

Defining Statin Associated Adverse Effects

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Potential Conflicts of Interest

- **Research Support:** Esperion, Amgen.
- **Consultant:** Amgen, Regeneron, Esperion, Amarin
- **Speaker Honoraria:** Amgen, Amarin, Boehringer
- **Stock Shareholder:** Abbvie, Abbott Labs, J&J; General Electric, Medtronic, Serapta, Myocardia, CVS, Moderna

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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Statin-Associated Side Effects



Paul D. Thompson, MD,^a Gregory Panza, MS,^{a,b} Amanda Zaleski, MS,^{a,b} Beth Taylor, PhD^{a,b}

VIEWPOINT

What to Believe and Do About Statin-Associated Adverse Effects

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Statins prevent cardiac death and reduce the incidence of acute coronary syndrome, stroke, and venous thromboembolic disease. Patients who take less than 80% of their statin dose have a 45% relative increase in total mortality compared with more adherent pa-


muscle cramps, or weakness with little or no increase in CK levels. Collins et al² reviewed the possible adverse effects found in RCTs of statin therapy and concluded that statin-associated muscle symptoms without marked CK elevations do not exist or are extremely rare because they are

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Paul D. Thompson
Beth A. Taylor *Editors*

Statin-Associated Muscle Symptoms

 Humana Press

2020

Statin-Associated Side Effects

Paul D. Thompson, MD,^a Gregory Panza, MS,^{a,b} Amanda Zaleski, MS,^{a,b} Beth Taylor, PhD^{a,b}

- Statin Associated Muscle Symptoms (SAMS) Including Statin - Induced Necrotizing Auto - Immune Myopathy
- Diabetes Mellitus
- Central Nervous System Effects (Sleep, Depression)
- Elevated LFTs
- Decreased Renal Function
- Tendon Rupture
- Hemorrhagic Stroke
- Interstitial Lung Disease
- Lower Testosterone Levels

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Definition of Statin - Associated Muscle Symptoms (SAMS) – Rhabdomyolysis

- For Clinical Trials - Rhabdomyolysis -
Muscle Sx with CK > 10 Times UNL
- For Practice - Renal Injury Can Occur
at Much Lower CKs Depending on
Multiple Factors

Definition of Statin - Associated Muscle Symptoms (SAMS)

Statin-Associated Autoimmune Myopathy

Andrew L. Mammen, M.D., Ph.D.

NEJM 2016

Statin-Associated Autoimmune Myopathy

Andrew L. Mammen, M.D., Ph.D.

- Muscle Weakness
- Markedly Elevated Creatine Kinase
- **UN** – Responsive To Statin Cessation
- Presence of HMG – Co A Reductase Antibodies

Statin Myalgia – Research Definition

- Unable To Tolerate 1, 2, or 3 Statins
- At Least 1 At The Lowest Approved Dose

Is There A Better Research Definition



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Contents lists available at ScienceDirect

Atherosclerosis

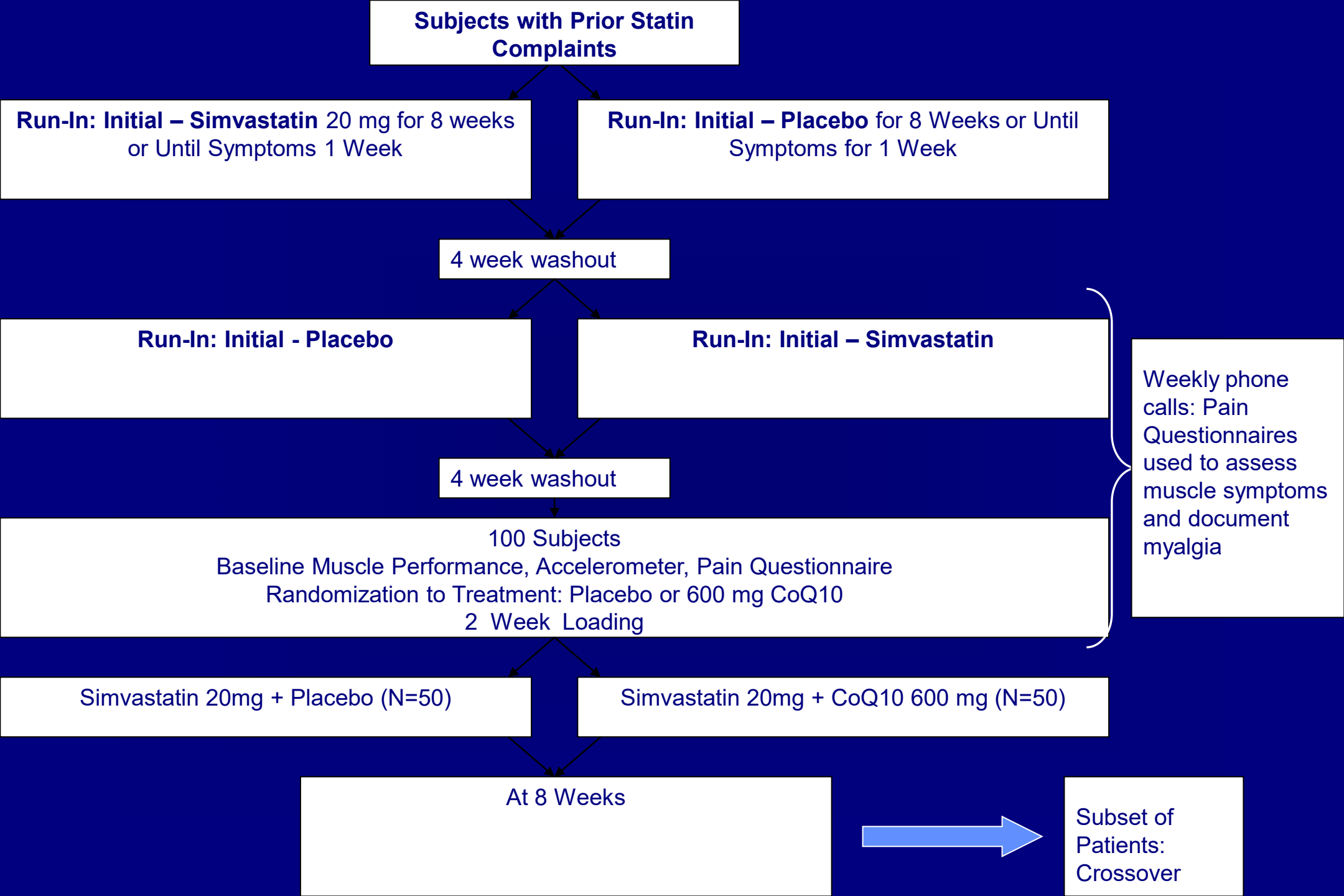
journal homepage: www.elsevier.com/locate/atherosclerosis



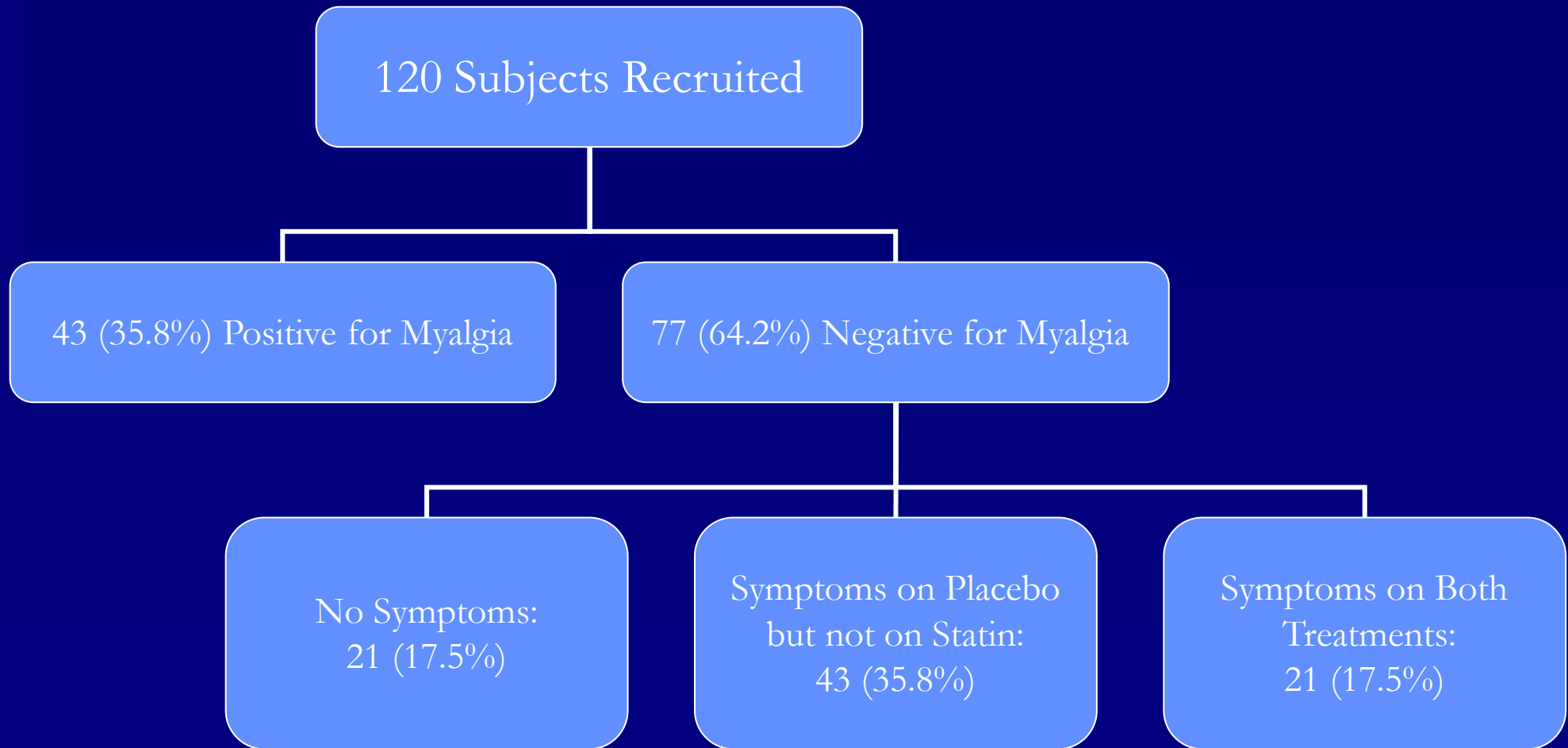
A randomized trial of coenzyme Q10 in patients with confirmed Statin Myopathy



Beth A. Taylor ^{a, b, c, *}, Lindsay Lorson ^a, C. Michael White ^{a, c}, Paul D. Thompson ^{a, c}



Few Met the Definition of Myalgia



Statin Myalgia – Clinical Definition

- Discomfort, Pain, “Weakness”
- Appears During Statin Therapy
- Disappears (Promptly) With Statin Cessation
- Reappears With Statin Reinitiation
- With / Without CK Elevation

**There Are Clinical Scoring
Formula**

Original Contribution

An assessment by the Statin Muscle Safety Task Force: 2014 update

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

Table 2 Proposed statin myalgia clinical index score

Clinical symptoms (new or increased unexplained muscle symptoms)	
Regional distribution/pattern	
Symmetric hip flexors/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 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 upon withdrawal (>4 weeks)	0
Challenge	
Same symptoms reoccur upon rechallenge <4 weeks	3
Same symptoms reoccur upon rechallenge 4–12 weeks	1
Statin myalgia clinical index score	
Probable	9–11
Possible	7–8
Unlikely	<7

Do SAS Even Exist ?

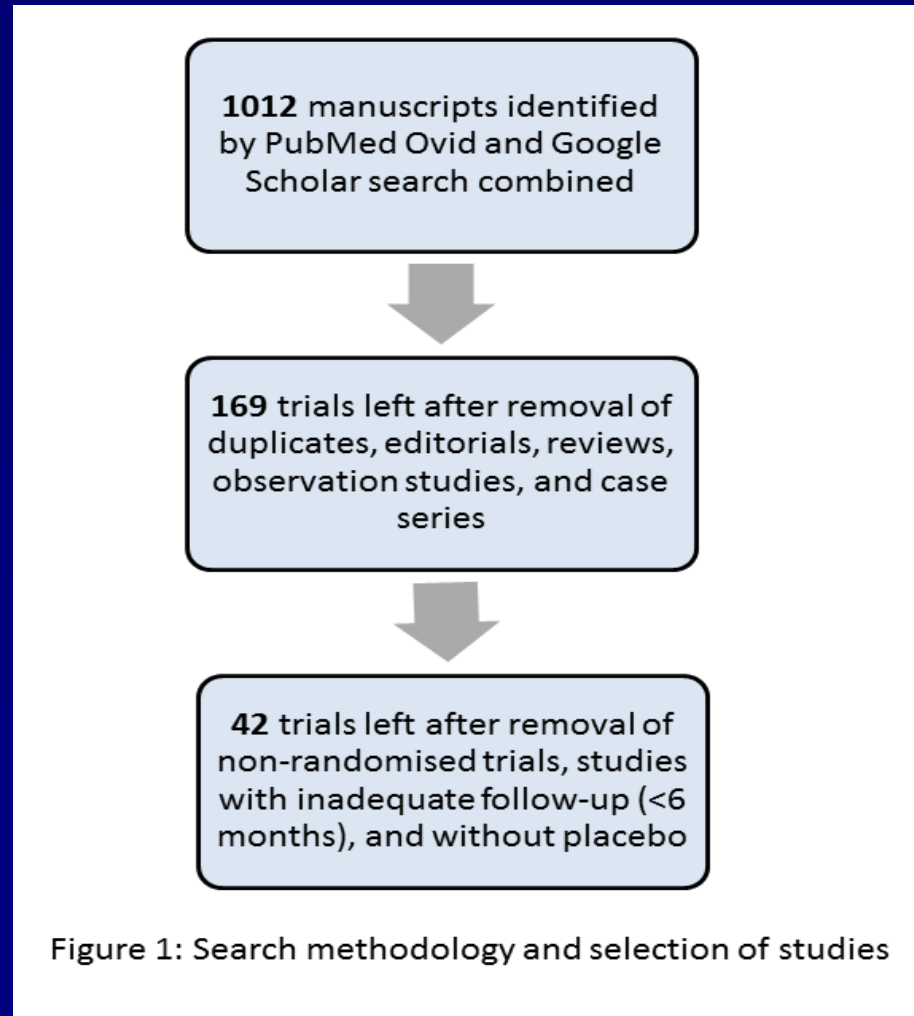
From: Jane Armitage [mailto:jane.armitage@ctsu.ox.ac.uk]

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.

Why No Muscle Symptoms in Randomized Clinical Trials ???



Ganga, Slim, Thompson.
Am H J (2014)

A Systematic Review of Statin-Induced Muscle Problems in Clinical Trials

4 Reported Average CK

26 Reported Muscle Problems

Only 1 Queried For Muscle Problems

Don't Ask....Don't Tell

But The Data Are Changing



ON MY MIND

Trust the Blinded Randomized Evidence That Statin Therapy Rarely Causes Symptomatic Side Effects

Richard Peto, FRS and Rory Collins, FRS

- HPS – Run-in: 1 mo Placebo 1 mo Statin –
Excess Myalgia of 1% Year #1

ON MY MIND

**Trust the Blinded Randomized Evidence That Statin
Therapy Rarely Causes Symptomatic Side Effects**

Richard Peto, FRS and Rory Collins, FRS

- SEARCH - Run-In: Statin 1 mo
- Muscle Symptoms: 43.5 vs 41.6%
- So Only A Small Increase Without CK
- 9 RCTs no Run-In – 5.2 vs 4.8% $p=0.002$

The STOMP Study

The Effect of Statins On Skeletal Muscle Performance

NHLBI (NIH): R01HL081893

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



American
Heart
Association®

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

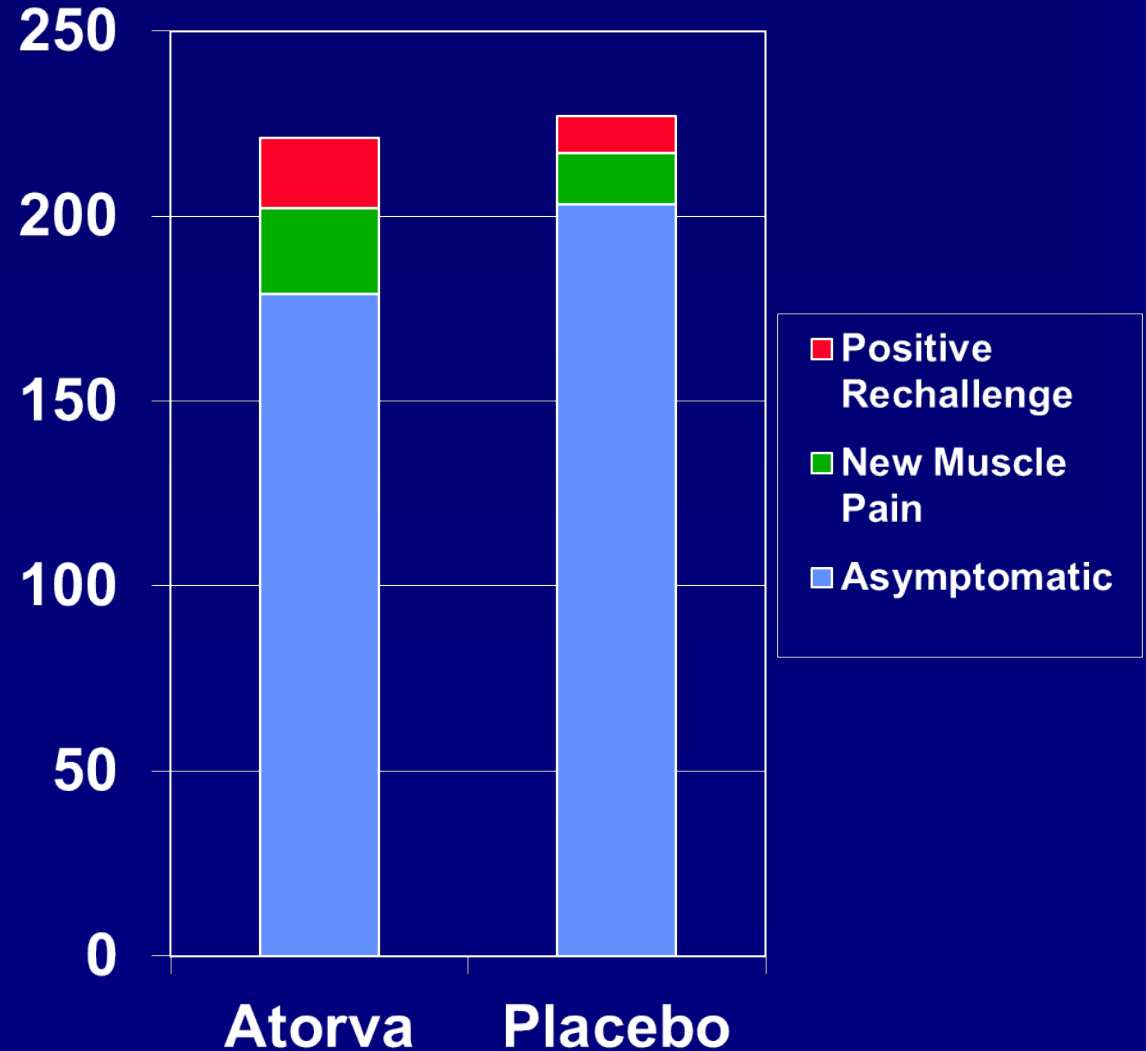
STOMP Myalgia Results

23 Atorva & 14
Placebo
Developed Pain

$X^2=3.16$; $p = 0.08$

19 Atorva & 10
Placebo Met
Myalgia
Definition

$X^2=3.74$; $p = 0.05$



Actually... $p=0.054$

BUT

Young Subjects (51 yrs)

Totally Healthy

Followed For Only 6 Months

**But The Definitions of “Statin
Intolerance” or “SAES”
Don’t Really Matter**

**“The Customer is Always
Right”**

Harry Gordon Selfridge
(1858 – 1947)

Selfridge Department Store
London England

Do Statins Cause Diabetes ?

Yes

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**
- **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**

Lancet 380: 565, 2012

**But All Cholesterol Reduction
May Cause Diabetes**

Association Between Familial Hypercholesterolemia and Prevalence of Type 2 Diabetes Mellitus

Joost Besseling, MD; John J. P. Kastelein, MD, PhD; Joep C. Defesche, PhD;
Barbara A. Hutten, PhD, MSc; G. Kees Hovingh, MD, PhD

- 63,320 Dutch Individuals - Genetic Testing
- Prevalence of Diabetes
- By Type of Genetic Defect

Table 2. Associations Between the Presence of Type 2 Diabetes and Familial Hypercholesterolemia

	Prevalence of Type 2 Diabetes		Unaffected Relatives		OR (95% CI)
	Familial Hypercholesterolemia				
	No. /Total	% (95% CI)	No. /Total	% (95% CI)	
Overall comparison					
Unadjusted	440/25 137	1.75 (1.59-1.91)	1119/38 183	2.93 (2.76-3.10)	0.62 (0.55-0.69) ^a
Adjusted ^b	177/12 300 ^c	1.44 (1.22-1.69)	812/24 898 ^c	3.26 (3.04-3.48)	0.49 (0.42-0.58) ^a
Affected gene					
No mutation			812/24 898 ^c	3.26 (3.04-3.48)	1 [Reference]
<i>APOB</i>					
Unadjusted	84/2125 ^c	2.42 (1.91-2.93)			0.65 (0.48-0.87) ^a
Adjusted ^b	41/2125 ^c	1.91 (1.44-2.52)			
<i>LDLR</i>					
Unadjusted	353/10 126 ^c	1.63 (1.46-1.80)			0.45 (0.38-0.54) ^a
Adjusted ^b	135/10 126 ^c	1.33 (1.12-1.57)			
Type of <i>LDLR</i> mutation					
None			812/24 898 ^c	3.26 (3.04-3.48)	1 [Reference]
Receptor-defective					
Unadjusted	226/6320 ^c	1.80 (1.57-2.03)			0.49 (0.40-0.60) ^a
Adjusted ^b	91/6320 ^c	1.44 (1.18-1.75)			
Receptor-negative					
Unadjusted	127/3806 ^c	1.41 (1.16-1.65)			0.38 (0.29-0.49) ^a
Adjusted ^b	43/3806 ^c	1.12 (0.88-1.43)			

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