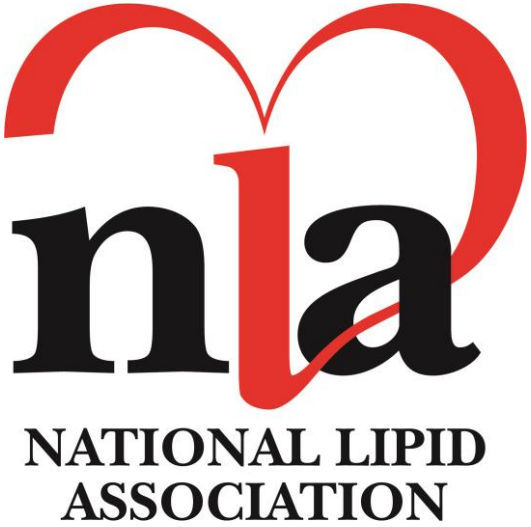


2014 NLA Statin Safety Task Force

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 (GRADE) system

TABLE OF CONTENTS

Case – Statin Intolerance

- 47 year-old man s/p anterior wall MI 3 weeks ago
- CHD Risk Factors: smoker, premature CHD in father at age 52; hypertension controlled on metoprolol XL, lisinopril 10mg, and aspirin
- Baseline lipids (at time of MI):
  - TC 205 mg/dL
  - LDL-C 151 mg/dL
  - HDL-C 43 mg/dL
  - TG 57 mg/dL
- Initial therapy: atorvastatin 80 mg daily – stopped after 3 weeks due to severe myalgias (normal CPK)
- After resolution of symptoms, subsequent intolerance to trials of simva/ezetimibe 10/40 mg, rosuvastatin 10 mg, and pravastatin 40 mg daily

In our statin intolerant patient, what would be the best next step?

47 yo male, man s/p anterior wall MI 2 years ago with TC 205 mg/dl, LDL-C 151 mg/dL, TG 57 mg/dL, HDL-C 43 mg/dl

Failed atorvastatin 80 mg, simva/ezetimibe 10/40 mg, rosuvastatin 10 mg, pravastatin 40 mg daily, and fluvastatin 80 mg XL due to severe myalgia

A) Fenofibrate alone
B) Niacin 1 g with 4 g prescription omega-3
C) Coenzyme Q (100mg/day), Vitamin D, plus Red Rice Yeast
D) Low dose rosuvastatin (5 mg) daily
E) Ezetimibe or colesevalam or alternate day dosing (MWF)

Incidence of Muscle AEs

(180,000 Patients in 21 Major Statin Trials for avg of 3 yrs)

Muscle AE	Incidence
Myalgias	1.5% to 3%
Myopathy (Sx + ↑CK)	5/100,000
Rhabdomyolysis	1.6/100,000

Law M et al. Am J Cardiol. 2006; 97 (suppl 8A): 52C-61C.

PRIMO: Patient Cohort

- The patient cohort comprised 7924 patients with hyperlipidemia who were receiving statin therapy in routine clinical practice in France and who met the following criteria:
  - Aged 18–75 years
  - Either
    - Receiving high dosage statin therapy for >3 months prior to the study or
    - Had discontinued high dosage statin therapy due to muscular side effects during the 3 months immediately prior to the study

Bruckert E et al. Cardiovascular Drugs and Therapy 2005 ;19: 403–414.

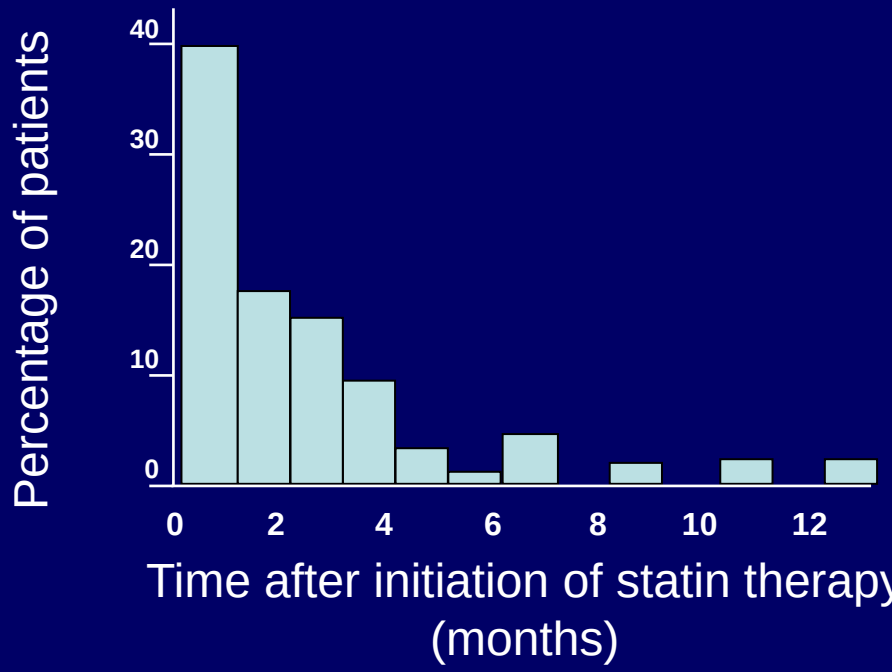
PRIMO: Risk of Muscular Symptoms with Individual Statins

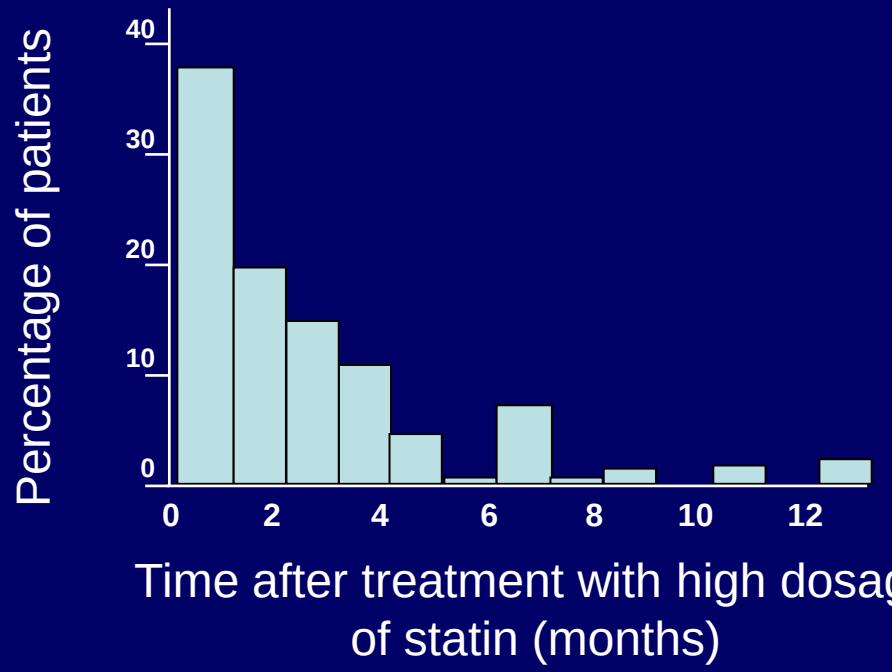
Statin	Dosage	Percentage of patients with muscular symptoms*	Odds Ratio† [95% CI]	P value‡
Pravastatin	40 mg/day	10.9%		
Atorvastatin	40–80 mg/day	14.9%	1.28 [1.02–1.60]	0.035
Simvastatin	40–80 mg/day	18.2%	1.78 [1.39–2.29]	<0.0001
Fluvastatin	80 mg/day	5.1%	0.33 [0.26–0.42]	<0.0001

***% values relative to the total number of patients with or without muscular symptoms.**
† Odds ratios were calculated using pravastatin as the reference.
‡ P values were determined by Pearson's Chi-squared test.

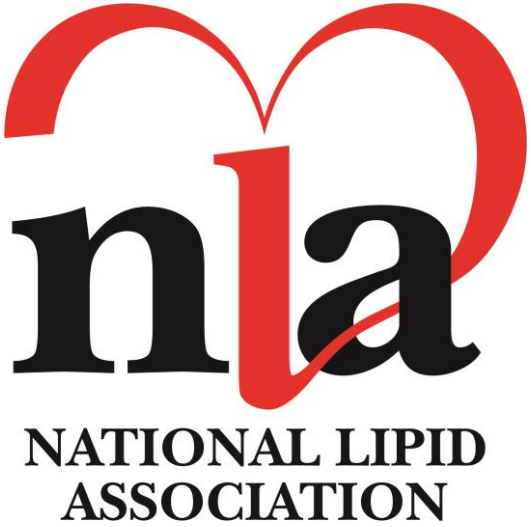
Bruckert E et al. Cardiovascular Drugs and Therapy 2005 ;19: 403–414.

Timing of Myalgia in PRIMO





Bruckert E et al. Cardiovascular Drugs and Therapy 2005 ;19: 403–414.



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)
- Of these manifestations, myalgia complaints are most common (1-5% in controlled clinical trials; 11-29% in observational cohorts).

NLA 2014 Definitions of Statin Associated Muscle Events

Table 1 Spectrum of statin-associated muscle adverse events

- Myalgia—unexplained muscle discomfort often described as "flu-like" symptoms with normal CK level. The spectrum of myalgia complaints includes:
  - Muscle aches;
  - Muscle soreness;
  - Muscle stiffness;
  - Muscle tenderness; and
  - Muscle cramps with or shortly after exercise (not nocturnal cramping).
- Myopathy—muscle weakness (not attributed to pain and not necessarily associated with elevated CK).
- Myositis—muscle inflammation
- Myonecrosis—muscle enzyme elevations or hyperCKemia
  - Mild >3-fold greater than baseline untreated CK levels or normative upper limit that are adjusted for age, race, and sex.
  - Moderate ≥10-fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race, and sex.
  - Severe ≥50-fold above baseline CK levels or normative upper limit that are adjusted for age, race, and sex.
- Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine ≥0.5 mg/dL (clinical rhabdomyolysis).

CK, creatine kinase.

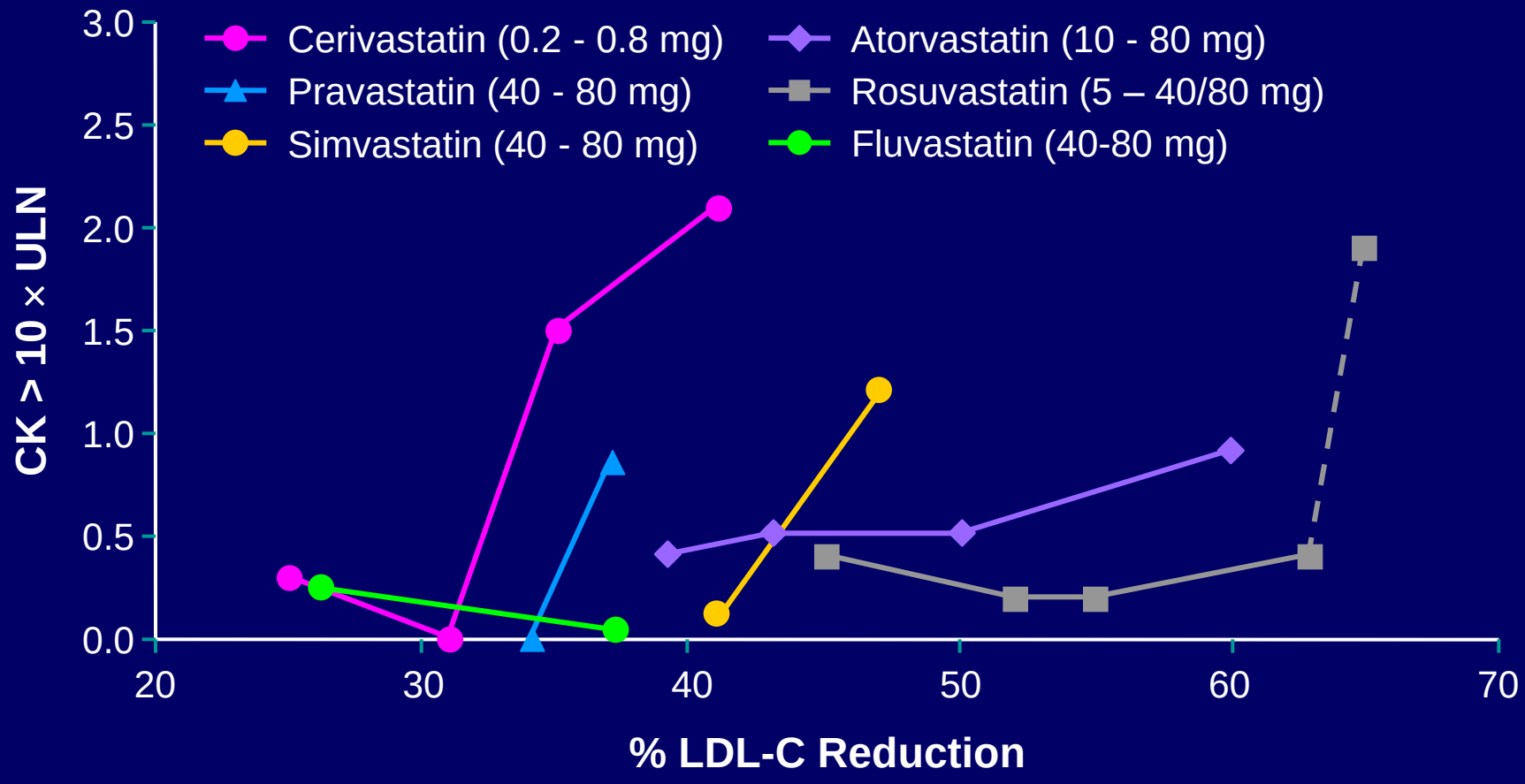
Adapted from Rosenson RS et al. J Clin Lipid 2014, 8: (S58-S71)

Factors That Increase the Risk of Statin-Induced Myopathy

Patient Characteristics
Increasing age
Female sex
Renal insufficiency
Hepatic dysfunction
Hypothyroidism
Diet (e.g., grapefruit juice with statins metabolized by 3A4)
Polypharmacy and multiple chronic diseases
Statin Properties
High systemic exposure (higher doses, high bioavailability, limited protein binding)
Potential for drug-drug interactions metabolized by CYP pathways (and common conjugation and transporter pathways)

Rosenson. *Am J Med.* 2004;116:408-416.

Creatine Kinase >10 X ULN Frequency by % LDL-C Reduction



Jacobson TA. Am J Cardiol. 2006; 97 (suppl 8A): 44C-51C.

Recommendations from the 2006 NLA Statin Safety Task Force for Muscle Issues

PATIENT MONITORING

- Rule out other etiologies of muscle symptoms or asymptomatic CK elevations (hypothyroidism, trauma, falls, seizures, infection, increased physical activity)
- Routine CK levels in asymptomatic patients not recommended
- Obtain baseline CK levels in high risk patients (renal dysfunction, transplants, polypharmacy), optional for others
- Symptom monitoring with CK measurement only in symptomatic patients
- Exacerbating factors should be considered (grapefruit juice consumption, concomitant medications, herbal remedies, infection, sepsis, alcohol abuse)

McKenney JM et al. *Am J Cardiol.* 2006;97:89C-94C.
Thompson PD et al. *Am J Cardiol.* 2006;97:69C-76C.

Recommendations from the NLA 2006 Statin Safety Task Force for Muscle Issues

MANAGEMENT OF MUSCLE SYMPTOMS

Intolerable muscle symptoms:

- Discontinue statin regardless of CK levels and rechallenge only after patient becomes asymptomatic

Tolerable muscle symptoms and:

- Mild CK elevation: May continue statin and use symptoms as guide to stop or continue treatment
- Moderate to severe CK elevation: Discontinue statin therapy and weigh risks and benefits
- CK elevation with elevated creatinine or need for IV hydration: Discontinue statin therapy

McKenney JM et al. *Am J Cardiol.* 2006;97:89C-94C.
Thompson PD et al. *Am J Cardiol.* 2006;97:69C-76C.

2014 Muscle Safety Expert Panel

Question	Strength of Recommendation
1. Can statin-associated myalgia be reliably differentiated from myalgia associated with a placebo?	YES (B)

Strength of Recommendation:
A- Strong; B- Moderate; C-Weak; D- Recommend Against; E-Expert Opinion;
N: No recommendation for or against

The STOMP Study

The Effect of STatins On Skeletal Muscle Performance

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

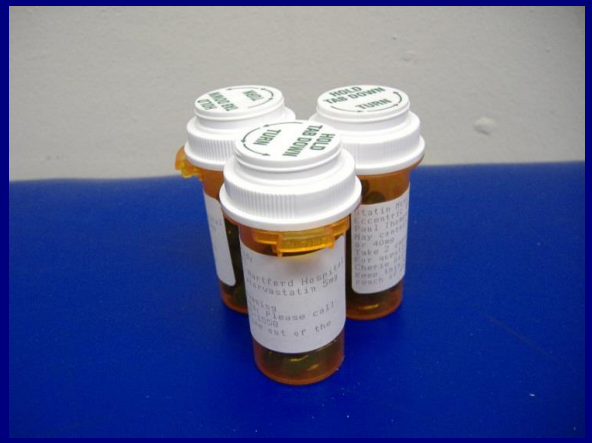
Effect of Statins on Skeletal Muscle Function

Beth A. Parker, Jeffrey A. Capizzi, Adam S. Grimaldi, Priscilla M. Clarkson, Stephanie M. Cole, Justin Keadle, Stuart Chipkin, Linda S. Pescatello, Kathleen Simpson, C. Michael White and Paul D. Thompson

Circulation. 2013;127:96-103; originally published online November 26, 2012;

Experimental Design

- Subjects (n=440)
  - Men and women
  - >20 yr
  - No prior statin use



- Design
  - Randomized, double blind
    - 80 mg dose of Atorva or placebo for six months
- Muscle function
  - Handgrip strength
  - Elbow flexor/extensor
  - Knee flexor/extensor
- Aerobic performance (VO_2Max)
- Physical activity (accelerometer)
- Muscle symptoms

Study Definition of Statin-Related Myalgia

1. Reported new or increased myalgia, cramps, or muscle aching,
2. Symptoms have persisted for at least 2 weeks,
3. Symptoms resolve within 2 weeks of stopping the study drug, and
4. Symptoms reoccur within 4 weeks of restarting the medication

Proposed Statin Myalgia Clinical Index Score

Table 2 Proposed statin myalgia clinical index score

Clinical symptoms (new or increased unexplained muscle symptoms)	
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Non-specific asymmetric, intermittent	1
Temporal pattern	
Symptoms onset <4 weeks	3
Symptoms onset <4 weeks	3
Symptoms onset 4–12 weeks	2
Symptoms onset >12 weeks	1
Dechallenge	
Improves upon withdrawal (<2 weeks)	2
Improves upon withdrawal (2–4 weeks)	1
Does not improve upon withdrawal (>4 weeks)	0
Challenge	
Same symptoms reoccur upon rechallenge <4 weeks	3
Same symptoms reoccur upon rechallenge 4–12 weeks	1
Statin myalgia clinical index score	
Probable	9–11
Possible	7–8
Unlikely	<7

2014 Muscle Safety Expert Panel

Question	Strength of Recommendation
1. Can statin-associated myalgia be reliably differentiated from myalgia associated with a placebo?	YES (B)
2. Are there currently validated scales that can accurately diagnosis statin-associated myalgia in clinical practice?	NO (A)
3. Are statin-associated muscle complaints altered by acute and chronic physical activity?	YES (A)
4. Are there tests available to support or confirm the diagnosis of statin-associated myopathy?	YES (A)

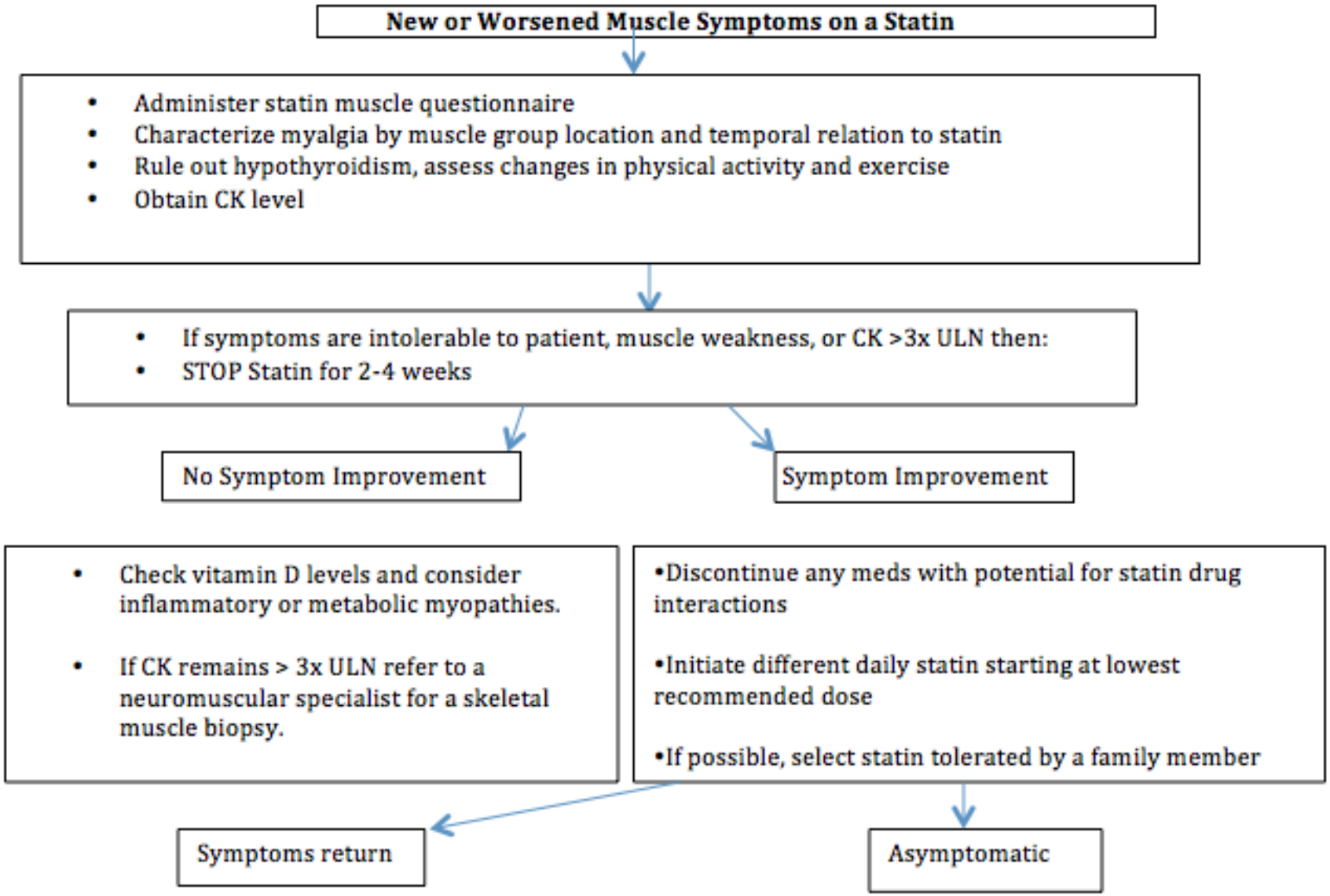
Strength of Recommendation:
A- Strong; B- Moderate; C-Weak; D- Recommend Against; E-Expert Opinion;
N: No recommendation for or against

Muscle Safety Expert Panel

	Question	Strength of Recommendation
5.	Are there recommendations when to obtain a muscle biopsy in patients with statin-associated muscle symptoms?	YES (A)
6.	Can patients who are initially intolerant to one statin generally tolerate a different statin?	YES (B)
7.	Does the evidence base for treating statin-associated muscle symptoms or statin muscle intolerance generally consist of high-quality, randomized controlled trials with appropriate placebo or control groups?	NO (E)

A- Strong; B- Moderate; C-Weak; D- Recommend Against; E-Expert Opinion; N: No recommendation for or against

Adapted from Rosenson RS et al. J Clin Lipid 2014, 8: (S58-S71)



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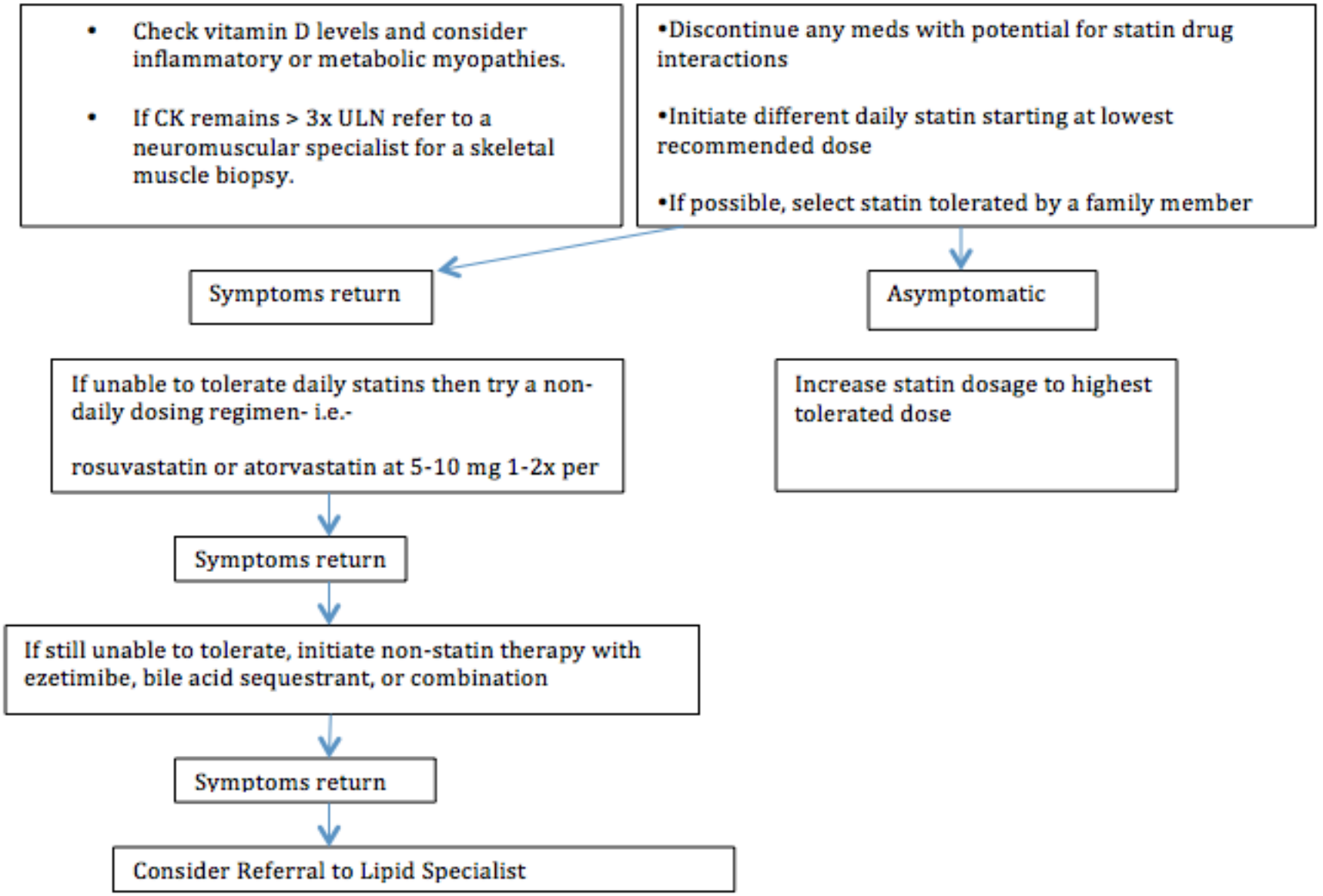


Adapted from Rosenson RS et al. J Clin Lipid 2014, 8: (S58-S71)

NLA Statin Muscle Safety Task Force: Tables

Table 3 Tests that might support or confirm the diagnosis of statin-associated muscle adverse events

- A validated muscle adverse event clinical score;
- elevated muscle enzymes (CK); (serum aldolase and myoglobin not recommended);
- if CK levels >50 times the upper limit of normal and/or dark brown urine, then obtain urinary myoglobin;
- general pain questionnaires (brief pain inventory [preferred because most widely used], McGill, adaptation of quality of life);
- strength and aerobic testing;
- metabolic tests (magnetic resonance spectroscopy, O_2 uptake intake);
- pharmacogenetic testing; and
- muscle biopsy.

CK, creatine kinase.

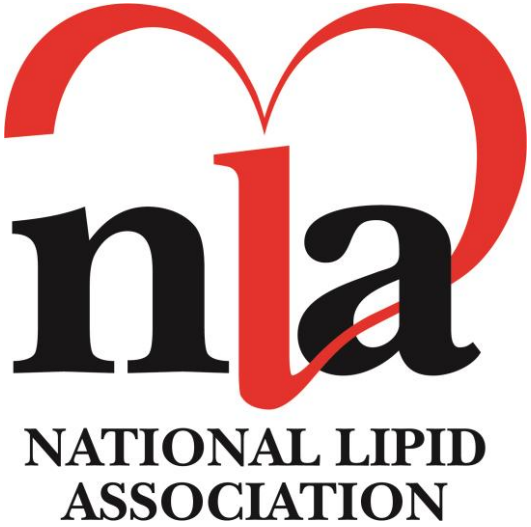
Table 4 Diagnostic criteria for myopathy

- Physical examination
  - Proximal weakness in upper and lower extremities ≤4 by Medical Research Council definition;
- Standardized muscle testing with isokinetic dynamometer, aerobic capacity, and respiratory exchange ratio with fasted patient and standardized procedure on metabolic cart (requires off drug/on drug comparison); and
- Confirmation by electromyography ± muscle biopsy.

Table 5 Indications for skeletal muscle biopsy after excluding increased physical activity, trauma, metabolic derangements, comorbid conditions associated with increased CK, and known drug interactions

- Threshold for biopsy—CK values should be adjusted ≥3 times the upper limit of normal above sex and racial norms in association with either severe myalgia or weakness. Isolated asymptomatic CK elevations between 3 and 10 times the ULN ought to be followed conservatively.
- Electromyography myopathic discharges with fibrillations and/or positive sharp waves in affected muscles (usually proximal).
- Proximal muscle weakness (≤4 on Medical Research Council scale) in upper and/or lower extremities.

CK, creatine kinase; ULN, upper limit of normal.



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.

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.

NLA Expert Panel on Statin Intolerance

Question	Strength of Recommendation
1. Does statin intolerance exist?	YES (A)
2. Are statins generally well tolerated and safe?	YES (A)
3. Do large randomized trials provide reliable estimates of statin intolerance?	NO (E)
4. Is statin intolerance best defined in the context of patient-centered medicine?	YES (E)

Strength of Recommendation:
A- Strong; B- Moderate; C-Weak; D- Recommend Against; E-Expert Opinion; N: No recommendation for or against

Guyton JR et al. J Clin Lipid 2014 8: S72-S81

NLA Expert Panel on Statin Intolerance

Question	Strength of Recommendation
5. Is it safe to advise a patient to continue statin therapy even when some degree of statin intolerance is present?	YES (B)
6. Are recommendations for widespread use of statins to prevent atherosclerotic cardiovascular disease appropriate, given the emerging evidence with regard to statin intolerance?	YES (A)
7. Are there clinical trial designs that may reliably address questions of statin intolerance?	YES (E)
8. Is there a universally accepted definition of statin intolerance that can be used by clinicians, researchers, insurers, and regulatory authorities?	NO (E)

A- Strong; B- Moderate; C-Weak; D- Recommend Against; E-Expert Opinion; N: No recommendation for or against

Guyton JR et al. J Clin Lipid 2014 8: S72-S81

Statin Intolerance Definition for Clinicians and Researchers

Statin intolerance is a clinical syndrome 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 re-challenge
- with other known determinants being excluded*

*such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, or underlying muscle disease

Recommendations for Research on Statin Intolerance

1. The frequency of statin intolerance may be best determined from the combined results of observational studies and prospective randomized clinical trials.

2. Development of a validated index of statin muscle intolerance is an important early goal for research.

3. The following design elements for clinical trials should be strongly considered: (a) statin tolerance as the primary end point; (b) randomized, blinded comparison of statin vs placebo medication; and (c) recruitment of patients with a personal history of statin intolerance.

4. Alternative strategies for achieving LDL-C–lowering goals should be investigated using varying combinations of statin and nonstatin drugs.

5. In addition to the foregoing, research on the causes, impact, and possible amelioration of statin intolerance should receive increased attention. Properly designed randomized trials should assess whether supplementation with vitamin D, coenzyme Q10, and other potential therapies may improve statin tolerability.

Guyton JR et al. J Clin Lipid 2014 8: S72-S81