Optimizing Cholesterol Lowering Therapy in Patients who Report Statin Adverse Events

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• Honoraria: Akcea, Kowa

• Royalties: UpToDate, Inc.
Cumulative risk for MI, CHD events, and all-cause mortality following MI

- 24,566 Medicare beneficiaries ≥65.5 years of age who had a MI between 2007 and 2011 and filled a high intensity statin, beta-blocker, ACE-I or ARB, and prescription antiplatelet agent (i.e., intensively medically managed) within 30 days following hospital discharge.

- Calculated the incidence of MI, CHD events, and all-cause mortality from 30 days after hospital discharge through December 31, 2012.

- Event rates for these beneficiaries were compared to two groups: 49,132 age, race-ethnicity, sex, and calendar-year matched beneficiaries each from:
  - (1) The general Medicare population
  - (2) Medicare beneficiaries with diabetes

Despite intensive medical management, substantial residual risk remains following MI

Clinical benefit of lower LDL-C is determined by absolute exposure to lower LDL

## Underutilization of statin therapy for secondary prevention

<table>
<thead>
<tr>
<th>Registry</th>
<th>Years</th>
<th>N</th>
<th>Statin prescribed</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINNACLE¹</td>
<td>2008-2012</td>
<td>1,029,633</td>
<td>72%†</td>
<td>Adults with confirmed ASCVD</td>
</tr>
<tr>
<td>TRIUMPH²</td>
<td>2005-2008</td>
<td>4,271</td>
<td>91% ± 23%‡</td>
<td>Adults hospitalized with ACS, discharged alive, no contraindications to statin</td>
</tr>
<tr>
<td>PREMIER + TRIUMPH³</td>
<td>2003-2008</td>
<td>6,748</td>
<td>88%§/33%‖</td>
<td>Adults hospitalized with ACS, discharged alive</td>
</tr>
<tr>
<td>GWTG⁴</td>
<td>2005-2009</td>
<td>65,396</td>
<td>89%†/38%*</td>
<td>Adults hospitalized with ACS, prescribed lipid-lowering therapy at discharge</td>
</tr>
</tbody>
</table>

† Any statin therapy  
‡ Maximally potent statin at hospital discharge (rosuvastatin 20–40 mg or atorvastatin 80 mg)  
§ Any statin therapy at hospital discharge  
‖ Statin at ≥75% of the target dose at hospital discharge  
* Intensive lipid-lowering therapy

What characteristics are associated with continued high adherence to statin therapy?

a. Participation in cardiac rehabilitation
b. More frequent outpatient cardiology visits
c. Low income subsidy
d. Use of internet
e. Choice a, b and c

Correct answer: d

Change in statin intensity pre- and post-hospitalization for acute coronary syndrome, 2007-2011

PRE-HOSPITALIZATION

16.8% High-intensity statin

53.1% Low/moderate-intensity statin

30.1% No statin

Hospitalization for ACS (MI or unstable angina requiring coronary intervention) in Medicare beneficiaries, <75 years

Evidence-based guideline therapy

Biomarker-(LDL-C) directed therapy or insufficient post-hospitalization transition

POST-HOSPITALIZATION

27.0% High-intensity statin

11.5% change over 365 days post discharge

73.0% Low/moderate-intensity statin

88.5% did not change over 365 days post discharge

No change in therapy

Type of statin filled after hospital discharge for myocardial infarction, 2011-2014

MarketScan beneficiaries
<65 years of age

Medicare beneficiaries
66–75 years of age

Trends in the use of high-intensity statin therapy

## Adherence to statin therapy for secondary prevention of CAD in registry databases

<table>
<thead>
<tr>
<th>Registry</th>
<th>Years</th>
<th>N</th>
<th>Statin adherence</th>
<th>Inclusion criteria</th>
<th>Follow-Up (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMIER¹</td>
<td>2003–4</td>
<td>2,498</td>
<td>78.5%*</td>
<td>Adults hospitalized with ACS, discharged alive, no contraindications to statin</td>
<td>1</td>
</tr>
<tr>
<td>KPCO²</td>
<td>2000–5</td>
<td>13,596</td>
<td>74%†</td>
<td>Patients in Kaiser CAD registry with prior MI, PCI, or CABG</td>
<td>4.1</td>
</tr>
<tr>
<td>CMS Chronic Condition Data Warehouse³</td>
<td>2007–9</td>
<td>2,695</td>
<td>63.8%‡</td>
<td>Medicare beneficiaries with CHD-related hospitalization, filled prescriptions for antihypertensive, initiation of statin therapy within 90 days of hospital discharge</td>
<td>1</td>
</tr>
<tr>
<td>Medicare Part D Enrolees⁴</td>
<td>2005–6</td>
<td>962,877</td>
<td>53.6%†</td>
<td>Medicare Part D enrollees with diabetes</td>
<td>0.5</td>
</tr>
<tr>
<td>PharmMetrics Patient Centric Database⁵</td>
<td>2003–5</td>
<td>11,331</td>
<td>50%§</td>
<td>Statin naïve adults with a prior cardiac event and ≥1 prescription for atorvastatin or simvastatin</td>
<td>0.75</td>
</tr>
<tr>
<td>MedStat MarketScan Commercial Claims and Encounters Database + Medicare Supplemental and Coordination of Benefit Database⁶</td>
<td>2000–2</td>
<td>5,548</td>
<td>61.4%</td>
<td>Patients who initiated statin treatment within 6 months of hospitalization for cardiovascular disease</td>
<td>1</td>
</tr>
</tbody>
</table>

* Interview with medication review  
† Proportion of days covered ≥80%  
‡ Proportion of days covered ≥50%  
§ Continuation without >60-day gap  
‖ Medication possession ratio ≥80%  
CAD, coronary artery disease

Adherence to High-Intensity Statins Following a Myocardial Infarction Hospitalization Among Medicare Beneficiaries

What are the healthcare consequences of statin downtitration/discontinuation?

a. Financial savings from reduced medication costs
b. Higher risk of cardiovascular events
c. Financial costs increase as a consequence of more outpatient visits/hospitalization costs
d. Choices: a, b, c
e. Choices: b, c

Correct answer: e
Side effects are commonly reported by people taking statins

- 16,362 currently active REGARDS participants
- 14,224 have completed the statin survey
- 7,803 reported having ever taken a statin
- 1,874 (24%) reported experiencing side effects
  - Of those experiencing side effects, 1,075 (57%) discontinued their statin
  - Of those who discontinued a statin, 73% did not want a rechallenge

## Statin-associated muscle symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On statin</td>
<td>On placebo</td>
<td></td>
</tr>
<tr>
<td>STOMP¹</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>NHANES²</td>
<td>22</td>
<td>17$</td>
<td></td>
</tr>
<tr>
<td>*CoQ10³</td>
<td>36</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>*GAUSS-3⁴</td>
<td>43</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Analysis of 42 clinical trials with 56,059 patients⁵</td>
<td>13</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

*Patients with a history of statin-associated muscle symptoms; §non-statin users

Nocebo effect – influence of blinding and unblinding on reported statin-related AEs

- ASCOT-LLA
  - Atorvastatin 10 mg qd versus matching placebo
  - 5.5 years’ follow-up

- During the blinded phase (median 3.3 years follow-up), there was no significant difference between atorvastatin and placebo in the proportion of patients reporting muscle-related symptoms
  - 2.03% vs 2.00% per annum

- However, during the unblinded phase (median 2.3 years follow-up), statin users reported a 41% excess of muscle-related symptoms compared with non-users ($P=0.006$)
  - 1.26% vs 1.00% per annum

- Muscle-related symptoms and statin intolerance have been attributed to a nocebo effect – subjective symptoms largely influenced by media hype about statins

Claims-based algorithm for the assessment of statin intolerance and clinical events

• Developed using claims data from 134,863 Medicare beneficiaries who initiated statin therapy between 2007 and 2013.

• Statin intolerance within 365 days after initiation based on clinical rationale and data availability.

• Those with statin intolerance were compared with those with high adherence to statins (proportion of days covered ≥80% following statin initiation).

Algorithm Definitions of Statin Intolerance

• **Definition 1:**
  1. Statin discontinuation with the initiation of ezetimibe;
  2. Initiation of ezetimibe within 7 days before or after down-titrating statin dose;
  3. A claim for rhabdomyolysis followed by statin down-titration discontinuation;
  4. An inpatient or outpatient claim for “adverse effect of an antihyperlipidemic agent” followed by statin down-titration or discontinuation; and
  5. Fills for ≥ 3 types of statins within one year.

• **Definition 2:**
  Included components of Definition 1 and down-titration of statin therapy.

• **Definition 3:**
  Included components of Definitions 1 and 2 and discontinuation of statin therapy.

Is Statin Intolerance Associated with Recurrent MI, CHD Events and Mortality?

• Medicare beneficiaries initiating moderate/high intensity statins after myocardial infarction (2007-2013).

• Exposure: statin intolerance by Definition 1 (n=1,741) versus high adherence to statins (n=55,567).

• Outcomes:
  - Recurrent myocardial infarction,
  - Coronary heart disease events, and
  - All-cause mortality.

• Medicare expenditures were also analyzed.

Is statin switch/down-titration/discontinuation (SDD) associated with recurrent MI, CHD events and mortality?

- Medicare beneficiaries initiating moderate/high intensity statins after MI (2007–2013)
- Exposure: statin SDD (n=1,741) versus high adherence to statins (n=55,567)
- Outcomes
  - Recurrent myocardial infarction
  - Coronary heart disease events
  - All-cause mortality

Composition of SDD group

- Switching between ≥3 types of statin within 1 year after initiation (59.3%)
- Switching from statins to ezetimibe monotherapy (17.0%)
- Having ICD-9 codes for rhabdomyolysis followed by statin down-titration or discontinuation (11.4%)
- Down-titrating statins and initiating ezetimibe (11.1%)
- Having ICD-9 codes for antihyperlipidemic adverse event followed by statin down-titration or discontinuation (1.2%)

Clinical outcomes associated with statin SDD

<table>
<thead>
<tr>
<th></th>
<th>High adherence (n=55,567)</th>
<th>Statin SDD (n=1,741)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrent myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>4,253</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>30.1 (29.2, 31.0)</td>
<td>41.1 (35.4, 46.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)*</td>
<td>1 (reference)</td>
<td>1.50 (1.30, 1.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CHD events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>5,966</td>
<td>284</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>43.8 (42.7, 44.9)</td>
<td>62.5 (55.3, 69.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)*</td>
<td>1 (reference)</td>
<td>1.51 (1.34, 1.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>13,903</td>
<td>408</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>94.2 (92.6, 95.7)</td>
<td>79.9 (72.1, 87.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)*</td>
<td>1 (reference)</td>
<td>0.96 (0.87, 1.06)</td>
<td>0.403</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; CI, confidence interval. Incidence rates are presented per 1,000 person-years. *Includes adjustment for age, race/ethnicity, sex, and history of diabetes, chronic kidney disease, stroke, heart failure, antihypertensive medication use and adherence, and Charlson comorbidity index.

Excess risk from statin SDD

Myocardial infarction (n = 105,329)

- High adherence 52.8%
- Statin SDD 1.65%

50% increased risk for recurrent MI*
51% increased risk for CHD*

*SDD, switch/down-titration/discontinuation
*Excess risk compared with high adherence after multivariable adjustment

Continued Statin Prescriptions After Adverse Reactions and Patient Outcomes: A Cohort Study

Organ System Distribution of the First Documented Adverse Reaction Among Study Patients, by Continuation of Statin Prescriptions During the First 12 Months After the Presumed Adverse Reaction*

<table>
<thead>
<tr>
<th>Adverse Reaction Category</th>
<th>All Patients (n=28,266)</th>
<th>Patients With Continued Statin Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes (n=19,989)</td>
</tr>
<tr>
<td>Myalgia or myopathy</td>
<td>6943 (24.6)</td>
<td>4903 (24.5)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders other than myalgia or myopathy</td>
<td>5044 (17.8)</td>
<td>3594 (18.0)</td>
</tr>
<tr>
<td>General disorders and administration site conditions†</td>
<td>3521 (12.5)</td>
<td>2517 (12.6)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>2965 (10.5)</td>
<td>2036 (10.2)</td>
</tr>
<tr>
<td>Drug intolerance‡</td>
<td>2223 (7.9)</td>
<td>1489 (7.5)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2517 (8.9)</td>
<td>1809 (9.1)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1021 (3.6)</td>
<td>751 (3.8)</td>
</tr>
<tr>
<td>Other</td>
<td>4032 (14.3)</td>
<td>2890 (14.5)</td>
</tr>
</tbody>
</table>

* Values are numbers (percentages). Adverse reactions were classified according to the Medical Dictionary for Regulatory Activities. A single adverse reaction could be classified only in a single category.
† Includes “generalized weakness,” “cold sweats,” and “lack of energy.”
‡ Includes “intolerance” and “decreased tolerance.”

Continued Statin Prescriptions After Adverse Reactions and Patient Outcomes: A Cohort Study

Inverse probability–weighted cumulative incidence curves: continued versus discontinued statin prescriptions during the first 12 months after the presumed adverse reaction

CV = cardiovascular. A. The composite primary outcome ($P < 0.0001$, weighted log-rank test). B. Death ($P < 0.0001$, weighted log-rank test). C. CV events ($P = 0.047$, weighted log-rank test).

Summary

- Underutilization of evidence-based (IA) recommendations remains a major healthcare challenge in the United States even for the highest-risk patients hospitalized for a CHD event.

- Down-titration or discontinuation of high intensity statins is common following hospitalization for MI.

- Maintaining high adherence to high or low/moderate intensity statins is associated with lower risk for CVD hospitalization and all-cause mortality.

- Strategies for improved adherence require health system factors, provider behavior and patient factors including early identification of statin intolerance using validated tools.
What is the best approach to evaluate and prevent statin adverse muscle events?

a. Recommend coenzyme Q10 for all statin users
b. Recommend vitamin D supplementation for all statin users.
c. Assess symptoms using validated clinical tool.
d. Communicate with patients regarding concerns/fears of statin therapy.
e. Encourage use of internet for assessment of adverse events
f. Choice: c,d

Correct answer: f
Statin-Intolerance

- The true incidence of statin intolerance has been questioned due to conflicting rates of muscle-related symptoms, isolated case reports of cognitive impairment and other rare adverse events in observational studies and randomized trials.

- Statin associated muscle symptoms accounts for 90% of statin intolerance

- Diagnosis of statin intolerance is primarily based on subjective patient complaints.

- Statin intolerance may be complete (inability to tolerate any statin at any dosage) or partial (ability to tolerate low or intermittent dosing of statin).
Non-Specificity of Self-Reported SAMS

- STOMP: 9.4% (4.6% on placebo)
- NHANES: 22% (16.7% non-statin users)
- *CoQ10: 36% (29% on placebo)
- *GAUSS-3: 43% (27% on placebo)

Analysis of 42 clinical trials with 56,059 patients: 13% (13% on placebo)

*Patients with a history of SAMS*

Definition Of Statin-Associated Muscle Symptoms (SAMS) NLA 2015 Statement

- **Myalgia** – unexplained muscle discomfort often described as “flu-like” symptoms with normal CK level
- **Myopathy** – muscle weakness
- **Myositis** – muscle inflammation often with muscle enzyme elevations
- **Myonecrosis** – elevation in muscle enzymes, severity graded by elevation of CK level above pre-treatment baseline levels or ULN.
- **Clinical rhabdomyolysis** – muscle injury with myoglobinuria and/or acute renal failure

Clinical Predictors Of Risk

- Older age, Asian race and gender (F>M)
- Exercise
- Comorbidity (*hypothyroidism, hyperuricemia, alcohol overconsumption*)
- Statin dose
- History of muscle pain with another lipid-lowering therapy
- Family history of muscular symptoms with lipid-lowering agents
- Concomitant medications (*CYP3A4 with simvastatin, inhibitors of CYP3A4 and SLCO1B1 including azole antifungals, ritonavir, verapamil and diltiazem; gemfibrozil*)

What is the Spectrum of Myalgia Symptoms?

- Muscle aches
- Muscle soreness
- Muscle stiffness
- Muscle tenderness
- Muscle cramps with or shortly after exercise. Not typically nocturnal cramping

Clinical Scoring Index For The Accurate Diagnosis Of SAMS

- **Clinical symptoms (new or increased unexplained muscle symptoms)**
- **Regional distribution/pattern**
  - Symmetric pelvic/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 4-12 weeks 2
  - Symptoms-onset > 12 weeks 1
- **Dechallenge**
  - Improves upon withdrawal (< 2 weeks) 2
  - Improves upon withdrawal (2-4 weeks) 1
  - Does not improve 0
- **Challenge**
  - Same symptoms recurs upon re-challenge <4 weeks 3
  - Same symptoms recur upon re-challenge 4-12 weeks 1

Clinical Scoring Index For The Accurate Diagnosis Of SAMS

SAMS Clinical Index Score

- Probably: 9-11
- Possible: 5-8
- Unlikely: <5

<table>
<thead>
<tr>
<th>SAMS category</th>
<th>Original Scoring*</th>
<th>Probable (9-11 Points)</th>
<th>Possible (7-8 Points)</th>
<th>Unlikely (2-6 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed SAMS</td>
<td>11</td>
<td>11</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Symptoms on placebo</td>
<td>0</td>
<td>1</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Symptoms on both</td>
<td>2</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Symptoms on neither</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Revised Scoring†</th>
<th>Probable (9-11 Points)</th>
<th>Possible (5-8 Points)</th>
<th>Unlikely (2-4 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed SAMS</td>
<td>11</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Symptoms on placebo</td>
<td>0</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>Symptoms on both</td>
<td>2</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Symptoms on neither</td>
<td>0</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>
Genetic Variations and SAMS

- Genetic variations may influence both an individual’s therapeutic response to statins and propensity for SAMS
- **SLCO1B1** reported to mediate hepatic transport of statins
- SNP rs4149056 has been associated with an increased risk of SAMS in simvastatin treated patients

**Serum [statin] associated with coding variant rs4149056 (Val174Ala) in \textit{SLCO1B1} gene**


\textit{SLCO1B1} = solute carrier organic anion transporter family, member 1B1
Sample Selection

- SAMS was confirmed in 149 adult Caucasians; 622 controls were on stable doses of statins in other evolocumab trials or were screen fails for SAMS in the GAUSS-3 study.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PHENOTYPE</th>
<th>SUBJECTS (N)</th>
<th>SAMPLES (n)</th>
<th>GENOTYPED* (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAUSS-3</td>
<td>Statin Rechallenge for Intolerance <strong>SAMS Confirmed</strong></td>
<td>500</td>
<td>434</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>Statin Rechallenge for Intolerance <strong>Screen Fails</strong></td>
<td></td>
<td></td>
<td>214</td>
</tr>
<tr>
<td>RUTHERFORD</td>
<td>HeFH on a Stable Dose of Statin + other lipid-lowering therapies</td>
<td>168</td>
<td>146</td>
<td>146</td>
</tr>
<tr>
<td>RUTHERFORD-2</td>
<td>HeFH on a Stable Dose of Statin + other lipid-lowering therapies</td>
<td>329</td>
<td>53</td>
<td>31</td>
</tr>
<tr>
<td>LAPLACE-TIMI 57</td>
<td>Stable Dose of Statins</td>
<td>631</td>
<td>360</td>
<td>356</td>
</tr>
</tbody>
</table>

*All samples meeting consent review and QC parameters were analyzed.
†Adult Caucasians selected from 159 total cases and 747 total controls.
Manhattan Plot Identifies 3 Genome-Wide Significant Loci of SAMS

- **MGAT5**
- **ATP5O/MRPS6**
- **KCNJ2/SOX9**

GW Significant
GW Suggestive
Biology of *MRPS6 / ATP5O*

- **MRPS6** gene: Mitochondrial Ribosomal Protein S6
  - Translation of ribosomal proteins – variants associated with CHD and early onset MI

- **ATP5O** gene: Mitochondrial ATP synthase Complex V
  - ATP production via mitochondrial respiratory chain – essential component of cellular energetics

- Mitochondria may provide a link between statins and SAMS, as statins potentially alter mitochondrial function by decreasing mitochondrial DNA, complex III activity, and oxidative phosphorylation

**Functional annotation clustering of DEGs seen in the muscle of patients experiencing statin myalgia (DAVID functional annotation clustering)**

<table>
<thead>
<tr>
<th>Process</th>
<th>Number of genes</th>
<th>P= *</th>
<th>FDR#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annotation Cluster 1: Protein Catabolism (Enrichment Score 6.89)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteolysis involved in protein catabolic process</td>
<td>37</td>
<td>1.8E-5</td>
<td>1.9E-5</td>
</tr>
<tr>
<td>Cellular protein catabolic process</td>
<td>37</td>
<td>1.0E-5</td>
<td>2.2E-5</td>
</tr>
<tr>
<td>Protein catabolic process</td>
<td>37</td>
<td>1.5E-5</td>
<td>4.8E-5</td>
</tr>
<tr>
<td>Modification-dependent protein catabolic process</td>
<td>35</td>
<td>1.6E-5</td>
<td>6.9E-5</td>
</tr>
<tr>
<td>Ubi conjugation pathway</td>
<td>31</td>
<td>1.2E-5</td>
<td>1.4E-4</td>
</tr>
<tr>
<td>Cellular macromolecule catabolic process</td>
<td>39</td>
<td>5.0E-5</td>
<td>2.6E-4</td>
</tr>
<tr>
<td>Proteolysis</td>
<td>42</td>
<td>1.8E-2</td>
<td>1.3E-1</td>
</tr>
<tr>
<td><strong>Annotation Cluster 2: Protein Ubiquitination (Enrichment Score 3.89)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small conjugating protein ligase activity</td>
<td>14</td>
<td>1.2E-2</td>
<td>3.7E-2</td>
</tr>
<tr>
<td>Ubiquitin-protein ligase activity</td>
<td>13</td>
<td>8.4E-3</td>
<td>5.0E-2</td>
</tr>
<tr>
<td>Acid-amino acid ligase activity</td>
<td>14</td>
<td>2.9E-2</td>
<td>2.6E-1</td>
</tr>
<tr>
<td><strong>Annotation Cluster 3: Nuclear and Organelle Proteins (Enrichment Score 3.91)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear lumen</td>
<td>51</td>
<td>4.5E-3</td>
<td>2.0E-2</td>
</tr>
<tr>
<td>Organelle</td>
<td>56</td>
<td>2.0E-2</td>
<td>2.7E-1</td>
</tr>
<tr>
<td>Intracellular organelle lumen</td>
<td>55</td>
<td>1.6E-2</td>
<td>2.8E-1</td>
</tr>
<tr>
<td>Membrane enclosed lumen</td>
<td>56</td>
<td>2.0E-2</td>
<td>4.5E-1</td>
</tr>
</tbody>
</table>

https://doi.org/10.1371/journal.pone.0181308.t007
AcetoacetateCoA + Acetyl-CoA
\[ \rightarrow \]
HMG-CoA reductase
\[ \downarrow \]
mevalonate
\[ \downarrow \]
Geranyl-PP
\[ \downarrow \]
Farnesyl-PP
\[ \downarrow \]
Squalene
\[ \downarrow \]
Lanosterol
\[ \downarrow \]
Cholesterol
\[ \rightarrow \] Vitamin D

Mitochondria

<table>
<thead>
<tr>
<th>Mitochondria</th>
<th>Ca++</th>
<th>Inflammation</th>
<th>Senescence/Apoptosis</th>
<th>Mevalonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFF, UCP3, ALDOA</td>
<td>CALM1, RyR, ANXA7, ITPR2, Calcineurin, Calpain</td>
<td>H-ras, Rac1, RAF, CXCL12, CST5, POU2F1, REL-A</td>
<td>TP53, BAD1, MRE1, RAD51, UBD, ATF</td>
<td>LS, FMDT1</td>
</tr>
</tbody>
</table>

Statin
Statin metabolites
Reduced Levels
Blockade
CENTRAL ILLUSTRATION: Clinical Approach to Patient With SAMS

Patient with suspected statin-associated muscle symptoms (SAMS)

Clinical assessment: Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)

Low SAMS-CI score

Evaluate for:
Other causes affecting musculoskeletal system
History of medication-related side effects
Depression and anxiety

× Statin discontinuation

After symptom resolution, initiate:
Same dose of same statin
(low likelihood that SAMS will reoccur)

or

Alternative high-intensity statin

Address concerns about side effects
Promote a healthy lifestyle

High SAMS-CI score

Before establishing a diagnosis of statin intolerance:
Review drug-drug interactions and co-morbidities
Check for hypothyroidism and vitamin D deficiency which could increase SAMS

× Statin discontinuation

After symptom resolution, initiate:
Lower dose of same statin
or
Alternative high-intensity statin

Readminister SAMS-CI

If still high SAMS-CI score, initiate:
Statin with different pharmacokinetic properties
Consider non-statin LDL-C lowering therapy

Address concerns about side effects
Promote a healthy lifestyle

## Clinical Pharmacokinetics of Statins

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Fluvastatin XL</th>
<th>Lovastatin</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction absorbed, %</td>
<td>30</td>
<td>50</td>
<td>98</td>
<td>98</td>
<td>80</td>
<td>30</td>
<td>34</td>
<td>60-80</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>12</td>
<td>19-29</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>33-60</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Lipophilicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Protein binding, %</td>
<td>80-90</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;95</td>
<td>99</td>
<td>55</td>
<td>88</td>
<td>94-98</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hydroxylation oxidation, CYP3A4</td>
<td>CYP2C9 (CYP2C8-3A4) (minor)</td>
<td>CYP2C9 (CYP2C8-3A4) (minor)</td>
<td>CYP3A4</td>
<td>Glucuronidation (UGT1A3-2B7) CYP2C8/9 (minor)</td>
<td>Sulfation, hydroxylation, oxidation</td>
<td>Biliary Excretion (CYP2C9-2C19) (minor)</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Active</td>
<td>Inactive</td>
<td>Inactive</td>
<td>Active</td>
<td>Inactive</td>
<td>Inactive</td>
<td>Active (minor)</td>
<td>Active</td>
</tr>
<tr>
<td>OAT1B1 transporter substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>T_{1/2}, h</td>
<td>15-30</td>
<td>0.5-2.3</td>
<td>4.7</td>
<td>2.9</td>
<td>12</td>
<td>1.3-2.8</td>
<td>19</td>
<td>2-3</td>
</tr>
<tr>
<td>Urinary excretion, %</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Fecal excretion, %</td>
<td>70</td>
<td>90</td>
<td>90</td>
<td>83</td>
<td>79</td>
<td>71</td>
<td>90</td>
<td>58</td>
</tr>
</tbody>
</table>

Rosenson RS, et al.  JACC 2017;70:1290-301
# Nutraceuticals Lowering LDL-C in SAMS Patients

## Table 5: Effects of Nutraceuticals on LDL-C in Patients With SAMS

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Sample Size</th>
<th>Study Design</th>
<th>Nutraceutical</th>
<th>LDL-C Reduction</th>
<th>Discontinuation due to SAMS</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAMS patients treated with ezetimibe 10 mg</td>
<td>57</td>
<td>Retrospective</td>
<td>Red yeast rice (monacolin) 3 mg daily and berberine 500 mg twice daily</td>
<td>19%</td>
<td>2%</td>
<td>(66)</td>
</tr>
<tr>
<td>SAMS patients treated with ezetimibe 10 mg</td>
<td>53</td>
<td>Retrospective</td>
<td>Berberine 500 mg twice daily</td>
<td>17%</td>
<td>0%</td>
<td>(66)</td>
</tr>
<tr>
<td>SAMS patients treated with ezetimibe 10 mg</td>
<td>32</td>
<td>Retrospective</td>
<td>Phytosterols 900 mg and psyllium fiber</td>
<td>10%</td>
<td>0%</td>
<td>(66)</td>
</tr>
<tr>
<td>SAMS</td>
<td>62</td>
<td>Case-control</td>
<td>Red yeast rice 1.8 g twice daily</td>
<td>21.3%</td>
<td>7%</td>
<td>(67)</td>
</tr>
<tr>
<td>SAMS</td>
<td>43</td>
<td>Randomized, controlled trial vs. pravastatin 20 mg twice daily</td>
<td>Red yeast rice 2.4 g twice daily</td>
<td>30.2</td>
<td>5% vs. 9% with pravastatin</td>
<td>(68)</td>
</tr>
</tbody>
</table>

LDL-C = low-density lipoprotein cholesterol; SAMS = statin-associated muscle symptoms.

Rosenson RS, et al. JACC 2017;70:1290-301
GAUSS 3: Study design: two double-blind phases

Phase A
- 511 patients with a history of intolerance to multiple statins due to muscle-related adverse effects
  - 10 weeks Atorvastatin 20 mg
  - 10 weeks Atorvastatin 20 mg

Phase B
- Participants entered Phase B only if they had muscle symptoms on atorvastatin, but not placebo, or CK ≥ 10 x ULN during statin treatment
  - 24 weeks Monthly SC evolocumab 420 mg
  - 24 weeks Daily oral ezetimibe 10 mg

## Phase A: study drug discontinuation events

<table>
<thead>
<tr>
<th>Intolerable muscle symptoms</th>
<th>N=491</th>
</tr>
</thead>
<tbody>
<tr>
<td>On atorvastatin, but not placebo</td>
<td>209 (42.6%)*</td>
</tr>
<tr>
<td>On placebo, but not atorvastatin</td>
<td>130 (26.5%)</td>
</tr>
<tr>
<td>On both placebo and atorvastatin</td>
<td>48 (9.8%)</td>
</tr>
<tr>
<td>No symptoms on either treatment</td>
<td>85 (17.3%)</td>
</tr>
<tr>
<td>Did not complete Phase A</td>
<td>20/511</td>
</tr>
<tr>
<td>Bypassed Phase A due to CK elevation ≥ 10 x ULN</td>
<td>19 (3.9%)*</td>
</tr>
</tbody>
</table>

*218 of these 228 patients proceeded to Phase B

Phase B: Adverse effects and drug discontinuations

<table>
<thead>
<tr>
<th></th>
<th>Ezetimibe (n=73)</th>
<th>Evolocumab (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total muscle-related events</strong></td>
<td>21 (28.8%)</td>
<td>30 (20.7%)</td>
</tr>
<tr>
<td><strong>Myalgia, muscle pain or weakness</strong></td>
<td>17 (23.3%)</td>
<td>25 (17.2%)</td>
</tr>
<tr>
<td><strong>Investigator reported CK Increase</strong></td>
<td>1 (1.4%)</td>
<td>4 (2.8%)</td>
</tr>
<tr>
<td><strong>Discontinuation of treatment for any reason</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation of oral treatment</td>
<td>14 (19.2%)</td>
<td>23 (15.9%)</td>
</tr>
<tr>
<td>Discontinued SC drug treatment</td>
<td>4 (5.5%)</td>
<td>7 (4.8%)</td>
</tr>
<tr>
<td><strong>Discontinuation of treatment for muscle symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued oral drug treatment</td>
<td>5 (6.8%)</td>
<td>11 (7.6%)</td>
</tr>
<tr>
<td>Discontinued SC drug treatment</td>
<td>0 (0%)</td>
<td>1 (0.7%)</td>
</tr>
</tbody>
</table>

**ODYSSEY ALTERNATIVE Study Design**

**Statin intolerant patients** (by medical history) with LDL-C ≥70 mg/dL (very-high CV risk) or ≥100 mg/dL (moderate/high risk)

- **Double-Blind Treatment Period (24 Weeks)**
  - **Alirocumab 75/150 mg SC Q2W + placebo PO QD**
    - Administered via single 1 mL injection using prefilled pen for self-administration
    - *Per-protocol dose ↑ possible depending on W8 LDL-C*
  - **Ezetimibe 10 mg PO QD + placebo SC Q2W**
  - *N=100*
  - **Atorvastatin 20 mg PO QD + placebo SC Q2W**
  - *N=50*

**Assessments**
- W -4
- W0
- W4
- W8
- W12
- W16
- W24

- **Primary endpoint** (LDL-C % change from baseline, ALI and EZE only)
- **Safety analysis** (all groups)

---

4-week single-blind placebo run-in follows 2-week washout of statins, ezetimibe and red yeast rice.

**OLTP**: Alirocumab open-label treatment period; W, Week.

Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event†

Cox model analysis:
HR ATV vs ALI = 1.63 (95% CI: 1.01 to 2.62), nominal $P=0.042$
HR EZE vs ALI = 1.41 (95% CI: 0.94 to 2.13), nominal $P=0.096$

†Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.

ALI, alirocumab; ATV, atorvastatin, EZE, ezetimibe.
Conclusions

• Statins are highly efficacious cholesterol lowering therapies with proven benefits in lowering cardiovascular events
• The inability to tolerate statins results in a higher cardiovascular event rate, more hospitalizations and more health care expenditures
• Strategies to accurately identify SAMS is an important healthcare challenge that involves validated screening tools and genetic markers
• Non-statin agents provide options for LDL-C lowering