Update on Statins

**Presenters**

Kristin Weitzel, PharmD, CDE, FAPhA
Editor-in-Chief
APhA DrugInfoLine
Associate Director, UF Health Personalized Medicine Program
University of Florida, College of Pharmacy
Gainesville, FL

Amber L. Briggs, PharmD, BC-ADM, CGP, BCPS, FASCP
Clinical Pharmacist/Pharmacy Consultant
Central Peninsula Hospital
Section Advisor for Focus on Lipids Care
APhA DrugInfoLine
Soldotna, AK

Edward F. Foote, PharmD, FCCP, BCPS
Professor and Chair
Department of Pharmacy Practice
Nesbit College of Pharmacy and Nursing
Wilkes University
Section Advisor for Nephrology
APhA DrugInfoLine
Wilkes-Barre, PA

Charles S. Fredes, PharmD, DPA, FAPhA, FASCP, FASHP, FCCP
Professor of Clinical Pharmacy and Family Medicine
School of Pharmacy and Science
University of North Dakota
Section Advisor for Focus on Diabetes Care
APhA DrugInfoLine
Grand Forks, ND

Edward F. Foote, PharmD, FCCP, BCPS
Professor and Chair
Department of Pharmacy Practice
Nesbit College of Pharmacy and Nursing
Wilkes University
Section Advisor for Nephrology
APhA DrugInfoLine
Wilkes-Barre, PA

Allana Sucher, PharmD, BCPS
Associate Professor of Pharmacy Practice
Rueckert-Hartman College of Health Professions
School of Pharmacy
Regis University
Section Advisor for Infectious Diseases
APhA DrugInfoLine
Denver, CO

**Development**

This activity was developed by the American Pharmacists Association.
Accreditation Information

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education (CPE). This activity, Update on Statins, is approved for 1.0 hours of CPE credit (0.1 CEUs). The ACPE Universal Activity Number assigned by the accredited provider is: 0202-0000-13-214-L01-P.

To obtain CPE credit for this activity, participants will be required to actively participate in the entire webinar and complete an online assessment and evaluation located at www.pharmacist.com by November 22, 2013.

Initial Release Date: November 12, 2013
Target Audience: Pharmacists
ACPE Activity Type: Knowledge-Based
Learning Level: 1
Fee: There is no fee for this activity

Disclosures

• Daniel Streetman, PharmD declares he and his spouse are employees of Lexicomp, Inc.

• All other speakers and APhA’s editorial staff declares no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria. For complete staff disclosures, please see the Education and Accreditation Information section at www.pharmacist.com/education.

Learning Objectives

• Summarize recently published medical literature in the area of dyslipidemia pharmacotherapy.

• Describe the clinical significance and appropriate management of statin-macrolide drug interactions.

• Identify common causes of statin nonadherence and strategies to help patients resume statins.

• Describe steps to avoid acute kidney injury with use of high-potency statins.
What to expect during the webinar…

• Section 1: Statins and drug interactions  
  – Amber Briggs, Allana Sucher, and Dan Streetman

• Section 2: Effects of nonadherence to statins and role of myopathy  
  – Amber Briggs, Charlie Ponte

• Section 3: Renal effects of statins  
  – Amber Briggs, Edward Foote

What to expect during the webinar…

• Expert panel will discuss patient care implications of each study and take questions at the end of each section.

• Submit questions throughout the webinar using the question function on the GoToWebinar panel.

• If you think of a question afterwards, submit it and we’ll try to get to it at the end of the webinar.

LET’S GET STARTED!
Update on Statin Drug Interactions

- Nearly 20% of individuals filling a statin Rx also had active prescriptions for an interacting drug with an existing warning or precaution.
- Over 1.5 million patients each year are dispensed a statin coprescribed with a contraindicated drug.


FDA Drug Safety Alert - 2011

http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm#aihp
All statins are not created equally

<table>
<thead>
<tr>
<th>Statin</th>
<th>Prodrug?</th>
<th>t1/2 (hrs)</th>
<th>Lipophilic?</th>
<th>Interacting Metabolic Path</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Yes</td>
<td>~3</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Yes</td>
<td>2-3</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td>15-30</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td>~21</td>
<td></td>
<td>Mostly through CYP2C9</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>0.5-2</td>
<td></td>
<td></td>
<td>CYP2C9 (75%)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1-3</td>
<td></td>
<td></td>
<td>Several pathways; &lt;1% through CYP enzymes</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td></td>
<td>~12</td>
<td>Yes</td>
<td>Mostly through CYP3A4, CYP2C9</td>
</tr>
</tbody>
</table>
All statins are not created equally

<table>
<thead>
<tr>
<th>Statin</th>
<th>Prodrug?</th>
<th>T1/2 (hrs)</th>
<th>Lipophilic?</th>
<th>Interacting Metabolic Path</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Yes</td>
<td>~3</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Yes</td>
<td>2-3</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Abiravastin</td>
<td>15-30</td>
<td>Yes</td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>~21</td>
<td>Minimal</td>
<td>CYP2C9</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>0.5-2</td>
<td>CYP2C9 (75%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1-3</td>
<td>Several</td>
<td>CYP2C9, CYP2C8, CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>~12</td>
<td>Yes</td>
<td>CYP2C9, CYP3A4</td>
<td></td>
</tr>
</tbody>
</table>

Clinical impact of drug interactions

- Increase risk of dose-dependent adverse effects such as rhabdomyolysis
  - ~60% of cases of statin-related rhabdomyolysis linked to drug interactions
  - Number needed to harm for rhabdomyolysis at 1 year
    - Statin monotherapy: 23,727
    - Statin + fibrate: 485
- Macroline-statin interaction
  - Clarithromycin and erythromycin – CYP3A4 inhibitors
  - Life-threatening reports of rhabdo with this combination
Patel, et al

• Population-based cohort study:
  – Adults aged 65 years and older from 2003 to 2010
  – Simvastatin, atorvastatin, or lovastatin
  – Clarithromycin, erythromycin, azithromycin

• Results:
  – Compared to azithromycin, use of one of these statins with clarithromycin or erythromycin associated with increased risk for:
    • Hospitalization with rhabdomyolysis
    • Acute kidney injury
    • All-cause mortality


Patel, et al

• This is a known interaction but use of these drugs is common and unintentional combination therapy is likely to be seen in practice

• Notable results
  – Nearly 75% of patients used atorvastatin
  – 60% used “lower-dose” statins
    • Atorvastatin <20 mg
    • Lovastatin <80 mg
    • Simvastatin <80 mg

Patel, et al

• Author recommendations:
  – Discontinue CYP3A4-metabolized statin during antibiotic therapy
  – Use a non-CYP3A4-metabolized statin
  – Choose a different antibiotic when clinically appropriate

Panel Discussion

• Amber L. Briggs, PharmD, BC-ADM, CGP, BCPS, FASCP
• Allana Sucher, PharmD, BCPS
• Daniel S. Streetman, PharmD, MS
Zhang et al

- Retrospective cohort study of >100,000 adults who received a statin over an 8-year period to determine why statins were discontinued
  - 17% of patients experienced a statin-related event, with myalgia or myopathy as most common event
  - Of these patients, ~60% discontinued statin at least temporarily
  - In patients who were re-challenged, 92% were still taking the statin 12 months after statin-related event

Zhang et al

- Clinical implications
  - Statins are commonly discontinued in clinical care
  - 17.4% rate of statin-reported events higher than 5% to 10% normally described in RCTs
  - Musculoskeletal symptoms comprised 40% of statin-related events
  - Most patients who were rechallenged were able to tolerate the statin

Statin Adverse Effects

- Muscle complaints/musculoskeletal pain
- Liver injury
- Neurological effects
  - Hemorrhagic stroke
  - Cognitive decline
  - Peripheral neuropathy
- Increased risk of diabetes
- Renal effects
Statins and Muscle Complaints

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy</td>
<td>Any disease of the muscles</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Muscle ache or weakness without CK elevations</td>
</tr>
<tr>
<td>Myositis</td>
<td>Muscle symptoms with CK elevation</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Muscle symptoms with significant CK elevation (&gt;10 times ULN) and creatinine elevation</td>
</tr>
</tbody>
</table>


Statins and Muscle Complaints

- Clinical trials – falsely low
  - Myopathy: 1.5% to 5%
  - Muscle pain with CK > 10 times ULN: 0.2% to 0.5%
  - Patients at highest risk often excluded
    - History of statin intolerance, muscle pain, or lab abnormalities with statins
    - Advanced age
    - Comorbidities, multiple medications
- Actual use
  - Up to 22% of patients have muscle complaints

Moving beyond muscle complaints with statins

<table>
<thead>
<tr>
<th>Most Evidence</th>
<th>Least Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative dosing (once every other day or longer)</td>
<td>~70% tolerated; rosuvastatin, atorvastatin</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Limited evidence</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Inconsistent evidence</td>
</tr>
<tr>
<td>Switching statins</td>
<td>Inconsistent evidence</td>
</tr>
</tbody>
</table>


Panel Discussion

- Amber L. Briggs, PharmD, BC-ADM, CGP, BCPS, FASCP
- Charles D. Ponte, PharmD, DPNAP, FAADE, FAPhA, FASHP, FCCP
Dormuth et al

• Methods
  – Retrospective, nested case-control study including more than 2,000,000 adults
  – Each person with acute kidney injury matched to 10 controls
  – High-potency statins (10 mg rosuvastatin, 20 mg atorvastatin, 40 mg simvastatin)

• Results
  – Patients on high-potency statins 34% more likely to be hospitalized for acute kidney injury than those on low-potency statins in first 120 days

Dormuth et al. BMJ. 2013;346:f880.

Editorialists wrote...

study results support a significant risk with statins, and “indicate that clinicians should use low potency statins whenever possible to provide cardiovascular benefits without the increased risk of acute kidney injury.”

Where do these findings fit into the literature?

• Rosuvastatin
  – Early evidence of renal disease/proteinuria at high doses
  – FDA review of all submissions for statins
    ▪ Statins do not cause renal toxicity, but are associated with proteinuria and/or hematuria

• JUPITER study
  – Increase in GFR with rosuvastatin

• Other studies are reassuring
  – ALERT, SHARP 4D, AURORA, PLANET

Bays H. Am J Cardiol. 2006;97:6C.
Where do these findings fit into the literature?

- Renal Expert Panel of the National Lipid Association:
  - Statins do not cause acute kidney injury (except in rhabdomyolysis), renal tubular or glomerular damage, hematuria, or chronic kidney disease
  - Routine monitoring of proteinuria or kidney function is not warranted

Kasiske BL et al. Am J Cardiol. 2006;97:82C.

Panel Discussion

- Amber L. Briggs, PharmD, BC-ADM, CGP, BCPS, FASCP
- Edward F. Foote, PharmD, FCCP, BCPS

Summary

- Statins are complex medications that are usually well tolerated
  - Drug interactions
  - Potential adverse effects

- Pharmacists play a key role in statin therapy
  - Promoting adherence and persistence
  - Identifying strategies to overcome challenges
  - Educating patients and providers
How to claim CPE Credit

- Record Attendance Code: Provided during webinar
- Please visit: http://www.pharmacist.com/live-activities and select the Claim Credit link for this activity
- You will need a pharmacist.com username and password
- Select Enroll Now or Add to Cart from the left navigation and successfully complete the Assessment (select correct attendance code), Learning Evaluation and Activity Evaluation for access to your statement of credit. You will need to provide your NABP e-profile ID number to access your statement of credit.
- You must claim credit by November 26, 2013. No credit will be awarded after that date.

Update on Statins