Statin Intolerance as a Barrier to Atherosclerotic Disease Risk Reduction

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Collaborators

• Brown University – Peter Herbert, Eileen Cullinane, Stan Sady
• University of Pittsburgh – Joe Zmuda, Rich Zimet, Susan Yurgalevitch
• Duke University – John Guyton
• Hartford Hospital - Beth (Parker) Taylor, Jeff Capizzi, Amanda Zaleski, William Roman, Lindsay Lorson, Brenda Foxen, Mary Beth Moran, Cherie Biblie, Rick Seip, Gualberto Ruano, Greg Panza
• Umass - Priscilla Clarkson, Maria Urso, Amy Kearns
• Tufts University – Richard Karas
• Washington Children’s Medical Center - Eric Hoffman
Conflicts of Interest

• **Research Support:** NHLBI, NIAMS, NCCAM, Genomas, Sanofi, Regeneron, Esperion, Amarin Pfizer.

• **Consultant:** Amgen, Regeneron, Merck, Genomas, Sanofi, Esperion, Amarin

• **Speaker Honoraria:** Merck, Pfizer, Regeneron, Astra Zenica

• **Stock Shareholder:** Abbvie, Abbott Labs, J&J; General Electric, Medtronic, JA Wiley
Statin Intolerance as a Barrier to Risk Reduction

Why Care About Statin Associated Symptoms (SAS) ?

What Are SAS ?

How Do We Diagnose SAS ?

How Frequent Are SAS ?

How Should We Manage SAS ?
Why Care About Statin Associated Symptoms (SAS) ?

- Patient Outcomes
- Medical Cost From -
  - Poorer Outcomes
- Medications
Performed a Systematic Review / Meta Analysis Of 44 Prospective Studies - 1,978,919 Participants

Good Adherence $\geq 80$

RR Good vs Less Good = 0.55 (0.46-0.67)

45% Lower Mortality With Good Adherence
Relative risks for all-cause mortality in good vs. poor adherence

<table>
<thead>
<tr>
<th>(1) Adherence to statins</th>
<th>11</th>
<th>291,864</th>
<th>29,605**</th>
<th>0.55 (0.46, 0.67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) Adherence to antihypertensive agents</td>
<td>11*</td>
<td>205,398</td>
<td>12,288**</td>
<td>0.71 (0.64, 0.78)</td>
</tr>
<tr>
<td>ACE inhibitors/Angiotensin receptor blockers</td>
<td>4</td>
<td>62,196</td>
<td>886**</td>
<td>0.74 (0.69, 0.80)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>7</td>
<td>67,991</td>
<td>5,441**</td>
<td>0.83 (0.69, 1.00)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1</td>
<td>9168</td>
<td>2696</td>
<td>0.97 (0.87, 1.09)</td>
</tr>
<tr>
<td>Multiple agents</td>
<td>3</td>
<td>81,342</td>
<td>2978</td>
<td>0.49 (0.23, 1.05)</td>
</tr>
<tr>
<td>(3) Adherence to aspirin</td>
<td>3</td>
<td>12,980</td>
<td>1573</td>
<td>0.45 (0.16, 1.29)</td>
</tr>
<tr>
<td>(4) Adherence to any CVD medication</td>
<td>23*</td>
<td>533,381</td>
<td>94,126**</td>
<td>0.62 (0.57, 0.67)</td>
</tr>
</tbody>
</table>

*For individual studies reporting data for more than one medication class the results for the different categories within that study were meta-analysed (fixed effect) before use in the composite calculation; **Groups in which not all studies reported the number of deaths.
## Figure 3

Relative risks for any cardiovascular disease in good vs. poor adherence to major cardiovascular disease medications.

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>No. of CVD events</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to statins</td>
<td>17</td>
<td>1,055,920</td>
<td>96,216</td>
<td>0.85 (0.81, 0.89)</td>
</tr>
<tr>
<td>Adherence to antihypertensive agents</td>
<td>12*</td>
<td>552,143</td>
<td>36,186</td>
<td>0.81 (0.76, 0.86)</td>
</tr>
<tr>
<td>ACE inhibitors/Angiotensin receptor blockers</td>
<td>4</td>
<td>68,781</td>
<td>4643</td>
<td>0.75 (0.55, 1.01)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>4</td>
<td>90,402</td>
<td>10,774</td>
<td>0.83 (0.71, 0.98)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1</td>
<td>9168</td>
<td>2249</td>
<td>0.91 (0.82, 1.01)</td>
</tr>
<tr>
<td>Multiple agents</td>
<td>7</td>
<td>443,264</td>
<td>22,714</td>
<td>0.80 (0.73, 0.89)</td>
</tr>
<tr>
<td>Adherence to aspirin</td>
<td>3</td>
<td>15,253</td>
<td>2274</td>
<td>0.60 (0.31, 1.16)</td>
</tr>
<tr>
<td>Adherence to any CVD medication</td>
<td>33*</td>
<td>1,615,126</td>
<td>135,627</td>
<td>0.80 (0.77, 0.84)</td>
</tr>
</tbody>
</table>

*For individual studies reporting data for more than one medication class the results for the different categories within that study were meta-analysed (fixed effect) before use in the composite calculation.
Why Care About Statin Associated Symptoms (SAS) ?

Patient Outcomes
Medical Cost From -
   Poorer Outcomes
Medications
Payers fret about the next drug doomsday: Pricey PCSK9 cholesterol meds

May 7, 2014 | By Tracy Staton

Quick! Which group of hotly anticipated, next-generation therapies for a widespread health problem is expected to cost payers beaucoup bucks when they hit the market? If you said the new crop of hepatitis C treatments, you’d be half right. Pharmacy benefits managers say they’re just as worried--perhaps even more so--by a coming class of cholesterol drugs known as PCSK9 inhibitors.

As the Pink Sheet reports, executives from CVS Caremark ($CVS) and Express Scripts ($ESRX), the two biggest U.S. PBMs, say these drugs are groundbreaking treatments that are proving safe and effective at controlling cholesterol in people who’ve had little success at that in the past. But at an estimated $10,000 per year, drugs like Sanofi ($SNY) and Regeneron's ($REGN) alirocumab, Pfizer's ($PFE) bococizumab, and Amgen's ($AMGN) evolocumab won't fit the healthcare budget.
Say what? CVS Health execs figure PCSK9 meds to cost up to $150B

February 17, 2015 | By Tracy Staton
Statin Intolerance as a Barrier to Risk Reduction

Why Care About Statin Associated Symptoms (SAS)?

What Are SAS?

How Do We Diagnose SAS?

How Frequent Are SAS?

How Should We Manage SAS?
What Is / Are SAS?

Statin Associated Muscle Symptoms (SAMS)
  Myalgia, Cramps, Weakness,
Central Nervous System Effects
  Memory Problems, Amnesia
Elevated LFTs
Worsening Glucose Tolerance
Tendinopathy
Definitions of Statin Myopathy

- Myalgia – Aching, Stiffness, Cramps
- Myopathy - Weakness
- Myositis - Inflammation
- Myonecrosis - ↑ CK
  - Mild: >3 Fold
  - Moderate: >10 Fold
  - Severe: >50 Fold
  - Clinical Rhabdomyolysis: Creatinine ↑ 0.5mg/dl

J Clin Lipidology June 2014
Damage to Type 1 Fibers

Patients who experienced muscle symptoms with normal CK levels

Statins withdrawn for 3 mo

When placebo was used, Symptoms disappeared

Stained For Lipid

Phillips et al., 2003
Weakness is Not An Uncommon Complaint...Complaints of Decreased Exercise Tolerance Are Uncommon

Very Few Statin Studies Have Examined Exercise Performance or Muscle Strength
Do Statins Affect Cognition?
Case Study #1

- 65-year-old Caucasian
- On atorvastatin 10 mg/day
  - Mood alteration, memory difficulties
- Cognitive evaluation and fMRI of the brain
- On and off (2 months) statin therapy
- Significant improvement in cognitive function off statins

Parker…Thompson. Pharmacotherapy. 2010
Neuronal activation during the difficult version of the Sternberg Task, depicted by colored regions on the 3D-rendered brains, during encoding (left) and response selection (right) while the subject was on 10 mg atorvastatin (bottom) and 2 months following atorvastatin cessation (top).
Pilot Study

- fMRI during two tasks
  - Sternberg Task
  - Figural Memory Test
- 19 adults from 6 month statin study
  - 14 on atorvastatin and 5 on placebo
- Pre-post scans
Grant Number: 1R01HL098085-01A1

Principal Investigator(s):
Beth Parker (contact), PHD
Donna Polk

Project Title: The Effect of High-Dose Atorvastatin on Neuronal Activity and Cognitive Function
Figure 2. FMRI activation on 3D-rendered brain showing changes in activation with statin use displayed at p=0.005 uncorrected level during the encoding (left) and recognition (right) phase of the Figural Memory Test.
Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial

Paul M Ridker, Aruna Pradhan, Jean G MacFadyen, Peter Libby, Robert J Glynn

- Jupiter Trial - 20 of Rosuva v. Placebo
- CRP > 2....in 17,603 Subjects
- Among Those with Diabetes Risk Factors (Metabolic S, Fasting Glucose > 100, BMI > 30, A1c > 6)...Risk Increased 25% (5-49%)
- New Diabetics: 270 v 216....54 More New Diabetics
- But...39% < CV Events, 36% < VTE, 18% < Deaths !!!!
- 134 < CV Events vs 54 New Diabetics in 17,603 Subjects
- If No DM Risk Factors, No New Diabetes

Tenocytes Degrade Type I Collagen to Repair Tendons
Using Matrix Metalproteinases (MMP) 2 & 9
Statins Reduce MMP – 9 mRNA

Am J Cardiol 2007;100:152–153
Statin Intolerance as a Barrier to Risk Reduction

Why Care About Statin Associated Symptoms (SAS) ?

What Are SAS ?

How Do We Diagnose SAS ?

How Frequent Are SAS ?

How Should We Manage SAS ?
How To Diagnose SAS?

There Are No Validated Diagnostic Strategies

CK May or May Not Be Elevated

Classic Symptoms & Temporal Relationship Help

Challenge / Rechallenge is? Best Diagnostic Approach But Subjective, Etc, Etc
Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey

G Kees Hovingh¹, Shravanthi R Gandra², Jan McKendrick³, Ricardo Dent², Heather Wieffer³, Alberico L Catapano⁴, Paul Oh⁵, Robert S Rosenson⁶, Erik S Stroes¹

Identification and management of patients with statin-associated symptoms

Atherosclerosis In Press
% Clinicians Trying ≥ Statin Before Diagnosing SAMS

Hovingh et. al. Atherosclerosis In Press
An assessment by the Statin Muscle Safety Task Force: 2014 update

Robert S. Rosenson, MD, FNLA\(^a\), Steven K. Baker, MSc, MD, FRCP(C), Terry A. Jacobson, MD, FNLA, Stephen L. Kopecky, MD, Beth A. Parker, PhD

<table>
<thead>
<tr>
<th>Clinical symptoms (new or increased unexplained muscle symptoms)</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional distribution/pattern</td>
<td></td>
</tr>
<tr>
<td>Symmetric hip flexors/thigh aches</td>
<td>3</td>
</tr>
<tr>
<td>Symmetric calf aches</td>
<td>2</td>
</tr>
<tr>
<td>Symmetric upper proximal aches</td>
<td>2</td>
</tr>
<tr>
<td>Non-specific asymmetric, intermittent</td>
<td>1</td>
</tr>
<tr>
<td>Temporal pattern</td>
<td></td>
</tr>
<tr>
<td>Symptoms onset &lt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms onset &lt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms onset 4–12 weeks</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms onset &gt;12 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Dechallenge</td>
<td></td>
</tr>
<tr>
<td>Improves upon withdrawal (&lt;2 weeks)</td>
<td>2</td>
</tr>
<tr>
<td>Improves upon withdrawal (2–4 weeks)</td>
<td>1</td>
</tr>
<tr>
<td>Does not improve upon withdrawal (&gt;4 weeks)</td>
<td>0</td>
</tr>
<tr>
<td>Challenge</td>
<td></td>
</tr>
<tr>
<td>Same symptoms reoccur upon rechallenge &lt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Same symptoms reoccur upon rechallenge 4–12 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Statin myalgia clinical index score</td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>9–11</td>
</tr>
<tr>
<td>Possible</td>
<td>7–8</td>
</tr>
<tr>
<td>Unlikely</td>
<td>&lt;7</td>
</tr>
</tbody>
</table>
But The Diagnosis is Tough
Coenzyme Q10 in Statin Myopathy

1 RC1 AT005836-01 NIH/NCCAM
Subjects with Prior Statin Complaints

**Run-In: Initial – Simvastatin** 20 mg for 8 weeks or Until Symptoms 1 Week

**Run-In: Initial – Placebo** for 8 Weeks or Until Symptoms for 1 Week

4 week washout

**Run-In: Initial - Placebo**

**Run-In: Initial – Simvastatin**

Weekly phone calls: Pain Questionnaires used to assess muscle symptoms and document myalgia

100 Subjects
Baseline Muscle Performance, Accelerometer, Pain Questionnaire
Randomization to Treatment: Placebo or 600 mg CoQ10
2 Week Loading

Simvastatin 20mg + Placebo (N=50)

Simvastatin 20mg + CoQ10 600 mg (N=50)

At 8 Weeks

Subset of Patients: Crossover
A randomized trial of coenzyme Q10 in patients with confirmed Statin Myopathy

Beth A. Taylor, Lindsay Lorson, C. Michael White, Paul D. Thompson
Few Met the Definition of Myalgia

120 Subjects Recruited

43 (35.8%) Positive for Myalgia

77 (64.2%) Negative for Myalgia

No Symptoms: 21 (17.5%)

Symptoms on Placebo but not on Statin: 43 (35.8%)

Symptoms on Both Treatments: 21 (17.5%)
Now This Is A Big Problem

If We Can’t Diagnose
Whom Do We Treat With Other Drugs?
How Do We Research Other Strategies?
Statin Intolerance as a Barrier to Risk Reduction

Why Care About Statin Associated Symptoms (SAS) ?
What Are SAS ?
How Do We Diagnose SAS ?
How Frequent Are SAS ?
How Should We Manage SAS ?
Do SAS Even Exist?

From: Jane Armitage [mailto:jane.armitage@ctsu.ox.ac.uk]
Sent: Thursday, July 16, 2015 1:30 PM
To: Thompson, Paul

.... I’m afraid we will just have to agree to differ on these points! But I’m sorry that you find it so difficult to believe the mass of randomized data showing no significant adverse muscle effects and your own data which support this lack of effect. I certainly agree that lots of people attribute their muscle symptoms to statins (often having been warned that statins might cause such symptoms) but this is exactly the problem with using non-blinded observational evidence to draw conclusions about causality.
A Systematic Review of Statin-Induced Muscle Problems in Clinical Trials

Identified 1012 Reports on Statin Trials - 42 Qualified for Analysis
4 Reported Average CK
26 Reported Muscle Problems
Only 1 Queried For Muscle Problems
All Studies: Muscle Problems on Statin (12.7%) vs Placebo (12.4%) (p=0.06)

Don’t Ask....Don’t Tell
PRedIction of Muscular Risk in Observational Conditions or PRIMO Study

- 7,924 French Patients on Fluva 80, Atorva 40-80, Prava 40, Simva 40-80, for 3 mos
- 10.5% Reported Muscular Symptoms

Bruckert CV Drugs & Therapy 2005
% New Statin Patients with Possible SAMS

Hovingh et. al. Atherosclerosis In Press
Hovingh et. al. Atherosclerosis In Press
The STOMP Study
The Effect of Statins On Skeletal Muscle Performance
NHLBI (NIH): R01HL081893

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 (VO₂Max)

• Physical activity (accelerometer)

• Muscle symptoms
Study Definition of Statin-Related Myopathy

1. They report new or increased myalgia, cramps, or muscle aching,
2. These symptoms have persisted for at least 2 weeks,
3. The symptoms resolve within 2 weeks of stopping the study drug, and
4. The symptoms reoccur within 4 weeks of restarting the medication
STOMP Myalgia Results

23 Atorva & 14 Placebo Developed Pain
$X^2 = 3.16; \ p = 0.08$

19 Atorva & 10 Placebo Met Myalgia Definition
$X^2 = 3.74; \ p = 0.05$
There Were No Differences in Maximal Exercise Capacity or Handgrip, Arm or Leg Strength

<table>
<thead>
<tr>
<th></th>
<th>ATOR (n=202)</th>
<th>PL (n=217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting RER</td>
<td>0.0 (−0.01 to 0.01)</td>
<td>0.0 (−0.03 to 0.03)</td>
</tr>
<tr>
<td>( \dot{V}_{O_2} \text{max}, \text{mL.kg}^{-1}.\text{min}^{-1} )</td>
<td>−0.8 (−1.3 to −0.3)</td>
<td>−0.8 (−1.4 to −0.2)</td>
</tr>
<tr>
<td>( V_T, \text{mL.kg}^{-1}.\text{min}^{-1} )</td>
<td>−0.9 (−1.6 to −0.2)</td>
<td>−0.6 (−1.6 to 0.4)</td>
</tr>
<tr>
<td>Hand grip, kg</td>
<td>0.1 (−0.5 to 0.7)</td>
<td>−0.6 (−1.3 to 0.1)</td>
</tr>
<tr>
<td>Arm strength (APT), N·m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isom Ext</td>
<td>0.8 (−0.2 to 1.8)</td>
<td>0.3 (−0.6 to 1.2)</td>
</tr>
<tr>
<td>Isom Flex</td>
<td>−0.5 (−2.1 to 1.1)</td>
<td>−0.2 (−1.1 to 0.7)</td>
</tr>
<tr>
<td>Isok Ext at 60°/s</td>
<td>0.5 (−0.2 to 1.2)</td>
<td>−0.2 (−0.9 to 0.5)</td>
</tr>
<tr>
<td>Isok Flex at 60°/s</td>
<td>0.0 (−0.6 to 0.6)</td>
<td>0.0 (−0.6 to 0.6)</td>
</tr>
<tr>
<td>Isok Ext at 180°/s</td>
<td>0.5 (−0.2 to 1.2)</td>
<td>0.6 (0.2 to 1.2)</td>
</tr>
<tr>
<td>Isok Flex at 180°/s</td>
<td>0.2 (−0.6 to 1.0)</td>
<td>0.1 (−0.5 to 0.7)</td>
</tr>
<tr>
<td>Leg strength (APT), N·m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isom Ext</td>
<td>−2.1 (−5.1 to 0.9)</td>
<td>−0.4 (−3.4 to 2.6)</td>
</tr>
<tr>
<td>Isom Flex</td>
<td>−1.8 (−3.2 to −0.4)</td>
<td>−1.3 (−2.6 to 0.0)</td>
</tr>
<tr>
<td>Isok Ext at 60°/s</td>
<td>1.2 (−0.8 to 3.2)</td>
<td>0.9 (−1.1 to 2.9)</td>
</tr>
<tr>
<td>Isok Flex at 60°/s</td>
<td>0.9 (−0.5 to 2.3)</td>
<td>−0.5 (−2.7 to 1.7)</td>
</tr>
<tr>
<td>Isok Ext at 180°/s</td>
<td>3.9 (2.0 to 5.8)</td>
<td>3.8 (2.3 to 5.3)</td>
</tr>
<tr>
<td>Isok Flex at 180°/s</td>
<td>2.7 (1.5 to 3.9)</td>
<td>2.1 (1.0 to 3.2)</td>
</tr>
<tr>
<td>Knee endurance fatigue index</td>
<td>−0.1 (−1.6 to 1.4)</td>
<td>0.2 (−0.8 to 1.2)</td>
</tr>
</tbody>
</table>

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
Journal of the American Heart Association
No Subject Had Any CK Value Persistently Greater Than 10 Times Normal...But
Average CK Increased 20.8 ± 141.1 U/L ($P<0.0001$) with Atorvastatin
Statin Intolerance as a Barrier to Risk Reduction

Why Care About Statin Associated Symptoms (SAS) ?
What Are SAS ?
How Do We Diagnose SAS ?
How Frequent Are SAS ?
How Should We Manage SAS ?
Managing Patients With SAS / SAMS?

- Are Symptoms Tolerable? Measure CK
- Stop Drug Until No SX
- Try Another Statin
- Try Lower Doses Plus Minus Ezetimibe
- Try Another Class of Drug
- Try Chinese Red Rice Yeast 2 Tabs HS
- Try Atorva / Rosuva / Pitava QOD or BIW
- Do “Pulse Therapy”
- Use Q10 Supplements ???
- Measure / Replete Vitamin D
- Use PCSK 9 Inhibitors
Statin Intolerance as a Barrier to Atherosclerotic Disease Risk Reduction

Paul D. Thompson, MD
Director of Cardiology
Henry Low Heart Center
Hartford Hospital
Hartford, CT