

# Effect of Statins on Skeletal Muscle Function

Beth A. Parker, PhD; Jeffrey A. Capizzi, MS; Adam S. Grimaldi, BS; Priscilla M. Clarkson, PhD; Stephanie M. Cole, PhD; Justin Keadle, BS; Stuart Chipkin, MD; Linda S. Pescatello, PhD; Kathleen Simpson, MS; C. Michael White, PharmD; Paul D. Thompson, MD

**Background**—Many clinicians believe that statins cause muscle pain, but this has not been observed in clinical trials, and the effect of statins on muscle performance has not been carefully studied.

**Methods and Results**—The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study assessed symptoms and measured creatine kinase, exercise capacity, and muscle strength before and after atorvastatin 80 mg or placebo was administered for 6 months to 420 healthy, statin-naïve subjects. No individual creatine kinase value exceeded 10 times normal, but average creatine kinase increased  $20.8 \pm 141.1$  U/L ( $P < 0.0001$ ) with atorvastatin. There were no significant changes in several measures of muscle strength or exercise capacity with atorvastatin, but more atorvastatin than placebo subjects developed myalgia (19 versus 10;  $P = 0.05$ ). Myalgic subjects on atorvastatin or placebo had decreased muscle strength in 5 of 14 and 4 of 14 variables, respectively ( $P = 0.69$ ).

**Conclusions**—These results indicate that high-dose atorvastatin for 6 months does not decrease average muscle strength or exercise performance in healthy, previously untreated subjects. Nevertheless, this blinded, controlled trial confirms the undocumented impression that statins increase muscle complaints. Atorvastatin also increased average creatine kinase, suggesting that statins produce mild muscle injury even among asymptomatic subjects. This increase in creatine kinase should prompt studies examining the effects of more prolonged, high-dose statin treatment on muscular performance.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00609063. (*Circulation*. 2013;127:96-103.)

**Key Words:** atorvastatin ■ exercise test ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ muscle strength ■ myopathy

Hydroxy-methyl-glutaryl CoA reductase inhibitors or statins are the most effective medications for reducing elevated concentrations of low-density lipoprotein (LDL) cholesterol and produce remarkable reductions in cardiovascular events.<sup>1</sup> Statins can produce life-threatening rhabdomyolysis, but this is rare.<sup>2</sup> Statins are more frequently associated with mild muscle complaints, including myalgia, cramps, and weakness, which may compromise medication compliance and quality of life. The reported incidence of myalgia during statin therapy ranges from 1% in controlled studies<sup>3</sup> to 25% in clinical reports.<sup>4</sup> Muscle weakness has also been reported with statin therapy, but muscle performance and exercise performance have not been carefully studied.<sup>5</sup>

## Clinical Perspective on p 103

The Effect of Statins on Muscle Performance study (STOMP; National Heart, Lung, and Blood Institute 5R01HL081893, NCT00609063) determined the incidence of statin-associated muscle complaints and examined the effect of statins on muscle performance and exercise capacity by

administering atorvastatin 80 mg daily or placebo to healthy subjects for 6 months or until subjects developed myalgia.

## Methods

### Study Overview

STOMP was a double-blind, random-assignment clinical trial; the methods used have been described previously.<sup>6</sup> Equal numbers of men and women across 3 age ranges (20–39, 40–54, and  $\geq 55$  years) were recruited over 4 years. Baseline lipid, liver, kidney, thyroid, and creatine kinase (CK) measurements were obtained. Subjects completed a baseline muscle symptom questionnaire and exercise testing, including a maximal exercise test with gas analysis; hand grip, elbow flexor, and knee extensor strength testing; and a knee extensor endurance exercise test. Subjects were then randomly assigned in a double-blind fashion to identical placebo or atorvastatin 80 mg daily (Lipitor; Pfizer, Inc, New York, NY). Atorvastatin tablets were crushed for compounding, but this does not influence relative bioavailability of the statin (Medical Information Letter 337882; Pfizer, Inc). Subjects were called twice monthly to ascertain symptoms. Subjects performed repeat testing after 6 months or after they developed muscle symptoms meeting the study definition of statin-induced myalgia. The study was approved by the Institutional Review boards at Hartford Hospital, the University of Massachusetts,

Received August 9, 2012; accepted November 13, 2012

From the Division of Cardiology, Henry Low Heart Center, Hartford Hospital, Hartford, CT (B.A.P., J.A.C., A.S.G., P.D.T.); University of Massachusetts, Amherst (P.M.C., S.M.C., J.K., S.C.); and University of Connecticut, Storrs (L.S.P., K.S., C.M.W.).

Correspondence to Paul D. Thompson, MD, Director of Cardiology, Henry Low Heart Center, Hartford Hospital, Hartford, CT 06102. E-mail [pthomps@harthosp.org](mailto:pthomps@harthosp.org)

© 2012 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.112.136101

and the University of Connecticut and was monitored by a Data Safety and Monitoring Board.

### Subject Inclusion/Exclusion Criteria

In total, 1415 possible subjects were evaluated. Subjects were not included if they had cancer within 5 years, a baseline alanine aminotransferase (ALT) value >2 times the upper limit of normal (ULN), a creatinine level >2 mg/L, an abnormal thyroid-stimulating hormone level, a history of cardiovascular disease, an ischemic-appearing ECG response to exercise testing, diabetes mellitus, subjective muscle complaints or weakness, or physical disabilities that would prohibit exercise testing. LDL cholesterol was not an inclusion/exclusion criterion because many patients with cardiovascular disease or other cardiovascular risk factors currently receive statin therapy regardless of their baseline LDL values. Women who were pregnant or planned to become pregnant were not recruited, and all women in the study of child-bearing age agreed to use an established method of birth control for the duration of the trial. Subjects presently or previously treated with lipid-lowering medications were excluded, as were individuals treated with medications known to affect skeletal muscle or to alter statin metabolism.<sup>7</sup> Subjects with hypertension were recruited if their blood pressure was controlled and  $\leq 140/90$  mmHg at baseline. A total of 468 subjects were randomized to atorvastatin or placebo, of whom 203 in the atorvastatin group and 217 in the placebo group provided complete data for analysis. Subjects were removed from the study if their CK exceeded 10 times the ULN on any occasion or if their ALT exceeded 3 times the ULN on 2 measurements performed within 1 week of the first elevated value. No subject was excluded for elevated CK values, but 9 atorvastatin and 1 placebo subjects were excluded for elevated ALT levels (Figure 1).

### Serological Markers

Total, LDL, and high-density lipoprotein cholesterol; triglyceride; ALT; creatinine; 25-hydroxy vitamin D (which measures both vitamin D<sub>2</sub> and D<sub>3</sub>); and CK levels were obtained at baseline and 6 months. Participants, their physicians and investigators were unaware of subjects' lipid values during the study.

### Study Measurements

Body anthropometrics, hand-grip isometric strength of the dominant hand, elbow and knee extension/flexion isometric and isokinetic strength, knee endurance fatigue index<sup>8</sup> of the dominant limb, maximal oxygen uptake, resting and peak respiratory gas exchange ratio and ventilatory threshold, and habitual self-reported and directly measured physical activity were measured at baseline and after 6 months of drug treatment as described.<sup>6</sup> Compliance with study medications was assessed by pill counts of unused medication at 3 months and again at 6 months.

### Myalgia/Muscle Symptoms

Muscle complaints were assessed at the baseline, at the 3- and 6-month visits, and by phone twice monthly with the Short-Form Brief Pain Inventory as described.<sup>6</sup> Subjects met the study definition for "myalgia" if all of the following occurred: (1) They reported new or increased muscle pain, cramps, or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the study drug; and (4) symptoms reoccurred within 4 weeks of restarting the study medication. Subjects who tested positive for myalgia with these criteria subsequently performed repeat serological, muscle, and aerobic testing immediately after reoccurrence of muscle symptoms.

### Sample Size

The primary outcome was the incidence of statin-associated myalgia. Thus, sample size estimates were based on the projection that 10% of the statin group would develop myalgia.<sup>9</sup> Assuming a non-specific muscle complaint rate of 2% with placebo, 162 subjects per

group were needed to detect a significant difference between groups ( $\alpha=0.05$ , power=0.80). In addition, groups of 200 subjects each provided power to detect a 5% to 10% change with statin therapy in all exercise outcomes.

### Statistical Analyses

Outcomes were assessed for normality by use of normal probability plots, histograms, and Kolmogorov test statistics. Transformations were used as necessary. All tests were 2 sided with statistical significance set at  $\alpha=0.05$ . Analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC).

Primary analyses were carried out on an intent-to-treat basis. We also compared outcomes excluding 23 subjects who did not reduce LDL cholesterol by  $\geq 20\%$  on atorvastatin (to exclude noncompliant subjects as denoted in the original published analysis plan), but this did not alter the main study findings. Therefore, the following data include all subjects who completed the study. To determine the incidence of statin muscle complaints, the proportion of subjects developing complaints was compared between the statin and placebo groups by use of a Pearson  $\chi^2$  test. The effect of atorvastatin on serological markers, muscle strength, and aerobic performance was assessed with *t* tests (or a Mann-Whitney *U* test for CK) comparing the change scores observed in the statin- and placebo-treated subjects before and after treatment. Models were also run controlling for sex and age as categorical covariates and random site effects, which did not alter findings. Further models examined 2-way and 3-way interactions with ANOVA by modeling change scores in study outcomes with age, sex, and drug treatment, again controlling for random site effects with nonsignificant interactions dropped for parsimony. Change scores according to myalgia status were also examined between treatment groups given the small number of myalgic subjects.

## Results

### Baseline Characteristics and Lipid Changes

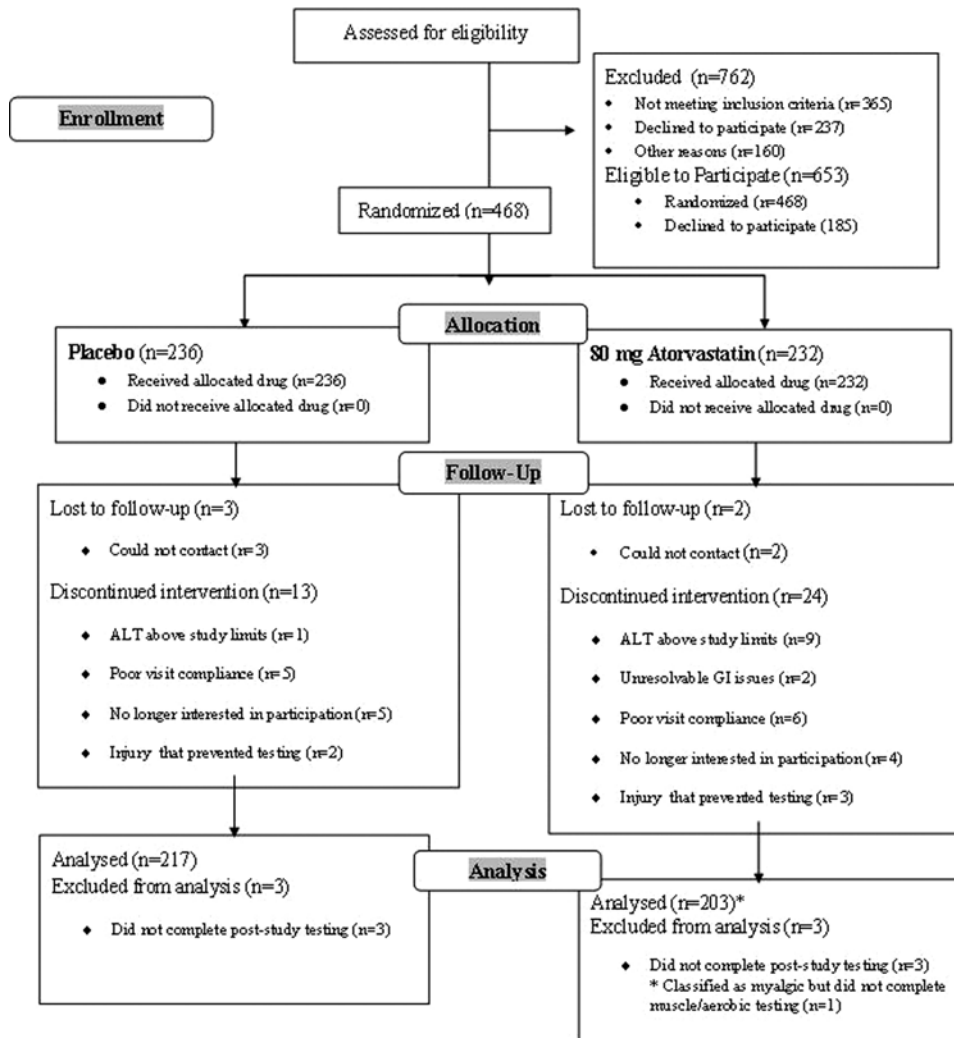
Subjects randomized to the atorvastatin and placebo groups were similar at baseline, although more women on atorvastatin used oral contraceptives or hormone therapy and more placebo subjects used prescription pain medication (Table 1). Compliance with treatment medication was similar in the atorvastatin and placebo groups (94.5 $\pm$ 7.0% versus 93.9 $\pm$ 8.2%). Atorvastatin subjects showed the expected reductions in LDL cholesterol (Table 2).

### Changes in Serological Markers

Atorvastatin produced a 20.8 $\pm$ 141.1 U/L ( $P<0.0001$ ) increase in CK, although no subject demonstrated a CK value >10 times the ULN (Figure 2). In addition, 40 subjects on atorvastatin versus 29 subjects on placebo demonstrated CK above the ULN ( $\chi^2=3.2$ ;  $P=0.08$ ). Atorvastatin also increased average ALT values 15.7 $\pm$ 27.4 U/L ( $P<0.0001$ ; Figure 2). There was no effect of 6 months of atorvastatin treatment on vitamin D (atorvastatin: 35.1 $\pm$ 12.4–34.2 $\pm$ 12.5 ng/mL versus placebo, 36.8 $\pm$ 14.6–35.1 $\pm$ 14.3 ng/mL;  $P=0.94$ ).

### Muscle Complaints

Twenty-three atorvastatin and 14 placebo subjects reported new, unexplained muscle pain. Nineteen atorvastatin and 10 placebo subjects ultimately met the study definition for myalgia ( $\chi^2=3.74$ ;  $P=0.05$ ). Myalgic subjects on atorvastatin reported predominantly leg symptoms: hip flexor, quadriceps, hamstring, and/or calf aches ( $n=10$ ); quadriceps or calf cramps ( $n=5$ ); and/or quadriceps, hamstring, and/or calf fatigue ( $n=6$ ). Myalgic subjects on placebo reported more diverse symptoms



**Figure 1.** Study flow diagram detailing numbers of participants who were screened, were randomized, completed the study, and were analyzed. ALT indicates alanine aminotransferase.

such as whole-body fatigue (n=3), worsening of pain in previous injuries (n=3), groin pain (n=3), and foot cramping (n=1), but they were otherwise similar (Table 1). Time to symptom onset was shorter in atorvastatin myalgic subjects than in myalgic subjects on placebo ( $35 \pm 31$  versus  $61 \pm 33$  days;  $P=0.045$ ). Myalgic versus nonmyalgic subjects on atorvastatin or placebo did not exhibit differences in CK, ALT, lipid (Table 2), or vitamin D changes with treatment ( $P>0.19$ ).

Pain severity and pain interference with daily life in all subjects with myalgia averaged  $0.7 \pm 1.2$  and  $0.3 \pm 0.6$  of a possible 10 at baseline, increased to  $2.4 \pm 1.8$  and to  $2.0 \pm 2.3$  with treatment ( $P=0.001$ ), and did not differ between the atorvastatin and placebo subjects ( $P=0.37$ ). Baseline pain severity and pain interference with daily life were similar in nonmyalgic subjects for the atorvastatin and placebo groups ( $0.4 \pm 0.9$  and  $0.2 \pm 0.7$ , respectively) and did not change with treatment ( $P=0.14$ ).

### Effects of Atorvastatin on Muscle and Exercise Performance

There were no baseline differences in measured strength and aerobic outcomes (all  $P>0.06$ ). There were no differential effects of atorvastatin on skeletal muscle strength and endurance, aerobic performance, or physical activity levels compared

with placebo (all  $P>0.17$ ; Table 3). Physical activity decreased ( $P=0.007$ ) regardless of drug treatment, but the decrease in the atorvastatin group was due to a decrease in activity among the oldest tertile of study participants ( $P=0.03$ ; Figure 3).

### Outcomes in Individuals With Myalgia

One atorvastatin subject with myalgia refused final testing and was not included in the analyses. Compared with the asymptomatic subjects on atorvastatin, myalgic subjects had lower muscle strength in 5 of 14 measured variables (Table 4). Compared with the asymptomatic subjects on placebo, placebo myalgic subjects had significantly lower muscle strength in 4 measured variables ( $\chi^2=0.16$ ;  $P=0.68$ ).

### Discussion

STOMP is, to the best of our knowledge, the first randomized, double-blind, clinical trial to confirm the common clinical impression that statins increase the incidence of myalgia. The definition of myalgia in STOMP was predefined and required resolution of muscle symptoms promptly after stopping study medication and reappearance of symptoms on restarting the medication. STOMP also documented that statin-associated mild muscle complaints do not

**Table 1. Subject Baseline Characteristics and Medication Use by Drug Assignment for All Subjects and Those Who Developed Myalgia**

	Entire Sample		Myalgic Sample	
	ATOR (n=203)	PL (n=217)	ATOR (n=19)	PL (n=10)
Women, n	103	113	11	5
White, n	192	201	18	10
Age, y	43.6 (41.4–45.8)	44.6 (42.4–46.8)	52.5 (47.1–50.9)*	56.9±8.0 (51.9–61.9)*
BMI, kg/m <sup>2</sup>	26.3 (25.6–27.0)	26.5 (25.8–27.2)	24.7 (22.8–26.6)	25.0±3.0 (23.1–26.9)
$\dot{V}O_{2\max}$ , mL·kg <sup>-1</sup> ·min <sup>-1</sup>	34.6 (33.3–35.9)	33.2 (31.9–34.5)	31.0 (26.7–35.3)	30.7 (26.0–35.4)
Resting SBP, mmHg	119.5 (117.7–121.3)	118.3 (116.5–120.1)	122.3 (117.4–127.2)	119.0 (112.7–125.3)
Resting DBP, mmHg	75.5 (74.2–76.8)	75.1 (73.8–76.4)	76.4 (73.2–79.6)	72.6 (68.9–76.3)
Total-C, mg/dL	198.7 (193.3–204.1)	194.8 (189.9–199.7)	215.3 (195.9–234.7)	212.0 (195.6–228.4)
LDL-C, mg/dL	119.0 (114.1–123.9)	116.0 (111.8–120.2)	128.9 (110.8–147.0)	130.2 (116.1–144.3)
HDL-C, mg/dL	57.6 (55.2–60.0)	58.6 (56.3–60.9)	68.7 (61.5–75.9)*	61.0 (53.2–68.8)
Triglycerides, mg/dL	110.5 (102.9–118.1)	103.1 (95.7–110.5)	88.1 (72.4–103.8)	114.2 (73.5–154.9)
Medication, n				
OTC pain	21	21	3	2
Prescription pain	5	16*	2	2
Blood pressure	9	15	2	0
Thyroid	12	13	4	2
Hormone therapy	31	18*	2	0

ATOR indicates atorvastatin; BMI, body mass index; C, cholesterol; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OTC, over-the-counter; PL, placebo; SBP, systolic blood pressure; and  $\dot{V}O_{2\max}$ , maximal oxygen uptake. OTC pain indicates regular use of such medications as nonsteroidal antiinflammatory drugs and acetaminophen; prescription pain, regular use of prescription pain medications; blood pressure, blood pressure-lowering drug; thyroid, synthetic thyroid drug; and hormone therapy, oral contraceptives or hormone replacement therapy if female. Data are presented as point estimates and 95% confidence intervals for atorvastatin versus placebo subjects in the entire sample and only in subjects classified as myalgic.

\*Significant difference between myalgic and nonmyalgic subjects within a treatment group at  $P<0.05$ .

appear to have measurable physiological consequences in that muscle strength was not reduced to a greater extent in myalgic participants on atorvastatin compared with placebo subjects also satisfying the study definition of myalgia. The observation that some placebo patients satisfied the myalgia definition documents the importance of using a double-blind trial to examine the incidence and characteristics of statin-associated myalgia and not relying solely on clinical characteristics. STOMP also demonstrated, we believe again for the first time, that high-dose statin treatment increases average CK levels, suggesting that statins produce low-level muscle injury in healthy subjects that occurs independently of muscle symptoms.

The reported incidence of myalgia during statin therapy has varied from 1% to 25%.<sup>3,10,11</sup> Determining the true incidence of

mild muscle complaints from prior studies is difficult because these complaints are typically not solicited and because most large trials typically define myopathy as either myositis or rhabdomyolysis and require CK levels to be >10 times the ULN. We used a standardized study protocol and definition and observed that high-dose atorvastatin doubled the incidence of reproducible muscle complaints, from 4.6% to 9.4% of subjects. STOMP enrolled equal numbers of young, middle-aged, and older men and women, but the incidence of myalgia was similar to the 10.5% rate reported among 7924 French patients.<sup>9</sup> Observational reports suggest that statin-associated muscle complaints are more frequent in older adults and/or women.<sup>12–14</sup> Subjects with statin myalgia in STOMP tended to be older and almost 60% were women, but the STOMP sample size was too small to detect sex differences in incidence.

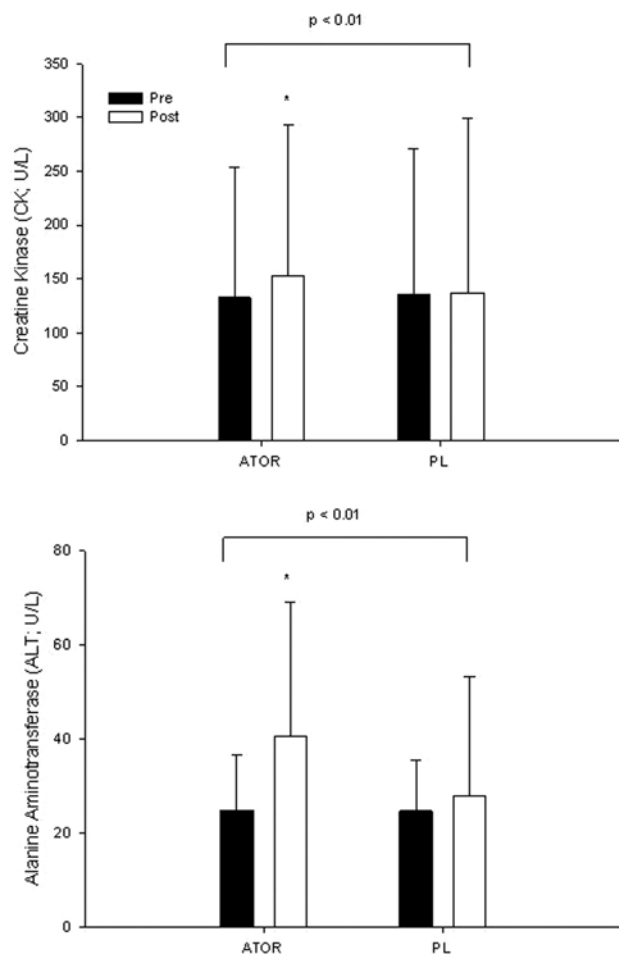
**Table 2. Lipid Changes by Drug Assignment and Myalgia Status**

	Total Sample		Myalgic Sample	
	ATOR (n=203)	PL (n=217)	ATOR (n=19)	PL (n=10)
ΔTotal-C, mg/dL	−65.3 (−70.1 to −60.5)*	2.7 (−0.2 to 5.6)	−73.9 (−88.0 to −59.8)*	12.2 (0.0 to 24.4)
ΔLDL-C, mg/dL	−59.0 (−63.4 to −54.6)*	0.9 (−1.8 to 3.6)	−70.6 (−83.5 to −57.7)*	10.1 (−1.4 to 21.6)
ΔHDL-C, mg/dL	−0.8 (−2.0 to 0.4)	0.4 (−0.7 to 1.5)	0.2 (−4.3 to 4.7)	−3.4 (−9.1 to 2.3)
ΔTRIG, mg/dL	−28.3 (−34.4 to −22.3)*	3.5 (−3.1 to 10.1)	−18.2 (−28.0 to −8.4)*	16.5 (−12.3 to 45.3)

Δ indicates absolute change from before to after the study; ATOR, atorvastatin; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PL, placebo; and TRIG, triglycerides. Data are presented as point estimates and 95% confidence intervals for atorvastatin versus placebo subjects in the entire sample and only in subjects classified as myalgic.

\*Significant change from baseline at  $P<0.01$ . There were no differences between myalgic and nonmyalgic subjects within a treatment group.





**Figure 2.** Group mean $\pm$ SD of creatine kinase (CK; top) and alanine aminotransferase (ALT; bottom) before (Pre) and after (Post) 6 months of atorvastatin (ATOR) or placebo (PL) treatment. Brackets indicate the  $P$  value for group-by-time interaction. \*Significant difference between groups within a time point at  $P < 0.05$ .

Interestingly, the French study<sup>9</sup> observed that muscle symptoms generally appeared within a month of drug initiation. This was also true in STOMP, and the time to symptom onset was significantly shorter in myalgic subjects on atorvastatin than on placebo, 1 versus 2 months.

Clinical trials define statin-associated myopathy as CK levels  $>10$  times the ULN.<sup>4,14</sup> No subject in STOMP recorded a CK  $>10$  times the ULN, but 6 months of treatment with atorvastatin resulted in a small ( $\sim 20$  U/L) but significant ( $P < 0.01$ ) increase in CK. This suggests that low-level muscle injury occurs with high-dose statins, although there are other possible explanations for the CK increase. Inflammatory conditions, including rheumatoid arthritis and systemic lupus, are associated with reduced CK levels.<sup>15</sup> Statins reduce systemic inflammation<sup>1</sup> and could increase average CK by decreasing inflammation. We did not measure inflammatory markers in STOMP and thus cannot evaluate this possible relationship. Alternatively, hepatic macrophages participate in the clearance of CK.<sup>16</sup> Decreasing the hepatic macrophages in animal models increases CK concentrations, suggesting that statins, if they decrease the hepatic macrophage content, could reduce CK clearance and increase CK levels. There was no

**Table 3. Absolute (Post Minus Baseline) Aerobic and Strength Data by Drug Assignment**

	ATOR (n=202*)	PL (n=217)
Resting RER	0.0 (−0.01 to 0.01)	0.0 (−0.03 to 0.03)
$\dot{V}O_{2\max}$ , mL·kg <sup>−1</sup> ·min <sup>−1</sup>	−0.8 (−1.3 to −0.3)	−0.8 (−1.4 to −0.2)
VT, mL·kg <sup>−1</sup> ·min <sup>−1</sup>	−0.9 (−1.6 to −0.2)	−0.6 (−1.6 to 0.4)
Hand grip, kg	0.1 (−0.5 to 0.7)	−0.6 (−1.3 to 0.1)
Arm strength (APT), N·m		
Isom Ext	0.8 (−0.2 to 1.8)	0.3 (−0.6 to 1.2)
Isom Flex	−0.5 (−2.1 to 1.1)	−0.2 (−1.1 to 0.7)
Isok Ext at 60°/s	0.5 (−0.2 to 1.2)	−0.2 (−0.9 to 0.5)
Isok Flex at 60°/s	0.0 (−0.6 to 0.6)	0.0 (−0.6 to 0.6)
Isok Ext at 180°/s	0.5 (−0.2 to 1.2)	0.6 (0.2 to 1.2)
Isok Flex at 180°/s	0.2 (−0.6 to 1.0)	0.1 (−0.5 to 0.7)
Leg strength (APT), N·m		
Isom Ext	−2.1 (−5.1 to 0.9)	−0.4 (−3.4 to 2.6)
Isom Flex	−1.8 (−3.2 to −0.4)	−1.3 (−2.6 to 0.0)
Isok Ext at 60°/s	1.2 (−0.8 to 3.2)	0.9 (−1.1 to 2.9)
Isok Flex at 60°/s	0.9 (−0.5 to 2.3)	−0.5 (−2.7 to 1.7)
Isok Ext at 180°/s	3.9 (2.0 to 5.8)	3.8 (2.3 to 5.3)
Isok Flex at 180°/s	2.7 (1.5 to 3.9)	2.1 (1.0 to 3.2)
Knee endurance fatigue index	−0.1 (−1.6 to 1.4)	0.2 (−0.8 to 1.2)

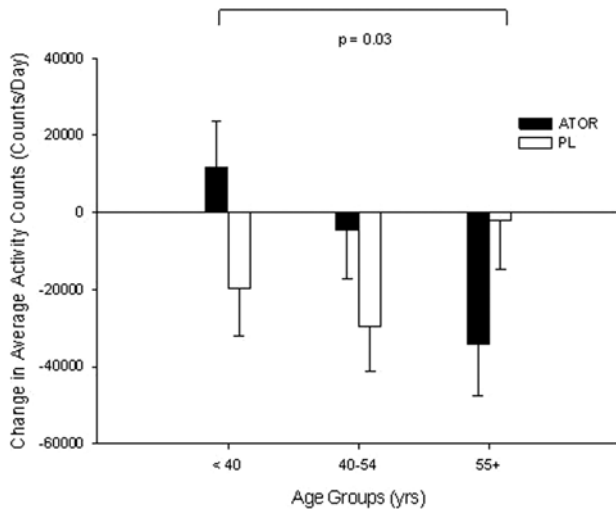
APT indicates average peak torque; ATOR, atorvastatin; Ext, extension; Flex, flexion; Isom, isometric; PL, placebo; RER, respiratory exchange ratio;  $\dot{V}O_{2\max}$ , maximal oxygen uptake; and VT, ventilatory threshold. There were no significant differences in change scores between atorvastatin and placebo treatment groups. Data are presented as point estimates and 95% confidence intervals for atorvastatin versus placebo subjects.

\*One ATOR subject with myalgia did not complete muscle and aerobic posttesting and thus was not included in analyses.

correlation between changes in CK and ALT in STOMP, but we cannot further evaluate this possibility. Both explanations seem less likely than the hypothesis that statins produce low-level muscle injury given the plethora of data linking statins to skeletal muscle damage,<sup>17–19</sup> even in the absence of muscle symptoms.<sup>20</sup>

The long-term clinical consequences of this mild CK elevation are unclear because the CK elevation was not accompanied by changes in muscle strength. Anecdotally, some patients with weakness attributed to statin therapy develop such complaints only after years of treatment.<sup>12</sup> Therefore, it is possible that low-level muscle injury, indicated by mild elevations in CK, will produce subsequent weakness in some statin-treated subjects. Testing this hypothesis will be difficult because it requires a long-term placebo-controlled trial, an ethically difficult proposition given the documented therapeutic value of statins. In addition, such a study would require sophisticated strength testing because we detected decreased strength among our myalgic subjects even though few complained of muscle weakness.

There were no significant changes in muscle strength, endurance, and aerobic performance in the total atorvastatin STOMP population. Previous investigations have been equivocal, with some studies suggesting that statins reduce muscle strength in older individuals and that statins may shift exercise



**Figure 3.** Group mean $\pm$ 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.

substrate use from fat to carbohydrate.<sup>21–24</sup> Most studies were small, used crude measures of strength and exercise performance, and were not blinded or placebo controlled.<sup>5</sup> STOMP provides reassurance that healthy adults who tolerate high-dose atorvastatin without muscle complaints experience no deleterious effects on muscle strength or performance over 6 months of treatment. We observed that average physical activity, measured by accelerometer, decreased significantly

in the oldest STOMP age group with atorvastatin therapy, but this could simply represent measurement variability because physical activity increased in the youngest atorvastatin-treated subjects.

In contrast to the total study sample, statin-treated subjects meeting the study definition of myalgia demonstrated reductions in muscle strength in 5 of 14 measured muscle strength variables (Table 4). Several observational studies have suggested that patients with myalgia experience a decrease in strength.<sup>4,25</sup> However, subjects in the placebo group meeting the study definition of myalgia also demonstrated muscle strength declines in 4 measured variables, suggesting that the majority of muscle strength changes with myalgia in STOMP may have been nonspecific. Caution should be exercised in the interpretation of these data, however, because the analyses were secondary to major study outcomes in a very small sample of patients. Therefore, larger studies of patients with true statin myalgia—rigorously tested with a double-blind, randomized, crossover period to confirm myalgia in the initial study population—are needed to determine the effects of statin on muscle outcomes in myopathic patients.

STOMP has significant advantages over prior observational studies, but it also has limitations. STOMP examined only the effect of atorvastatin on muscle complaints and function and thus cannot evaluate whether other statins at comparable doses would produce similar results. STOMP enrolled only healthy individuals; therefore, it cannot address the frequency or severity of muscular complaints in patients

**Table 4. Absolute (Post Minus Baseline) Aerobic and Strength Data by Drug Assignment in Myalgic Patients**

	ATOR (n=18*)	PL (n=10)
Resting RER	0.0 (–0.05 to 0.05)	0.1 (–0.1 to 0.3)
$\dot{V}O_{2\max}$ , mL·kg <sup>–1</sup> ·min <sup>–1</sup>	–0.5 (–1.3 to 0.3)	–1.3 (–2.8 to 0.2)
VT, mL·kg <sup>–1</sup> ·min <sup>–1</sup>	–2.1 (–3.9 to 0.3)	–2.3 (–5.9 to 1.3)
Hand grip, kg	–1.4 (–3.4 to 0.6)	–1.0 (–3.7 to 1.7)
Arm strength (APT), N·m		
Isom Ext	–0.4 (–4.2 to 3.4)	1.1 (–2.4 to 4.6)
Isom Flex	–3.2 (–7.5 to 1.1)	0.7 (–3.6 to 5.0)
Isok Ext at 60°/s	–2.6 (–6.2 to 1.0)	0.3 (–1.9 to 2.5)
Isok Flex at 60°/s	–3.8 (–7.8 to 0.2)†	0.8 (–1.2 to 2.8)
Isok Ext at 180°/s	–1.3 (–4.4 to 1.8)	–0.4 (–2.2 to 1.4)†
Isok Flex at 180°/s	–0.5 (–4.1 to 3.1)	0.2 (–2.2 to 3.6)
Leg strength (APT), N·m		
Isom Ext	–17.3 $\pm$ (–25.1 to –9.5)†	–21.5 (–30.6 to –12.4) †
Isom Flex	–5.3 (–10.4 to –0.2)	–4.3 (–10.2 to 1.6)
Isok Ext at 60°/s	–10.4 (–20.2 to –0.6)†	–6.6 (–14.5 to 1.3)
Isok Flex at 60°/s	–3.6 (–8.6 to 1.4)†	–4.6 (–8.7 to –0.5)
Isok Ext at 180°/s	–3.0 (–8.9 to 2.9)†	–4.1 (–10.1 to 1.9)†
Isok Flex at 180°/s	–1.0 (–4.6 to 2.6)	–3.9 (–6.8 to –1.0)†
Knee endurance fatigue index	–2.1 (–4.4 to 0.2)	–3.6 (–5.7 to –1.5)

APT indicates average peak torque; ATOR, atorvastatin; Ext, extension; Flex, flexion; Isom, isometric; PL, placebo; RER, respiratory exchange ratio;  $\dot{V}O_{2\max}$ , maximal oxygen uptake; and VT, ventilatory threshold. Data are presented as point estimates and 95% confidence intervals for atorvastatin versus placebo subjects in subjects classified as myalgic.

\*One ATOR subject with myalgia did not complete muscle and aerobic posttesting and thus was not included in analyses.

†Significant difference in change scores between myalgic and nonmyalgic groups (from Table 3) within a treatment group at *P* < 0.05.

with concomitant diseases and medications. The inclusion of younger subjects and both sexes may have reduced the number of subjects with myalgia during atorvastatin treatment because subjects with statin myalgia in STOMP tended to be older and more were woman. STOMP lasted only 6 months and therefore may underestimate the incidence of myopathic complaints during longer-term statin therapy, although the onset of myalgia with atorvastatin occurred an average of 1 month after initiation of therapy. Longer placebo-controlled trials to examine the frequency of myopathic complaints in sicker subjects will be difficult, however, given the general reluctance to assign statin-eligible subjects to placebo treatment. On the other hand, given that statins have been clinically available and widely used in the United States since 1987 and the paucity of documented decreases in muscle strength among statin-treated patients, STOMP may overestimate the frequency and strength changes of statin-associated myalgia. This seems unlikely, however, given the rigor of the STOMP design.

### Conclusions

STOMP is, to the best of our knowledge, the first randomly assigned, double-blind study designed to examine the effects of statins on muscular complaints, muscle strength, and exercise performance. The results are reassuring in that there was no effect of atorvastatin 80 mg daily on muscle strength or exercise performance over 6 months of treatment in healthy subjects. On the other hand, STOMP documented that atorvastatin significantly increased the frequency of myalgia. STOMP also demonstrated an increase in average CK in the atorvastatin-treated cohort, suggesting that statins could produce low-level muscle injury. These results should prompt additional studies examining muscular performance with long-term statin treatment in both healthy patients and those with confirmed statin-associated myalgia.

### Acknowledgments

We wish to acknowledge the following individuals for their participation on the Data Safety Monitoring Board: JoAnne Foody, MD; Pamela Hartigan, PhD; and Ira Ockene, MD (chair). In addition, Gualberto Ruano, MD, PhD and Benjamin Levine, MD provided statistical and scientific assistance with data interpretation.

### Sources of Funding

The STOMP study is funded by National Heart, Lung, and Blood Institute/National Institutes of Health grant RO1 HL081893 (Dr Thompson).

### Disclosures

Dr Thompson reports receiving research grants from the National Institutes of Health, GlaxoSmithKline, Anthera, B. Braun, Genomas, Roche, Aventis, Novartis, and Furiex; serving as a consultant for AstraZeneca, Furiex, Regeneron, Merck, Roche, Genomas, Abbott, Lupin, *Runner's World*, Genzyme, Sanofi, Pfizer, and GlaxoSmithKline; receiving speaker honoraria from

Merck, Pfizer, Abbott, AstraZeneca, GlaxoSmithKline, and Kowa; owning stock in General Electric, JA Wiley Publishing, J&J, Sanofi-Aventis, and Abbott; and serving as a medical legal consultant on cardiac complications of exercise, statin myopathy, tobacco, ezetimibe, and nonsteroidals. The other authors report no conflicts.

### References

1. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
2. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med*. 2002;346:539–540.
3. *Physicians' Desk Reference*. Montvale, NJ: Medical Economics; 2002:56.
4. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, Vladutiu GD, England JD. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med*. 2002;137:581–585.
5. Krishnan GM, Thompson PD. The effects of statins on skeletal muscle strength and exercise performance. *Curr Opin Lipidol*. 2010;21:324–328.
6. Thompson PD, Parker BA, Clarkson PM, Pescatello LS, White CM, Grimaldi AS, Levine BD, Haller RG, Hoffman EP. A randomized clinical trial to assess the effect of statins on skeletal muscle function and performance: rationale and study design. *Prev Cardiol*. 2010;13:104–111.
7. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA*. 2003;289:1681–1690.
8. Katsiras A, Newman AB, Kriska A, Brach J, Krishnaswami S, Feingold E, Kritchevsky SB, Li R, Harris TB, Schwartz A, Goodpaster BH. Skeletal muscle fatigue, strength, and quality in the elderly: the Health ABC Study. *J Appl Physiol*. 2005;99:210–216.
9. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients: the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19:403–414.
10. Phillips PS, Haas RH. Observations from a statin myopathy clinic. *Arch Intern Med*. 2006;166:1232–1233.
11. El-Salem K, Ababneh B, Rudnicki S, Malkawi A, Alrefai A, Khader Y, Saadeh R, Saydam M. Prevalence and risk factors of muscle complications secondary to statins. *Muscle Nerve*. 2011;44:877–881.
12. Cham S, Evans MA, Denenberg JO, Golomb BA. Statin-associated muscle-related adverse effects: a case series of 354 patients. *Pharmacotherapy*. 2010;30:541–553.
13. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman II, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol*. 2002;40:567–572.
14. Maningat P, Breslow JL. Needed: pragmatic clinical trials for statin-intolerant patients. *N Engl J Med*. 2011;365:2250–2251.
15. Lee YH, Choi SJ, Ji JD, Song GG. Serum creatine kinase in patients with rheumatic diseases. *Clin Rheumatol*. 2000;19:296–300.
16. Radi ZA, Koza-Taylor PH, Bell RR, Obert LA, Runnels HA, Beebe JS, Lawton MP, Sadis S. Increased serum enzyme levels associated with Kupffer cell reduction with no signs of hepatic or skeletal muscle injury. *Am J Pathol*. 2011;179:240–247.
17. Hanai J, Cao P, Tanksale P, Imamura S, Koshimizu E, Zhao J, Kishi S, Yamashita M, Phillips PS, Sukhatme VP, Lecker SH. The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. *J Clin Invest*. 2007;117:3940–3951.
18. Urso ML, Clarkson PM, Hittel D, Hoffman EP, Thompson PD. Changes in ubiquitin proteasome pathway gene expression in skeletal muscle with exercise and statins. *Arterioscler Thromb Vasc Biol*. 2005;25:2560–2566.
19. Parker BA, Augeri AL, Capizzi JA, Ballard KD, Troyanos C, Baggish AL, D'Hemecourt PA, Thompson PD. Effect of statins on creatine kinase levels before and after a marathon run. *Am J Cardiol*. 2012;109:282–287.
20. Mohaupt MG, Karas RH, Babychuk EB, Sanchez-Freire V, Monastyrskaya K, Iyer L, Hoppeler H, Breil F, Draeger A. Association between statin-associated myopathy and skeletal muscle damage. *CMAJ*. 2009;181:E11–E18.
21. Paolisso G, Barbagallo M, Petrella G, Ragno E, Barbieri M, Gior-dano M, Varricchio M. Effects of simvastatin and atorvastatin

- administration on insulin resistance and respiratory quotient in aged dyslipidemic non-insulin dependent diabetic patients. *Atherosclerosis*. 2000;150:121–127.
22. Phillips PS, Phillips CT, Sullivan MJ, Naviaux RK, Haas RH. Statin myotoxicity is associated with changes in the cardiopulmonary function. *Atherosclerosis*. 2004;177:183–188.
  23. Mullen PJ, Zahno A, Lindinger P, Maseneni S, Felser A, Krähenbühl S, Brecht K. Susceptibility to simvastatin-induced toxicity is partly determined by mitochondrial respiration and phosphorylation state of Akt. *Biochim Biophys Acta*. 2011;1813:2079–2087.
  24. Wu JS, Buettner C, Smithline H, Ngo LH, Greenman RL. Evaluation of skeletal muscle during calf exercise by 31-phosphorus magnetic resonance spectroscopy in patients on statin medications. *Muscle Nerve*. 2011;43:76–81.
  25. Dobkin BH. Underappreciated statin-induced myopathic weakness causes disability. *Neurorehabil Neural Repair*. 2005;19:259–263.

### CLINICAL PERSPECTIVE

Many clinicians believe that statins cause muscle pain, but this has not been observed in clinical trials, and the effect of statins on muscle performance has not been carefully studied. The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study assessed symptoms and measured creatine kinase, exercise capacity, and muscle strength before and after atorvastatin 80 mg or placebo was administered for 6 months to 420 healthy, statin-naïve subjects. No creatine kinase value exceeded 10 times normal in any subject during the trial, but average creatine kinase increased  $20.8 \pm 141.1$  U/L ( $P < 0.01$ ) with atorvastatin. There were no significant changes in several measures of muscle strength or exercise capacity with atorvastatin, but more atorvastatin than placebo subjects developed myalgia (19 versus 10;  $P = 0.05$ ). Myalgic subjects on atorvastatin or placebo had decreased muscle strength in 5 of 14 and 4 of 14 variables, respectively ( $P = 0.43$ ). These results indicate that high-dose atorvastatin treatment for 6 months does not decrease average muscle strength or exercise performance in healthy, previously untreated subjects. Nevertheless, this blinded, controlled trial confirms the undocumented impression that statins increase muscle complaints. Atorvastatin also increased average creatine kinase, suggesting that statins produce mild muscle injury even among asymptomatic subjects. This increase in creatine kinase should prompt studies examining the effects of more prolonged, high-dose statin treatment on muscle performance.



## 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;  
doi: 10.1161/CIRCULATIONAHA.112.136101

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2012 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the  
World Wide Web at:

<http://circ.ahajournals.org/content/127/1/96>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation* is online at:  
<http://circ.ahajournals.org/subscriptions/>