Statin Safety: What Every Health Care Provider Needs to Know

Carl E. Orringer, MD, FACC, FNLA
Associate Professor of Medicine
University of Miami Miller School of Medicine

Disclosures

• Served on sitagliptin Cardiovascular Adjudication Committee for Merck (completed March 2014)

Importance of Statin Safety

• Statins are the most widely prescribed category of medications in the United States
• Because of their demonstrated benefits in ASCVD risk reduction, their use has been advocated by all major cardiovascular prevention guidelines
• Use of high-intensity statins has been documented to be associated with the greatest degree of risk reduction
• Because of their widespread use, safety considerations are of paramount importance

Jacobson TA. Journal of Clinical Lipidology 2014;8:S1-4
Limitations of Randomized Controlled Trials for Assessment of Statin Safety

- Exclusion of patients with multiple comorbidities
- Exclusion of patients with previously documented statin intolerance
- Frequent lack of designation of active versus passive inquiry methods about harm
- Absence of validated instruments for symptom assessment

Broad-Based Evidence to Consider

- Observational and clinical epidemiologic studies
- FDA adverse event reporting systems
- Meta-analyses of clinical trials
- Analyses of large health care data bases
- Case reports

2014 NLA Statin Safety Task Force

Journal of Clinical Lipidology 2014;8:S1-81
Statins and Cognitive Dysfunction

- Multiple case reports and data from 2 RCT and 1 challenge-de-challenge study suggested a possible association between statins and cognitive dysfunction.
- In 2012 US FDA expanded the warning label of all statins to include the statement that statins may contribute to "... notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy."

Ann Pharmacother 2012;46:549–57
http://www.fda.gov/drugs/drugsafety/ucm293101.htm

NLA Statin Cognitive Safety Task Force: 2014 Update: Key Questions

- Should a baseline cognitive assessment be performed before beginning a statin?
  - No. Strength of Recommendation (SOR): Expert Opinion (E); Quality of Evidence (QOE): Low
- Are statins as a class associated with adverse effects on cognition?
  - No. SOR: Strong (A); QOE: Low to moderate

Rojas-Fernandez CH et al. Journal of Clinical Lipidology 2014;8:S5-S16

NLA Statin Cognitive Safety Task Force: 2014 Update: Key Questions

- What should the provider do if a patient reports cognitive symptoms after beginning a statin?
  - Obtain cognitive testing
  - Rule out other potential contributors
  - Assess risk of stopping statin
  - Based upon individual characteristics, consider lowering dose or stopping statin to assess for reversibility and restarting an alternative statin

- SOR: Expert Opinion; QOE: Low

Rojas-Fernandez CH et al. Journal of Clinical Lipidology 2014;8:S5-S16
Statin therapy is sometimes associated with an elevation in liver enzymes

In 2012 the FDA revised statin labeling to remove the need for periodic monitoring of liver enzymes in patients taking statins, as serious liver injury is rare and unpredictable in individual patients and periodic liver enzyme measurement is not effective in detecting or preventing serious liver injury.

The FDA recommends measurement of liver enzymes before starting a statin and as clinically indicated thereafter.

http://www.fda.gov/drugs/drugsafety/ucm293101.htm

NLA Statin Liver Safety Task Force: 2014 Update: Key Questions

- Have any unexpected safety concerns arisen since the FDA’s change in liver enzyme monitoring recommendations?
  - No; SOR: A; QOE: Low

- Should baseline liver enzymes be obtained before starting statin therapy?
  - Yes; SOR: E; QOE: Low

- Are statins safe in patients with non-alcoholic fatty liver disease?
  - Yes; SOR: B (moderate); QOE: Moderate

Bays H et al. Journal of Clinical Lipidology 2014;8:S47-57

NLA Statin Liver Safety Task Force: 2014 Update: Key Questions

- Do statins have drug interactions with medications used to treat infections such as hepatitis B or C that require change in statins, change in dosing or change in anti-viral regimen dosing?
  - Yes; SOR: A; QOE: High

- Can statins be safely used in liver transplant recipients?
  - Yes; SOR: C (weak); QOE: Low

- Can statins be safely used in patients with autoimmune hepatitis?
  - Yes; SOR: E; QOE: Low

Bays H et al. Journal of Clinical Lipidology 2014;8:S47-57
Statins and Diabetes

• Examination of data from RCT’s revealed a small, but statistically significant increase in the incidence of newly diagnosed type 2 DM in patients treated with statin therapy
• Based on this finding the FDA in 2012 added a statement to the label of statins indicating that increases in HgbA1C and glucose levels have been reported with statin use

Statins and Diabetes
Magnitude of Risk and Significance

• Meta-analysis of 13 RCT of statin therapy vs. placebo (N=91,140) in pts. without DM at baseline showed weighted odds ratio for new onset DM of 1.09 (95% CI 1.02-1.17)
• NNT over 4 years to produce 1 new case of DM was 255
• Using CTT data, treating 255 patients with statin to lower LDL-C by 39 mg/dL would prevent 5.4 CHD events over 4 years

NLA Diabetes Statin Safety Task Force

• What is the impact of statin therapy on glycemic control?
  – If there is an adverse effect it is small (≤0.3% increase in HgbA1C)
  – New diabetes occurs only in those with pre-existing risk factors for DM (glucose >100 mg/dL, TG >150 mg/dL, BMI >30 kg/m2, or history of HBP)
  – Risk for DM has potential for attenuation based upon improved glycemic control
  • SOR: E; QOE: Low
High Intensity Statins and DM Risk

- Meta-analysis of 5 RCT (N=32,572) using high intensity versus moderate intensity statin on new DM risk showed weighted odds ratio of 1.12 (95% CI 1.04-1.22)
- NNT over 4 years to produce 1 new case of DM was 498
- Use of high-intensity versus moderate intensity statin therapy would prevent 3.2 CVD events for every 1 excess case of DM

NLA Statin Muscle Task Force
2014 Update

- Myalgia
  - Unexplained muscle discomfort with normal CK
- Myopathy
  - Muscle weakness without pain ± CK elevation
- Myositis
  - Muscle inflammation
- Myonecrosis
  - Muscle enzyme elevation with CK elevation ≥3X ULN for age, sex and race
- Myonecrosis with myoglobinuria or acute renal failure
  - Increase in serum creatinine ≥0.5 mg/dL (rhabdomyolysis)

Factors That Increase the Risk of Statin-Induced Myopathy

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

Rosenson et al. Journal of Clinical Lipidology 2014;8:S58-71
2014 Muscle Safety Expert Panel

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

Strength of Recommendation:
- 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: (S58-71)

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Muscle Safety Expert Panel

<table>
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<tr>
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<tbody>
<tr>
<td>5. Are there recommendations when to obtain a muscle biopsy in patients with statin-associated muscle symptoms?</td>
<td>YES (A)</td>
</tr>
<tr>
<td>6. Can patients who are initially intolerant to one statin generally tolerate a different statin?</td>
<td>YES (B)</td>
</tr>
<tr>
<td>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?</td>
<td>NO (E)</td>
</tr>
</tbody>
</table>

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Indications for Muscle Biopsy

NLA Statin Intolerance Task Force 2014 Update

• Definition
  – 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
NLA Expert Panel on Statin Intolerance

<table>
<thead>
<tr>
<th>Question</th>
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<tr>
<td>1. Does statin intolerance exist?</td>
<td>YES [A]</td>
</tr>
<tr>
<td>2. Are statins generally well tolerated and safe?</td>
<td>YES [A]</td>
</tr>
<tr>
<td>3. Do large randomized trials provide reliable estimates of statin intolerance?</td>
<td>NO [E]</td>
</tr>
<tr>
<td>4. Is statin intolerance best-defined in the context of patient-centered medicine?</td>
<td>YES [E]</td>
</tr>
</tbody>
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**Question Strength**
- A: Strong; B: Moderate; C: Weak; D: Recommended Against; E: Expert Opinion; N: No recommendation for or against


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NLA Expert Panel on Statin Intolerance

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

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


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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.