The Muscle and Statin Safety
Disclosure of Affiliations

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• Cardiology Associates of N. Mississippi

• No disclosures
Is my Patient FOS?

Failing on Statin?
## Terminology to Describe Muscle Injury

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>Muscle ache or weakness <em>without</em> creatine kinase (CK) elevation(^1)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Muscle symptoms <em>with</em> increased CK levels &gt;10 x ULN(^2)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Muscle symptoms with marked CK elevation (typically &gt;10 x ULN) and with creatinine elevation (usually with brown urine and urinary myoglobin)(^1)</td>
</tr>
</tbody>
</table>

\(^1\) Pasternak RC et al. *Circulation*. 2002;106:1024-1028  
\(^2\) Evans M, Rees A. *Drug Saf*. 2002;25:649-663
Rates of Statin Myopathy/Rhabdomyolysis

DATA SOURCES:

• Case Reports
• Cohort Studies
• Randomized Clinical Trials
• Adverse Event Reporting System (AERS)
• Managed Care Claims Databases
## Incidence of Muscle AEs

<table>
<thead>
<tr>
<th>Muscle AE</th>
<th>Incidence above placebo (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>1,500 to 3,000</td>
</tr>
<tr>
<td>Myopathy (Sx + CK)</td>
<td>5</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Law M, Rudnicka AR. *Am J Cardiol.* 2006;97:52C-60C
Muscle Adverse Events with Atorvastatin in Randomized controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Atorva Dose</th>
<th>N</th>
<th>CPK + Muscle Sx</th>
<th>Rhabdo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT</td>
<td>10 mg</td>
<td>5168</td>
<td>Same as Placebo</td>
<td>1 (0.02%)</td>
</tr>
<tr>
<td>AVERT</td>
<td>80 mg</td>
<td>164</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GREACE</td>
<td>10-80 mg</td>
<td>800</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MIRACL</td>
<td>80 mg</td>
<td>1526</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>80 mg</td>
<td>2099</td>
<td>0*</td>
<td>0</td>
</tr>
<tr>
<td>TNT</td>
<td>10/80 mg</td>
<td>5006/4995</td>
<td>0</td>
<td>3/2 (0.05%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>19,758</td>
<td></td>
<td>0.03%</td>
</tr>
</tbody>
</table>

*CK changes only = 69 (3.3%)

## Muscle AEs with Simvastatin in RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Simva Dose</th>
<th>n</th>
<th>CPK +/- Muscle Sx</th>
<th># Rhabdo Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>20/40 mg</td>
<td>2221</td>
<td>6 (0.05%)</td>
<td>1 (0.05%)</td>
</tr>
<tr>
<td>HPS</td>
<td>40 mg</td>
<td>10,269</td>
<td>5 (0.05%)</td>
<td>5 (0.05%)</td>
</tr>
<tr>
<td>A to Z</td>
<td>80 mg</td>
<td>2265</td>
<td>6 (0.3%)</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>14,755</td>
<td></td>
<td>0.06%</td>
</tr>
</tbody>
</table>

## Muscle Adverse Events with Rosuvastatin
Reported in New Drug Application

(Doses 5 – 40 mg)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Pts</th>
<th>CK &gt; 10x ULN &amp; Muscle Sx</th>
<th>Rhabdomyolysis CK &gt; 10x ULN &amp; Renal Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>5</td>
<td>1,324</td>
<td>3</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>8,325</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>20</td>
<td>4,651</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>40</td>
<td>4,450</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>All doses</td>
<td>13,395</td>
<td>29</td>
<td>0.2</td>
</tr>
</tbody>
</table>

(Doses 5 – 40 mg)
Pravastatin and Fluvastatin — Muscle Safety

- Rhabdomyolysis
  - Clinical trials — 0 cases of rhabdo
- CK >10 times ULN
  - Fluvastatin- 17 (0.3%) out of 8975 pts experienced CK >10 times ULN
  - Pravastatin- 15 (0.08%) out of 19,592 experienced CK >10 times ULN

Law M, Rudnicka AR. *Am J Cardiol.* 2006;97:52C-60C
Rates of Statin Myopathy/Rhabdomyolysis

DATA SOURCES:

• Case Reports
• Cohort Studies
• Randomized Clinical Trials
• Adverse Event Reporting System (AERS)
• Managed Care Claims Databases
# Reported Cases of Fatal Rhabdomyolysis and Statin Prescriptions in the US*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lova</th>
<th>Prava</th>
<th>Simva</th>
<th>Fluva</th>
<th>Atorva</th>
<th>Ceriva</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal cases of rhabdomyolysis</td>
<td>19</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>6</td>
<td>31</td>
<td>73</td>
</tr>
<tr>
<td>Number of prescriptions (millions†)</td>
<td>99</td>
<td>81</td>
<td>116</td>
<td>37</td>
<td>140</td>
<td>10</td>
<td>484</td>
</tr>
<tr>
<td>Reporting rate (per 1 million prescriptions)</td>
<td>0.19</td>
<td>0.04</td>
<td>0.12</td>
<td>0</td>
<td>0.04</td>
<td>3.16</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Since the product launch; †rounded to the nearest million

Reporting Rates of Rhabdomyolysis With Statin Therapy

Semiannual Reporting Rates for All Reports of Rhabdomyolysis

**US Cases***

- Cerivastatin
- Total Statin Class (including cerivastatin)
- Lovastatin
- Simvastatin
- Total Statin Class (excluding cerivastatin)
- Atorvastatin
- Fluvastatin
- Pravastatin
- Rosuvastatin

**Worldwide Cases‡**

*Expedited, periodic, and spontaneous reports.
**US reporting rate for all statins based on FDA Adverse Events Reporting System made available through Freedom of Information Act divided by US prescribing data supplied by IMS through February 2003.
†Cerivastatin reports received after September 1, 2001, are excluded.
‡Global reporting rate for rosuvastatin based on case counts of rhabdomyolysis within AstraZeneca global drug safety database divided by estimated worldwide prescriptions through February 2004. Total prescriptions based on IMS data from US, Canada, UK, and the Netherlands; rest of world prescriptions based on actual sales calculations.
## AERS Reports of Serious Rhabdomyolysis for Statins

<table>
<thead>
<tr>
<th>Category</th>
<th>All Statins</th>
<th>Atorva</th>
<th>Fluva</th>
<th>Lova</th>
<th>Prava</th>
<th>Rosuva</th>
<th>Simva</th>
<th>Vytorin</th>
<th>Ezet</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Spontaneous Serious Rhabdomyolysis</td>
<td>1362</td>
<td>348</td>
<td>56</td>
<td>45</td>
<td>75</td>
<td>103</td>
<td>760</td>
<td>2</td>
<td>68</td>
</tr>
<tr>
<td>Total Prescriptions (Millions)</td>
<td>383.9</td>
<td>209.5</td>
<td>16.3</td>
<td>16.7</td>
<td>46.0</td>
<td>7.61</td>
<td>87.74</td>
<td>0.80</td>
<td>15.2</td>
</tr>
<tr>
<td>Reporting Rate (Per Million Prescriptions)</td>
<td>3.55</td>
<td>1.66</td>
<td>3.50</td>
<td>2.65</td>
<td>1.63</td>
<td>12.88</td>
<td>8.64</td>
<td>2.00</td>
<td>4.53</td>
</tr>
<tr>
<td>Total AE Reports</td>
<td>10842</td>
<td>3713</td>
<td>517</td>
<td>251</td>
<td>965</td>
<td>2562</td>
<td>3072</td>
<td>35</td>
<td>920</td>
</tr>
<tr>
<td>Proportion Reporting Rate</td>
<td>0.13</td>
<td>0.09</td>
<td>0.11</td>
<td>0.18</td>
<td>0.08</td>
<td>0.04</td>
<td>0.25</td>
<td>0.06</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Davidson MH et al. *Am J Cardiol.* 2006;97:32C-43C
Rates of Statin Myopathy/Rhabdomyolysis

DATA SOURCES:

• Case Reports
• Cohort Studies
• Randomized Clinical Trials
• Adverse Event Reporting System (AERS)
• Managed Care Claims Databases
Incidence of Rhabdomyolysis

Managed care claims database, 42 month follow-up, 6 month minimal use, 875,000 pts

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient-Years</th>
<th>Incidence Rates (per 10,000 person-years)* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>261,567</td>
<td>2.4 (1.9-3.1)</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>12,635</td>
<td>1.6 (0.2-5.7)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>26,122</td>
<td>2.3 (0.8-4.5)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>64,254</td>
<td>3.4 (2.1-5.2)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>8,213</td>
<td>2.4 (0.3-8.8)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>54,394</td>
<td>3.5 (2.1-5.6)</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>4,719</td>
<td>10.6 (3.4-24.7)</td>
</tr>
</tbody>
</table>

*Incidence of rhabdomyolysis (ICD-9: 791.3x , 728.88, 728.89 [myoglobinuria, rhabdomyolysis, other disorders in the inpatient setting]) per 10,000 patient-years of therapy

Cziraky MJ et al. *Am J Cardiol.* 2006;97:61C-68C
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</td>
</tr>
<tr>
<td>Female sex</td>
<td>Lipophilicity</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>High bioavailability</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>Limited protein binding</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Potential for drug-drug interactions metabolized by CYP pathways (particularly CYP450 3A4)</td>
</tr>
<tr>
<td>Diet (i.e. grapefruit juice)</td>
<td></td>
</tr>
<tr>
<td>Polypharmacy</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Rosenson RS. *Am J Med.* 2004;116:408-416
Serum Drug Concentrations Affect Risk of Myopathy and Rhabdomyolysis

• Risk of statin-associated myopathy and rhabdomyolysis increases as statin serum concentrations rise

• Anything that raises statin serum concentrations can affect risk of rhabdomyolysis

Elevations in CK and LDL-C Reduction

### Human Cytochrome P450 Isoenzymes Known to Oxidize Clinically Used Drugs

<table>
<thead>
<tr>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprenolol</td>
<td>Diazepam</td>
<td>Amitriptyline</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Ibobrufen</td>
<td>Codeine</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td><strong>Fluvastatin</strong></td>
<td>Mephenytoin</td>
<td>Dextromethorphan</td>
<td>Cyclosporine A</td>
</tr>
<tr>
<td>Hexobarbital</td>
<td>Methylophenobarbital</td>
<td>Flecainide</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>N-desmethyl diazepam</td>
<td>Omeprazol</td>
<td>Metoprolol</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Proguanil</td>
<td>Nortriptyline</td>
<td>Mibefradil</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Phenoytoin</td>
<td>Perphenazine</td>
<td>Mibefradil</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>Propanolol</td>
<td>Midazolam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thioridazine</td>
<td>Nefazodone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sildefanil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sildefanil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simvastatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Verapamal</td>
</tr>
</tbody>
</table>

### 38% of Rhabdomyolysis Cases Associated With Concomitant Fibrates

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mibefradil</td>
<td>2%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>38%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4%</td>
</tr>
<tr>
<td>Macrolide Antibiotics</td>
<td>3%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5%</td>
</tr>
<tr>
<td>Azole Antifungals</td>
<td>1%</td>
</tr>
</tbody>
</table>

Thompson PD et al. *JAMA.* 2003;289:1681-1690
# Statin/Fibrate Combination Therapy: Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th></th>
<th>GEMFIBROZIL</th>
<th>FENOFIBRATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>↑ in C&lt;sub&gt;max&lt;/sub&gt; (expected)</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>↑ in C&lt;sub&gt;max&lt;/sub&gt; by 2-fold</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Pravastatin</strong></td>
<td>↑ in C&lt;sub&gt;max&lt;/sub&gt; by 2-fold</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Rosuvastatin</strong></td>
<td>↑ in C&lt;sub&gt;max&lt;/sub&gt; by 2-fold</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Fluvastatin</strong></td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Lovastatin</strong></td>
<td>↑ in C&lt;sub&gt;max&lt;/sub&gt; by 2.8-fold</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Cerivastatin</strong></td>
<td>↑ in C&lt;sub&gt;max&lt;/sub&gt; by 2-3–fold</td>
<td>No effect</td>
</tr>
</tbody>
</table>

Potential Mechanisms of Statin-Induced Myopathy and Rhabdomyolysis

THEORY 1: Blocking cholesterol synthesis reduces cholesterol content of skeletal muscle membranes, making them unstable

THEORY 2: Statins lead to a reduced synthesis of ubiquinone (coenzyme Q10), an essential element of mitochondria, thereby disturbing normal cell respiration

THEORY 3: Reduction of small GTP-binding proteins leads to muscle apoptosis

Thompson PD et al. JAMA. 2003;289:1681-1690
Recommendations from the NLA Statin Safety Task Force for Muscle Issues

PATIENT MONITORING

• Obtain baseline CK levels in high risk patients (renal dysfunction, liver disease, polypharmacy), optional for others

• Routine CK levels in asymptomatic patients not recommended

• Symptom monitoring with CK measurement only in symptomatic patients recommended

• Rule out other etiologies in symptomatic patients or asymptomatic CK elevation (hypothyroidism, trauma, falls, seizures, infection, physical activity)

• Exacerbating factors should be considered (grapefruit juice consumption, concomitant medications, herbal remedies)

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 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
Recommended New Definitions

- **Myopathy**
  
  * Complaints of myalgia, weakness, cramps
  + CK >10 times ULN (preferably repeated)

- **Rhabdomyolysis**
  
  * CK >10,000 IU/L
  OR a CK >10 times ULN †
  + an elevation in serum creatinine, or the need for medical intervention with IV hydration

* Intolerable muscle symptoms with CK <10 times ULN may be considered myopathy
† CK value <10 times ULN may be obtained depending on the temporal relationship

McKenney JM et al. *Am J Cardiol.* 2006;97:89C-94C
Management of Intolerable Muscle Symptoms on Statin Therapy

- Low dose statins (5mg / day)
- Alternative-day statin dosing (eg, Rosuvastatin 5, 10)
- Hydrophillic statins (Rosuva, Prava, Fluvastatin) Theoretical
- Fluvastatin XL (+/- ezetimibe) (Stein E. Am J Cardiol 2008; 101:490-496)
- Non-statin therapy (ezetimibe, bile acid sequestrants or niacin)
- Plant Sterols (~5-10% LDL reduction)
- Vitamin D supplementation (anectodal)
- Coenzyme Q10 – unproven
- Red rice yeast – contains very low dose lovastatin
Alternative Statin Dosing

• Before trying alternate day statin dosing
  1. Try same of different statin at a lower dose
  2. Consider using low-dose rosuvastatin (5mg)
  3. Consider other hydrophillic statins
     (pravastatin, fluvastatin)
Vitamin D

- Low vitamin D levels associated with myalgia
- Low vitamin D levels associated with reduced muscle function
- A specific nuclear receptor for vitamin D has been isolated in myocytes
Vitamin D

• In 128 statin patients who experienced myalgia

82 of 128 patients had Vitamin D levels <32ng/ml

38 of 82 continued statins and agreed to therapy with ergocalciferol 50,000 units / week for 3 months

35 of 38 patients (98%) became myalgia free

Study limitations: non randomized, unblinded and had no placebo control
Coenzyme Q10 (Ubiquinone)

- Statins have been shown to reduced plasma / serum levels of Co-Q10
- However statin treatment does not consistently reduce intramuscular Co-Q10 levels
- There are only limited data demonstrating reduction of myopathic pain with Co-Q10 therapy. Most studies demonstrate no benefit to Co-Q10 therapy
- Co-Q10 prophylactic or acute treatment cannot be formally recommended at this time
The Future:

• PCSK9 inhibitors
  – 3 compounds under development
  – Injectable monthly or bimonthly
  – In isolation may lower cholesterol 50%
  – May also lower Lpa
  – Clinical trials underway (Spire, Fourier)
CONCLUSIONS

• Statins are as safe as aspirin and at least as beneficial, if not more so, in reducing CVD risk

• If a million at-risk patients with high cholesterol were treated with a statin:
  • about 10,000 heart attacks or strokes could be prevented each year
  • 1-2 patients might experience a serious side effect

• The problem is not that too many patients are having adverse effects with statins – the problem is that too many people may be avoiding statins because of an unnecessary fear of adverse effects.
Conclusions

• Alternate (every other) day dosing or weekly dosing are effective options for lowering LDL levels in statin intolerant patients

• Nonstatin therapies such as ezetimibe, colesevelam, and niacin should be considered

• Vitamin D may be an option for some statin-intolerant patients, but well-designed clinical trials are needed to test this hypothesis

• Coenzyme Q10 has not been consistently shown to be effective in randomized trials