Effect of Statins on Exercise Performance

Paul D. Thompson, MD
Director of Cardiology
Henry Low Heart Center
Hartford Hospital
Hartford, CT
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 Augieri, William Roman, Lindsay Lorson, Brenda Foxen, Mary Beth Moran, Cherie Biblie, Rick Seip, Gualberto Ruano
- 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, Roche, Sanolfi, Regeneron, Esperion, Amarin and Pfizer.

• **Consultant:** Amgen, Astra Zenica, Regeneron, Merck, Genomas, Runners World, Sanolfi, Esperion, Amarin, Novartis

• **Speaker Honoraria:** Merck, Pfizer, Abbott, Astra Zenica, GlaxoSmithKline

• **Stock Shareholder:** Abbvie, Abbott Labs, J&J; General Electric, JA Wiley
Exercise & Statins Take Home Messages

1. Exercise Magnifies “Statin” Myalgia
2. Exercise Causes & Magnifies Many of The CK Elevations Attributed to Statins
3. Some Patients Report Weakness, But There is Little Objective Data on Muscle in Asymptomatic Patients
4. Statins Appear to Block the Aerobic Training Response
5. Long Term Muscle Effects of Statins Are Not Defined
Exercise & Statins Take Home Messages

1. Exercise Magnifies “Statin” Myalgia
Collected Cases

• Among 22 Professional Athletes
• With LDL Receptor Defects
• Only 6 Could Tolerate Statins
• Despite Multiple Attempts With Fluva, Lova, Prava, Atorva, & Simva

Sinzinger Br J Clin Phar 2004
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
PRIMO Study

• 10.5% Reported Muscular Symptoms
• The Rate was 14.7% in Patients Practicing “Intense Form of Sport” vs 10.8% Who Did “Only Leisure Time Activities”
• Pain Was Triggered in 41% - 53% by “Unusual Physical Activity”

Bruckert CV Drugs & Therapy 2005
Exercise & Statins Take Home Messages

1. Exercise Magnifies “Statin” Myalgia
2. Exercise Causes & Magnifies Many of The CK Elevations Attributed to Statins
Exercise ALONE Can Produce Remarkable CK Increases

So That Many CK Increases Attributed to Statins Are Due to Exercise
### CK Levels in Runners in The 1979 Boston Marathon

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<td>Over 3:30 (5)</td>
<td>130 (U/L)</td>
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Functional SNPs Associated with Human Muscle Size and Strength

**10 Men**

- Performed 45 Minutes Of Non-Dominant Arm Exercises
- Standing Curls, Preacher Curls, Triceps Extensions
- On Days 1 & 3
- CK’s Obtained on Daily For 5 Days
Plasma Creatine Kinase (U/L)

Day

Subj 1
Subj 2
Subj 3
Subj 4
Subj 5
Subj 6
Subj 7
Subj 8
Subj 9
Subj 10

Bilbie SM, Seip RL, Bilbie CL, Clarkson, PM, Thompson, PD. Submitted.
Exercise - Induced CK Elevations With Statins

- 59 Men Aged 18-65
- LDL > 130 mg/dl
- Randomly to Placebo or Lova 40 mg
- 5 Weeks of Treatment
- At 4 Weeks: Maximal EXT, Downhill Walking at 65% HR for 3 X 15 Min Bouts
- At 5 Weeks: Biceps 1 RM, Then 4 X 10 Curls @ 50%

Thompson et al Metabolism 1997
CK Elevations After Downhill Walking

![Graph showing CK elevations after downhill walking withLovastatin and Placebo treatments.](image-url)
Exercise - Induced CK Elevations -

Two Men Excluded Because of Marked CK Increases

Thompson et al Metabolism 1997
CK Elevations After Eccentric Biceps Curls

Thompson et al Metabolism 1997
Atorvastatin 10mg, n=42: 80 mg, n=37, 1 Month of Treatment
A History of Medical Reports on the Boston Marathon: 112 Years and Still Running

PAUL D. THOMPSON and CARMELO V. VENERO

Henry Low Heart Center, Hartford Hospital, Hartford, CT

Study Design

- 3 Blood Draws
  - CK Isoenzymes
Study Population

• 43 controls  
  – 51 ± 7 yrs  
  – 29 Men and 8 Women  
• 37 Statin Users  
  – 56 ± 8 yrs  
  – 30 Men & 13 Women
Effect of Statins on Creatine Kinase Levels Before and After a Marathon Run

Beth A. Parker, PhD a,*, Amanda L. Augeri, MS a, Jeffrey A. Capizzi, MS a, Kevin D. Ballard, PhD b, Christopher Troyanos, ATC c, Aaron L. Baggish, MD d, Pierre A. D’Hemecourt, MD c, and Paul D. Thompson, MD a

Am J Cardiol 2012;109:282–287
Exercise & Statins Take Home Messages

1. Exercise Magnifies “Statin” Myalgia
2. Exercise Causes & Magnifies Many of The CK Elevations Attributed to Statins
3. Some Patients Report Weakness, But There is Little Objective Data on Muscle Strength
Weakness is Not An Uncommon Complaint...Complaints of Decreased Exercise Tolerance Are Uncommon

Very Few Statin Studies Have Examined Exercise Performance or Muscle Strength
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
The effects of statins on skeletal muscle strength and exercise performance
Guru M. Krishnan\textsuperscript{a} and Paul D. Thompson\textsuperscript{b}

Current Opinion in Lipidology 2010

- 6 Studies Examined Statins & Muscle Strength
- 9 Studies Examined Statins & Exercise Tolerance
- Studies Were Small & Used Crude Measures
- Insufficient Data to Determine if Statins Affect Strength and Exercise Performance
Tasmanian Older Adults Cohort Study

Prospective Cohort Design Statins in 402 men, 372 women, Aged 50–79
Statin Users at 2.6 yr Had Lower Leg Strength
Strength in Users was Decreased vs Stoppers
Suggests Statins Decrease Strength in Older Subjects
Decrease is Reversible with Statin Cessation
The STOMP Study
The Effect of Statins On Skeletal Muscle Performance
NHLBI (NIH): R01HL081893
STOMP Recruitment Sites

• Hartford Hospital:
  – PI: Paul D. Thompson, MD

• University of Connecticut (Storrs):
  – PI: Linda Pescatello, PhD

• University of Massachusetts (Amherst):
  – PI: Pricilla Clarkson, PhD
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
The Effect of Statins on Skeletal Muscle Function
NIH RO1 081893

- 440 Subjects
- Randomized to Atorvastatin 80 or Placebo
- 6 Months
- Strength - Handgrip, Biceps, Quadriceps - Static & Dynamic Strength
- Quadriceps Endurance
- Exercise Oxygen Uptake & Respiratory Quotient
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 between the Atorva & Placebo groups with 6 mos of therapy.

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<th>PL (n=217)</th>
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<td>0.0 (−0.03 to 0.03)</td>
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<td>( \dot{V}O_2 \max ) mL·kg(^{-1} )·min(^{-1} )</td>
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</table>

Knee endurance fatigue index

Effect of Statins on Skeletal Muscle Function
Beth A. Parker, Jeffrey A. Capizzi, Adam S. Grimaldi, Priscilla M. Clarkson, Stephanie M. Cole, Justin Kendle, Stuart Chipkin, Linda S. Pescatello, Kathleen Simpson, C. Michael White and Paul D. Thompson
Average CK Increased
20.8±141.1 U/L ($P<0.0001$) with Atorvastatin
Spontaneous Physical Activity Decreased in The >55 Year Group

Figure 3. Group mean±SD of changes in physical activity (average counts per day) by age group after 6 months of atorvastatin (ATOR) or placebo (PL) treatment. Brackets indicate the P value for treatment-by-age interaction.
Statins and Physical Activity in Older Men: The Osteoporotic Fractures in Men Study

1,801 Non Users
1,195 New Users
1,801 Users

Lee et al Arch IM
Exercise & Statins Take Home Messages

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Overweight Adults With 2 Metabolic Risk Factors
12 wks Exercise Training With (18) / Wo (19) Simvastatin (40)
VO2 Increased 10% Wo Statin; 1.5% With Statin
Citrate Synthase Increased 13% Wo & Decreased by 4.5% With Statin
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5. Long Term Muscle Effects of Statins Are Unknown
Possible Mechanisms of Statin Induced Muscle Injury

1. Reduced Sarcolemmal Cholesterol
2. Reduced T-Tubule & Sarcoplasmic Recticulum Cholesterol [Draeger JPath 2006]
3. Reduced Isoprenoids: Ubiquinone - Co-enzy Q10
4. Reduced Prenylation of GTP Binding Proteins - Ras, Rac and Rho - Cell Maintenance, Growth & Reduced Apoptosis [Coleman Cell Death Differ 2002]
5. Changes in Fat Metabolism [Phillips P Atherosclerosis 2005]
7. Failure to Appropriately Repair Damaged Muscle [Urso .... Thompson ATVB 2005]
8. Vitamin D Deficiency
9. Inflammation (Inflammatory Myopathy)
A statin-dependent QTL for GATM expression is associated with statin-induced myopathy

Lara M. Mangravite\textsuperscript{1*}, Barbara E. Engelhardt\textsuperscript{2†}, Marisa W. Medina\textsuperscript{3}, Joshua D. Smith\textsuperscript{4}, Christopher D. Brown\textsuperscript{5}, Daniel I. Chasman\textsuperscript{6}, Brigham H. Mecham\textsuperscript{1}, Bryan Howie\textsuperscript{2}, Heejung Shim\textsuperscript{2}, Devesh Naidoo\textsuperscript{3}, QiPing Feng\textsuperscript{2}, Mark J. Rieder\textsuperscript{4†}, Yii.-Der I. Chen\textsuperscript{8}, Jerome I. Rotter\textsuperscript{8}, Paul M Ridker\textsuperscript{6}, Jemma C. Hopewell\textsuperscript{9}, Sarah Parish\textsuperscript{9}, Jane Armitage\textsuperscript{9}, Rory Collins\textsuperscript{9}, Russell A. Wilke\textsuperscript{7}, Deborah A. Nickerson\textsuperscript{1}, Matthew Stephens\textsuperscript{2,10} & Ronald M. Krauss\textsuperscript{3}

- Glycine Amidinotransferase
- Rate Limiting Enzyme in Creatine Synthesis
- Less Creatine = Less Rhabdo with Statins

Ballard & Thompson – Cell Metab Previews 2013
Possible Mechanisms of Statin Induced Muscle Injury

1. Reduced Sarcolemmal Cholesterol
2. Reduced T-Tubule & Sarcoplamic Recticulum Cholesterol

Draeger JPath 2006

3. Reduced Isoprenoids: Ubiquinone - Co-enzy Q10

4. Reduced Prenylation of GTP Binding Proteins - Ras, Rac and Rho - Cell Maintenance, Growth & Reduced Apoptosis

Coleman Cell Death Differ 2002

5. Changes in Fat Metabolism

Phillips P Atherosclerosis 2005

6. Increased Muscle Cholesterol & Plant Sterol 2nd to LDL Receptor Activity

Paiva Clin Pharmacol Ther 2005

7. Failure to Appropriately Repair Damaged Muscle

Urso .... Thompson ATVB 2005

8. Vitamin D Deficiency

9. Inflammation (Inflammatory Myopathy)
Atrogin 1 Background #1
Hanai ... Lecker. J. Clin. Invest. 2007

- Ubiquitin Proteosome Pathway Breaks Down Skeletal Muscle
- Ubiquitin Protein Ligase E3 or Atrogin 1 (AT-1)
- AT-1 Increases in Failing Hearts, PP Uteri
EXPERIMENTAL DESIGN

D1
8h

4 wks

D31
8h

Experiments:
- D1: Exercise Right Leg
- 8h
- Statin/Placebo
- Exercise Left Leg

Biopsies:
- Right & Left Vastus Lateralis

D31:
- Exercise Left Leg
- 8h
- Statin/Placebo
- Exercise Right Leg
- Biopsy Right & Left Vastus Lateralis
GENE EXPRESSION

• GeneChip® Human Genome U133 plus 2.0 array
• 47,000 transcripts and variants
• 38,500 genes

The chip is covered with genetic probes. The mRNA binds to the probes that hold complementary sequences.

Source: Indrani Bagchi and Affymetrix, Inc.
There Are Few Changes With Statin Treatment & No Exercise, But Lots of Gene Change With Statin & Exercise
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qRT-PCR Results - Atrogin-1

FBX032 (Atrogin) Gene Expression

Urso et al. ATVB 2006
The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity

Do Statins Cause Diabetes?
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

Systematic review
Three meta-analyses published between 2009 and 2011 suggested that all statins are associated with a small increase in the risk of incident type 2 diabetes (hazard ratio [HR] 1.09, 95% CI 1.02–1.17) and that intensive-dose statin therapy is associated with higher risk than is lower-dose therapy (HR 1.12, 95% CI 1.04–1.22). In absolute terms, however, these risks are low compared with the absolute benefit of statin therapy in the setting of secondary prevention, from which most data are derived. We were unable to find any data directly addressing the cardiovascular benefits and diabetes risks in the setting of primary prevention, an issue that has caused much controversy in both the medical and lay press. Further, we were unable to find any data addressing whether the risks and benefits of statin therapy in primary prevention differ between people with and without risk factors for diabetes.
Why Diabetes?

Something is going on in the muscle.
Statins Decrease P13k / Akt 
Increasing the Forkhead Box Gene Group (FOXO) 
FOXO Increases the 2 Muscle Specific Ubiquitin E3 Ligases 
  Mu Atrophy F Box (MAFbx) 
  Mu RING Finger –1 (MURF-1) 
They Conjugate to Protein Substrate Initiating Protein Degradation
FOXO Also Activates Pyruvate Dehydrogenase Kinase (PDK) Transcription Upregulating PDK Inactivates Muscle Pyruvate Dehydrogenase Complex. Which Limits CHO & Promotes Fat Oxidation.
Exercise & Statins Take Home Messages

1. Exercise Magnifies “Statin” Myalgia
2. Exercise Causes & Magnifies Many of The CK Elevations Attributed to Statins
3. Some Patients Report Weakness, But There is Little Objective Data on Muscle in Asymptomatic Patients
4. Statins Appear to Block the Aerobic Training Response
5. Long Term Muscle Effects of Statins Are
Can Statins Cause Tendonopathy?
Tenocytes Degrade Type I Collagen to Repair Tendons Using Matrix Metalproteinases (MMP) 2 & 9
Statins Reduce MMP – 9 mRNA

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Thank You

Paul D. Thompson, MD
Chief of Cardiology
Hartford Hospital
Hartford, CT