortly after exercise)
 - Myalgia: muscle pain
 - Myopathy: muscle weakness
 - Myositis: muscle inflammation determined by skeletal muscle biopsy and/or magnetic resonance imaging
 - Myonecrosis: muscle enzyme elevations or hyperCKemia (categorized as mild, moderate or severe)
 - Clinical rhabdomyolysis: severe form of myonecrosis with myoglobinuria and/or acute renal failure
- Of these manifestations, myalgia complaints are most common (1-5% in controlled clinical trials; 11-29% in observational cohorts).

Statin Muscle Safety Highlights

- There are many causes of myalgia; differential diagnosis of myalgia occurring during statin therapy is difficult.
- This report proposed a statin myalgia clinical index score, based on symptoms and signs reported by participants in the STOMP and PRIMO studies. The scoring system includes categories for regional distribution/pattern, temporal pattern, and dechallenge/rechallenge.
- Statin therapy may evoke a greater incidence of muscle-related side effects in chronically physically active individuals and may also exacerbate creatine kinase release and presumably the skeletal muscle damage associated with acute exercise.

Statin Muscle Safety Highlights

- Tests that support or confirm the diagnosis of statin-associated muscle adverse events include: validated muscle adverse event clinical score; elevated muscle enzymes (creatine kinase, and if severely elevated, urinary myoglobin), strength and aerobic testing, metabolic testing, pharmacogenetic testing, and muscle biopsy.
- Indications for the above tests are described in the Muscle Safety report, and a recommended algorithm for the evaluation of statin-associated muscle injury is provided.



A Clinician's Guide to Statin Drug-Drug Interactions

Kenneth A. Kellick, PharmD, FNLA

Michael Bottorff, PharmD, FNLA

Peter P. Toth, MD, PhD, FNLA

Statin Drug-Drug Interactions Highlights

- This report provides information to assist the practitioner with:
 - Understanding the different enzyme systems involved in statin metabolism and intra-patient differences
 - Predicting potential drug interactions based upon changes in the area under the curve for statin concentrations
 - Interpreting package labeling with respect to drug-drug interactions
 - Identification of common prescription and non-prescription medications that interact with statins
 - Identification of special populations that may be at risk for statin drug-drug interactions