Journal of the American College of Cardiology Vol. 47, No. 5, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.10.052

# Statin Use and Functional Decline in Patients With and Without Peripheral Arterial Disease

Jay Giri, MD, MPH,* Mary M. McDermott, MD,† Philip Greenland, MD,† Jack M. Guralnik, MD, PHD,‡ Michael H. Criqui, MD, MPH,§ Kiang Liu, PHD,† Luigi Ferrucci, MD, PHD,‖ David Green, MD, PHD,† Joseph R. Schneider, MD, PHD,¶ Lu Tian, SCD†

*Boston, Massachusetts; Chicago and Evanston, Illinois; Bethesda, Maryland; and San Diego, California*

**OBJECTIVES** We determined whether statin use (vs. non-use) is associated with less annual decline in lower-extremity functioning in patients with and without lower-extremity peripheral arterial disease (PAD) over three-year follow-up.

**BACKGROUND** It is unclear whether statin use is associated with less functional decline in patients with PAD.

**METHODS** Participants included 332 men and women with an ankle brachial index (ABI) <0.90 and 212 with ABI 0.90 to 1.50. Functional outcomes included 6-min walk distance and usual and rapid-pace 4-m walking velocity. A summary performance score combined performance in walking speed, standing balance, and time for five repeated chair rises into an ordinal score ranging from 0 to 12 (12 = best).

**RESULTS** Adjusting for age, race, gender, comorbidities, education, health insurance, total cholesterol/high-density lipoprotein level, body mass index, pack-years of smoking, leg symptoms, immediately previous year functioning, statin use/non-use, ABI, and change in ABI, the PAD participants using statins had less annual decline in usual-pace walking velocity (0.002 vs. −0.024 m/s/year, p = 0.013), rapid-pace walking velocity (−0.006 vs. −0.042 m/s/year, p = 0.006), 6-min walk performance (−34.5 vs. −57.9 feet/year, p = 0.088), and the summary performance score (−0.152 vs. −0.376, p = 0.067) compared with non-users. These associations were attenuated slightly by additional adjustment for high-sensitivity C-reactive protein levels. Among non-PAD participants, there were no significant associations between statin use and functional decline.

**CONCLUSIONS** The PAD patients on statins have less annual decline in lower-extremity performance than PAD patients who are not taking statins. (J Am Coll Cardiol 2006;47:998–1004) © 2006 by the American College of Cardiology Foundation

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor drugs (statins) have beneficial effects on atherosclerosis over and above modification of the lipid profile. These include reduction of vascular inflammation, atheromatous plaque stabilization, and increases in nitric oxide concentrations leading to greater endothelium-dependent vasodilation (1–4). Such properties may contribute to reductions in cardiac and cerebrovascular events in patients taking statins (5–7).

In cross-sectional analyses, men and women with lower-extremity peripheral arterial disease (PAD) have impaired functioning proportionate to the PAD severity, as measured by the ankle-brachial index (ABI), compared with those without PAD (8). A previous cross-sectional study showed statin users with PAD to have less functional impairment than statin non-users (9). Recent clinical trials have shown mixed results regarding treadmill walking performance among PAD patients with intermittent claudication taking statins compared with those not taking statins (10–12). To our knowledge, no prior studies have described associations between statin use and annual decline in objectively assessed functional outcome measures in a large group of patients with PAD, including those with and without classic symptoms of intermittent claudication. In a three-year prospective study of men and women with and without PAD, we hypothesized that statin use would be associated with less annual functional decline than statin non-use in patients with and without PAD.

## METHODS

Methods for this longitudinal study of functional outcomes in men and women with and without PAD have been reported previously and are summarized here (13).

**Participant identification.** The protocol was Institutional Review Board-approved by Northwestern University Feinberg School of Medicine and Catholic Health Partners Hospitals. Participants gave informed consent. The PAD participants were identified consecutively from patients diagnosed with PAD in three Chicago-area non-invasive vascular laboratories. Non-PAD participants were identified consecutively from patients with normal lower-extremity arterial studies in three Chicago-area non-invasive vascular laboratories and from patients with appointments in a large general medicine practice at Northwestern University. Non-PAD participants were identified from the general medicine

From *Massachusetts General Hospital, Boston, Massachusetts; †Northwestern University Feinberg School of Medicine, Chicago, Illinois; ‡Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, Maryland; §University of California at San Diego, San Diego, California; ‖Clinical Research Branch, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; and ¶Evanston/Northwestern Hospital, Evanston, Illinois. Supported by grants R01-HL58099 and R01-HL64739 from the National Heart, Lung, and Blood Institute and by grant RR-00048 from the National Center for Research Resources, National Institutes of Health. David Waters acted as the Guest Editor for this paper.

Manuscript received March 31, 2005; revised manuscript received October 5, 2005, accepted October 7, 2005.

**Abbreviations and Acronyms**

ABI = ankle-brachial index
BMI = body mass index
HDL = high-density lipoprotein
hsCRP = high-sensitivity C-reactive protein
PAD = peripheral arterial disease

practice because these individuals are comparable to patients without PAD who are typically encountered in general medical practice. Non-PAD participants were identified from the non-invasive vascular laboratory because these individuals were expected to more closely resemble the PAD population (i.e., with regard to leg symptoms and demographics) except for the presence versus absence of PAD.

Identified individuals were invited to return to the medical center for a baseline study visit between October 1998 and January 2000. Participants were asked to return annually for follow-up.

**Exclusion criteria.** Presence of PAD was defined as ABI $<0.90$. Absence of PAD was defined as ABI $\geq 0.90$ and $\leq 1.50$ (8). Individuals with ABI $>1.50$ were excluded because this indicates poorly compressible leg arteries and inability to gauge arterial perfusion accurately (14).

Individuals with PAD diagnosed in the non-invasive vascular laboratory were excluded if their study visit ABI indicated an absence of PAD. This occasionally occurred when PAD participants were revascularized between vascular laboratory testing and their study visit. It also occurred in individuals with borderline ABI values of approximately 0.90 because of measurement variation. Patients with dementia were excluded because of the inability to answer questions accurately. Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded because they were unable to perform many of the functional measures. Non–English-speaking patients were excluded because investigators were not fluent in non-English languages. Patients with recent major surgery were excluded. Participants with a normal ABI and a history of prior lower-extremity revascularization were excluded because these individuals could not be clearly classified as non-PAD participants, yet did not meet our inclusion criterion for PAD participants. The PAD participants who underwent lower-extremity revascularization after baseline were excluded because the revascularization may have altered their functional decline, independent of statin use versus non-use.

**Ankle brachial index measurement.** The ABI was measured using established methods (8,14). After participants rested supine for five minutes, a hand-held Doppler probe (Nicolet Vascular Pocket Dop II, Golden, Colorado) was used to measure systolic pressures in the right brachial artery, right dorsalis pedis and posterior tibial arteries, left dorsalis pedis and posterior tibial arteries, and left brachial artery. Each pressure was measured twice: in the order listed and then in the reverse order. The ABI was calculated in each leg by dividing average pressures in each leg by the average of the four brachial pressures. Average brachial pressures in the arm with the highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets and the two brachial pressures differed by $\geq 10$ mm Hg in at least one measurement set, because in such cases subclavian stenosis was possible (14). The lowest leg ABI was used in analyses.

**High-sensitivity C-reactive protein levels.** High-sensitivity C-reactive protein (hsCRP) levels were determined using an immunotechnique on the Behring BN II analyzer (Dade Behring, Wilmington, Delaware) (15).

**Cholesterol levels.** Total cholesterol levels were measured using enzymatic reaction with peroxidase/phenol-4-aminoiphenazone indicator reaction (16). High-density lipoprotein (HDL) cholesterol was measured using a direct enzymatic colorimetric assay (17).

**Comorbidities.** Algorithms developed for the Women's Health and Aging Study and the Cardiovascular Health Study were used to document comorbidities (18). These algorithms combine data from patient reports, physical examinations, medical record reviews, medications, laboratory values, and a primary care physician questionnaire. American College of Rheumatology criteria were used to diagnose knee and hip osteoarthritis (19,20). Comorbidities assessed were angina, diabetes mellitus, myocardial infarction, stroke, heart failure, pulmonary disease, knee and hip arthritis, spinal stenosis, disk disease, Parkinson disease, and hip fracture. These comorbidities were chosen because they are associated with impaired functioning (21,22).

**Statin use.** All prescription and over-the-counter medications were recorded at each study visit. Doses were not recorded. The study principal investigator (M.M.M.) identified statin medications from all recorded medications while blinded to all other participant data.

**Functional measures.** Functional measures were performed at baseline and at each follow-up visit by a health interviewer blinded to the ABI value. Our primary outcome measure was the 6-min walk test.

**6-min walk.** Following a standardized protocol (23), participants walked up and down a 100-foot hallway for six minutes after instructions to cover as much distance as possible.

**Summary performance score.** The summary performance score is a global measure of lower-extremity functioning that predicts mobility loss, nursing home placement, and mortality among community-dwelling older men and women (24–27). To calculate the summary performance score, a 0 to 4 score is assigned for performance on 4-m walking velocity, time to rise from a seated position five times, and standing balance, respectively (24–27). Individuals receive a 0 score for each task they are unable to complete. Scores of 1 to 4 for each task are assigned based on quartiles of performance for over 5,000 community-dwelling men and women (24–27). Scores are summed to

obtain the summary performance score, ranging from 0 to 12.

**Repeated chair rises.** Participants sat in a straight-backed chair with arms folded across their chest and stood five times consecutively as quickly as possible. The time for five chair rises was measured.

**Standing balance.** Participants were asked to hold three increasingly difficult standing positions for 10 s each: standing with both feet together side-by-side and parallel (side-by-side stand), standing feet parallel with the toes of one foot adjacent to and touching the heel of the opposite foot (semi-tandem stand), and standing with one foot directly in front of the other (tandem stand) (24–27).

**The 4-m walking velocity.** Walking velocity was measured with a 4-m walk performed at "usual" and "fastest" pace. Each walk was performed twice. The faster walk in each pair was used in analyses (24–27).

**Other measures.** Height and weight were measured at the baseline and follow-up visits. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Pack-years of cigarette smoking, education level, and type of medical insurance were determined based on patient report.

**Follow-up.** Some participants who returned for follow-up testing refused to complete functional assessments. In these instances, we used the following a priori defined criteria to determine whether these participants were too disabled to complete functional measures. First, individuals for whom data collection forms indicated that the participant was unable to complete functional measures because of wheelchair confinement, exhaustion, shortness of breath, or other significant symptom were considered too disabled to complete functional measures. The study principal investigator (M. M. M.) made these decisions from information on the data collection forms, blinded to participant characteristics including ABI, PAD status, and functional performance at baseline. When data collection forms provided no information on the reason(s) that an individual refused to walk, a priori criteria were used to determine whether the participant was likely to have been too disabled to walk. These criteria were: 1) the participant reported walking fewer than five blocks during the previous week; 2) the score for repeated chair rises equaled 0 or 1; 3) the score for the standing balance test equaled 0 or 1. Participants who did not complete functional assessments and met two of these three criteria were considered too disabled to walk. Participants classified as too disabled to complete functional assessments were assigned the minimum value of performance for each test that they did not complete. The minimum value for each test was equivalent to the poorest performance among those who completed testing.

**Statistical analyses.** Baseline characteristics of participants were expressed according to their group classification (baseline statin use vs. baseline non-use) as means (SD) for continuous variables and proportions for binary variables (Table 1). The test for comparing the baseline statin users and non-users was performed using a two-sample *t* test for continuous variables and a chi-square test for binary variables.

In comparing functional performance across the time-dependent variable statin use versus non-use, a longitudinal or repeated measures analysis of covariance was carried out using mixed linear regression models (28). The subject-specific random effect was used to accommodate the likely correlation between repeated measurements for the same participant. The primary dependent variable for each analysis was the successive difference in the particular functional performance measure of interest (from baseline to year 1, from year 1 to year 2, and from year 2 to year 3). The analyses were performed in two steps. The independent variables in the first model include baseline covariates (gender, age, race, comorbidities, education, and health insurance) and time-dependent covariates (immediately previous year functioning and ABI, annual change in ABI, current year BMI, leg symptom, pack-years of smoking, and statin use). The time-dependent covariate changes over time for the same participants, e.g., statin use at year 1, 2, and 3, are covariate values for successive changes in functional performances from baseline to year 1, from year 1 to year 2, and from year 2 to year 3, respectively. The fully adjusted analyses were also adjusted for total cholesterol at baseline, annual hsCRP level, and other cardiovascular medication use.

Under mixed effects linear models, statistically valid inference is guaranteed provided any missing data caused by patient dropout are unrelated to observed or unobserved data (i.e., any missing data are missing at random). As a safeguard against violations to this assumption, we repeated the fully adjusted comparisons of functional performance between groups using a repeated measures pattern-mixture analysis of covariance model (29,30). These analyses yielded similar results to those of our primary analyses.

## RESULTS

Of 641 patients who completed all baseline testing, 544 (84.9%) completed at least one follow-up visit and were included in analyses. The mean time between annual follow-up visits for all participants was 12.4 months (SD = 1.4). Table 1 shows baseline characteristics of participants according to presence versus absence of PAD and statin use/non-use at baseline. Among PAD and non-PAD participants combined, statin users had significantly lower ABIs and total cholesterol levels, higher BMIs, and higher prevalences of cardiac and cerebrovascular disease compared with non-users. Statin users included more college graduates. Of 332 patients with PAD, 69 (20.7%) discontinued statins, and a total of 52 (15.7%) were newly initiated on statins over the three-year follow-up period. Of 212 patients in the non-PAD group, 29 (13.7%) discontinued statins, and 24 (11.3%) were newly initiated on them over the three-year follow-up period. At baseline, nine of the non-

**Table 1.** Baseline Characteristics of Participants With and Without Peripheral Arterial Disease According to Presence Versus Absence of Statin Use

| | PAD N = 332 | | Non-PAD N = 212 | | All Participants N = 544 | |
|---|---|---|---|---|---|---|
| | Statin Users (n = 152) | Non-Users (n = 180) | Statin Users (n = 61) | Non-Users (n = 151) | Statin Users (n = 213) | Non-Users (n = 331) |
| Age (yrs) | 70.9 (7.7) | 72.1 (9.1) | 69.2 (7.5) | 69.6 (8.3) | 70.5 (7.7) | 70.9 (8.8) |
| Male (%) | 64.5 | 60.0 | 55.7 | 49.7 | 62.0 | 55.3 |
| African-American race (%) | 12.5 | 14.4 | 16.4 | 17.2 | 13.6 | 15.7 |
| Ankle-brachial index | 0.66 (0.14) | 0.64 (0.15) | 1.08 (0.10) | 1.11 (0.12) | 0.78 (0.23)* | 0.86 (0.27) |
| Body mass index | 27.5 (4.5)† | 25.9 (6.3) | 28.2 (5.4) | 27.5 (6.5) | 27.7 (4.8)‡ | 26.6 (6.4) |
| Total cholesterol (mg/dl) | 171 (37.6)§ | 188 (37.4) | 165 (32.3)‖ | 182 (38.1) | 169 (36.1)§ | 186 (37.8) |
| Ratio of total cholesterol/HDL | 4.75 (2.02)‡ | 5.19 (1.67) | 4.09 (1.29) | 4.41 (1.73) | 4.56 (1.86) | 4.83 (1.74) |
| Smoking (pack years) | 37.6 (33.2) | 38.6 (34.2) | 13.4 (23.6) | 19.6 (27.6) | 30.7 (32.6) | 30.0 (32.7) |
| Diabetes (%) | 30.9 | 33.3 | 18.0 | 18.5 | 27.2 | 26.6 |
| Heart disease and stroke (%) | 69.7§ | 47.8 | 55.7¶ | 28.5 | 65.7§ | 39.0 |
| Health insurance | | | | | | |
| Medicare + private (%) | 48.7 | 55.0 | 45.9 | 34.4 | 47.9 | 45.6 |
| Medicare (%) | 25.7 | 18.3 | 21.3 | 24.5 | 24.4 | 21.1 |
| Public aid/Medicaid/no health insurance (%) | 3.3 | 6.7 | 4.9 | 7.9 | 3.8 | 7.2 |
| Education: college graduate or higher (%) | 46.7# | 35.6 | 50.8 | 40.0 | 47.9** | 37.6 |
| Functional performance | | | | | | |
| 6-min walk distance (ft) | 1184 (361) | 1116 (375) | 1466 (442) | 1408 (446) | 1264 (406) | 1249 (433) |
| Normal-pace 4-m walking velocity (m/s) | 0.915 (0.179)†† | 0.869 (0.228) | 0.990 (0.192) | 0.941 (0.216) | 0.937 (0.185) | 0.902 (0.225) |
| Normal-pace 4-m walking time (s) | 4.55 (1.00)‡‡ | 5.05 (2.08) | 4.23 (1.09) | 4.61 (1.79) | 4.46 (1.03)§§ | 4.85 (1.96) |
| Rapid-pace 4-m walking velocity (m/s) | 1.258 (0.231)‖‖ | 1.184 (0.297) | 1.316 (0.262) | 1.287 (0.304) | 1.275 (0.241) | 1.231 (0.304) |
| Rapid-pace 4-m walking time (s) | 3.31 (0.76)¶¶ | 3.70 (1.50) | 3.19 (0.80) | 3.41 (1.58) | 3.27 (0.77)§§ | 3.57 (1.54) |
| Summary performance score (0 to 12 score, 12 = best) | 10.2 (2.0)## | 9.2 (2.9) | 10.6 (2.1)*** | 10.0 (2.6) | 10.3 (2.1)††† | 9.5 (2.8) |

Values are expressed as mean (SD) unless otherwise indicated. Superscripts indicate p values for comparisons between statin users and statin non-users within each of the three groups: PAD, non-PAD, and all participants. *p = 0.001, †p = 0.033, ‡p = 0.029, §p < 0.0001, ‖p = 0.002, ¶p = 0.0002, #p = 0.019, **p = 0.022, ††p = 0.043, ‡‡p = 0.008, §§p = 0.009, ‖‖p = 0.012, ¶¶p = 0.003, ##p = 0.0003, ***p = 0.090, †††p = 0.0005.

HDL = high-density lipoprotein; PAD = peripheral arterial disease.

PAD participants had an ABI >1.30 and three had an ABI >1.40.

Adjusting for age, race, gender, comorbidities, education, health insurance, total cholesterol/HDL level, and the time-dependent variables BMI, pack-years of smoking, leg symptoms, immediately previous year functioning, statin use/non-use, ABI, and change in ABI (Table 2), PAD participants on statins had significantly less annual functional decline in usual-pace walking velocity (p = 0.013) and fastest-pace walking velocity (p = 0.006) when compared with PAD participants not taking statins. In these adjusted analyses, PAD participants on statins had less annual decline in 6-min walk performance (p = 0.088) and the summary performance score (p = 0.067).

Among patients with PAD who were on statins for the entire follow-up period and attended all three follow-up visits, the average time to walk 4 m at a usual pace increased by a total of 0.71 s (4.53 s at baseline and 5.24 s at three-year follow-up) as compared with an increase of 1.74 s (5.20 s at baseline and 6.94 s at three-year follow-up) in those PAD patients who never used statins over the three-year follow-up period. The results were similar for total time to walk 4 m rapidly, with increases of 0.39 s for PAD patients always on statins (3.29 and 3.68 s at baseline and three-year follow-up, respectively) and 1.07 s for PAD patients who never took statins (3.77 and 4.84 s, respectively).

Among participants with PAD, results shown in Table 2 were attenuated slightly when analyses were repeated with additional adjustment for hsCRP. For the normal-pace 4-m walking velocity, average annual changes were 0.006 versus −0.017 m/s/year, p = 0.037, after additional adjustment for hsCRP. For fast-paced 4-m walking velocity, average annual changes were 0.002 versus −0.032 m/s/year, p = 0.011, after additional adjustment for hsCRP. Additional adjustment for other cardiovascular medication use (aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors) did not substantially affect our results.

We found no significant associations between statin use and functional decline among participants without PAD (Table 2).

**Table 2.** Adjusted Associations Between Statin Use and Functional Decline According to Statin Use Among Patients With and Without Peripheral Arterial Disease*

| | Peripheral Arterial Disease (n = 332) | | | Non-Peripheral Arterial Disease | | |
|---|---|---|---|---|---|---|
| | Statin Users (n = 152) | Statin Non-Users (n = 180) | p Value | Statin Users (n = 61) | Statin Non-Users (n = 151) | p Value |
| 6-min walk distance (ft) | −34.5 (−65.5 to −3.43) | −57.9 (−89.3 to −26.5) | 0.088 | −57.8 (−107 to −8.5) | −77.7 (−121 to −34.3) | 0.241 |
| Normal-pace 4-m walking velocity (m/s) | 0.002 (−0.021 to 0.025) | −0.024 (−0.047 to −0.001) | 0.013 | −0.047 (−0.080 to −0.015) | −0.045 (−0.074 to −0.016) | 0.841 |
| Rapid-pace 4-m walking velocity (m/s) | −0.006 (−0.035 to 0.023) | −0.042 (−0.071 to −0.013) | 0.006 | −0.080 (−0.124 to −0.036) | −0.075 (−0.112 to −0.037) | 0.743 |
| Summary performance score (0 to 12 score, 12 = best) | −0.152 (−0.437 to 0.132) | −0.376 (−0.665 to −0.086) | 0.067 | −0.456 (−0.853 to −0.059) | −0.699 (−1.040 to −0.359) | 0.095 |

Adjusted average annual change (95% confidence interval). Analyses are adjusted for age, gender, race, prior year performance, ankle-brachial index (ABI), change in ABI, education, baseline health insurance, comorbidities, ratio of cholesterol level/HDL, time-dependent variables (body mass index, smoking, and leg symptoms, PAD only), and patterns of missing data. *Results of mixed linear regression models. The outcome variable in each mixed model was successive annual change in lower-extremity functional. Statin use was modeled as a time-dependent covariate in the analyses. The p values compare mean functional performance between statin users and non-users within each group (PAD, non-PAD, and all participants) for unadjusted analyses, and adjusted average annual change between statin users and non-users for the repeated measure analyses.
Abbreviations as in Table 1.

## DISCUSSION

Among people with PAD, statin users had less average annual functional decline compared with statin non-users over three years of follow-up, adjusting for a number of known and potential confounders. Among people without PAD, we observed no significant associations between statin use and functional decline.

We previously reported that people with PAD taking statins have better lower-extremity functioning than non-statin users in cross-sectional analyses (9). Subsequently, three placebo-controlled randomized trials evaluated statin use in PAD patients with intermittent claudication. Of these, two trials showed significant improvements in pain-free treadmill walking time, but no significant improvement

in maximum treadmill walking distance (10,11). The third trial showed significant improvements in both pain-free and maximal treadmill walking distance among PAD participants randomized to simvastatin as compared with placebo (12). Based on the mixed results from these three trials, the association between statin therapy and functional outcomes in people with PAD is still unclear.

Our study differed in several important ways from these previous clinical trials of statin use in patients with PAD. First, whereas previous studies assessed the effects of statin use on walking impairment in PAD patients with intermittent claudication, we included PAD participants with and without classic symptoms of intermittent claudication. Previous study shows that most men and women with PAD do not have classic symptoms of intermittent claudication (31,32). To our knowledge, no other studies have prospectively assessed associations between statin use and functional decline in PAD patients with and without classical intermittent claudication. Second, the three-year follow-up in the study reported here is longer than the duration of follow-up in the clinical trials of statin use in PAD. Third, our study simultaneously examined associations between statin use and functional decline in participants without PAD. Fourth, functional assessments reported here included measures other than walking endurance, such as usual and fastest-pace walking speed over 4 m. Finally, the functional outcomes assessed and reported here may be more relevant to real-world functioning than treadmill performance (24–27,33–36). For example, available data suggest that the six-minute walk test may be a better measure of walking endurance in the community than treadmill performance in older populations (33–36). Usual walking speed and the summary performance score have been shown to predict risk of future mobility loss, nursing home placement, disability in activities of daily living, and mortality in community-dwelling older men and women (24–27). Thus, 4-m walking velocity and the summary performance score are clinically meaningful outcome measures that are relevant for assessing risk of future mobility loss, nursing home placement, and other important functional outcome measures.

Studies examining biochemical markers of inflammation in statin users suggest that the anti-inflammatory effects of statins are most pronounced over the initial six weeks of use and may level off somewhat over ensuing months (37,38). Because participants in this report were likely to have been on statins for more than six weeks, our findings may underestimate the full magnitude of the effect of statin use on functional decline in PAD participants if attenuation of inflammation immediately after statins are prescribed is partly responsible for our observed findings regarding statin use and functional decline.

Several potential mechanisms may account for the associations observed between statin use and functional decline in people with PAD. First, regression of arterial plaque may be responsible for these associations. However, statins have been shown to have only a modest effect on arterial plaque regression (39), and our findings were independent of the ABI level. Secondly, anti-inflammatory effects of statins may explain the association of statin use with less functional decline. Systemic inflammation may contribute to sarcopenia, an age-related reduction in muscle strength and mass (40–42). Impairments in muscle mass and function may contribute to a causal pathway between inflammation and functional decline (42). Consistent with this hypothesis, our findings were attenuated slightly after additional adjustment for hsCRP, a systemic inflammatory marker. Lastly, recent studies show that statins improve endothelial function in peripheral arteries (43).

Our study does not allow us to ascertain why statin use was associated with significantly less functional decline in 4-m walking velocity but not in six-minute walk performance. However, mechanisms by which statins might contribute to less functional decline, such as improved endothelial function, may be more important for walking speed over short distances than walking endurance. Alternatively, anti-inflammatory effects of statins may affect type II (fast-twitch) muscle fibers to a greater degree than type I (slow-twitch) muscle fibers. Further study is necessary to determine the mechanisms by which statin use is associated with less functional decline in PAD.

Our study has some limitations. First, our study was not a randomized placebo-controlled clinical trial. Second, we did not have data on medication adherence. It is possible that our results may underestimate the effects of statins if all of the participants were not adherent. Third, statin dosage information was not available, and therefore was not considered in our analyses. We also did not have information on duration of statin use. In addition, we cannot rule out the possibility that positive associations between statin use and functioning are attributable to unmeasured confounders associated with better medical care, healthier lifestyle, or higher socioeconomic status that we could not fully adjust for in our analyses.

In conclusion, statin use was associated with less annual decline in walking speed among patients with PAD, independent of cholesterol level and other confounders. Further study is needed to determine the mechanisms of findings reported here. Further study is also needed to determine whether higher doses of statins are associated with less functional decline than lower doses of statins among people with PAD.

**Reprint requests and correspondence:** Dr. Mary M. McDermott, 676 North St. Clair, Suite 200, Chicago, Illinois 60611. E-mail: mdm608@northwestern.edu.

## REFERENCES

1. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxyl-3methylglutaryl coenzyme a reductase inhibitors. Arterioscler Thromb Vasc Biol 2001;11:1712–9.

2. Van Haelst PL, van Doormaal JJ, May JF, et al. Secondary prevention with fluvastatin decreases level of adhesion molecules, neopterin, and C-reactive protein. Eur J Intern Med 2001;12:503–9.
3. Hernandez-Perera O, Perez-Sala D, Navarro-Antolin J, et al. Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide in vascular endothelial cells. J Clin Invest 1998;101:2711–9.
4. Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998;97:1129–35.
5. O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. Circulation 1997;95:1126–3.
6. Crisby M, Nordin-Fredriksson G, Shah PK, et al. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. Circulation 2001;103:926–33.
7. Treasure CB, Klein JL, Weintraub WS, et al. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. N Engl J Med 1995;332:481–7.
8. McDermott MM, Greenland P, Liu K, et al. The ankle brachial index is associated with leg functioning and physical activity: the Walking and Leg Circulation Study. Ann Intern Med 2002;136:873–83.
9. McDermott MM, Guralnik JM, Greenland P, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation 2003;107:757–61.
10. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. Am J Cardiol 2003:92:711–2.
11. Mohler E, Hiatt W, Creager M. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation 2003;1088:1481–6.
12. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. Am J Med 2003;114:359–64.
13. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA 2004;292:453–61.
14. Olin JW. The clinical evaluation and office based detection of peripheral arterial disease. In: Hirsch AT, Olin FW, editors. An Office-Based Approach to the Diagnosis and Treatment of Peripheral Arterial Disease. I: The Epidemiology and Practical Detection of Peripheral Arterial Disease. Am J Med (Continuing Education Series) 1998:10–7.
15. Ledue TB, Weiner DL, Sipe JD, et al. Analytical evaluation of particle-enhanced immunonephelometric assays for C-reactive protein, serum amyloid A and mannose-binding protein in human serum. Ann Clin Biochem 1998;35:745–53.
16. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20:470–5.
17. Sugiuchi H, Uji Y, Okabe H, et al. Direct measurement of high-density lipoprotein cholesterol in serum with polyethylene glycol-modified enzymes and sulfated alpha-cyclodextrin. Clin Chem 1995; 41:717–23.
18. Guralnik JM, Fried LP, Simonsik EM, Kasper JD, Lafferty ME. The Women's Health and Aging Study: health and social characteristics of older women with disability. Bethesda, MD. National Institute on Aging, 1995. NIH publication No. 95-4009, Appendix E.
19. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.
20. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Arthritis Rheum 1986; 29:1039–49.
21. Ettinger WH Jr., Fried LP, Harris T, et al. Self-reported causes of physical disability in older people: the Cardiovascular Health Study. CHS Collaborative Research Group. J Am Geriatr Soc 1994;42:1035–44.
22. Boult C, Kane RL, Louis TA, Boult L, McCaffrey D. Chronic conditions that lead to functional limitation in the elderly. J Gerontol A Biol Sci Med Sci 1994;49:M28–36.
23. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The six-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132:919–23.
24. Guralnik JM, Ferrucci L, Simonsick E, Salive ME, Wallace RB. Lower extremity function in persons over 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556–61.
25. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–94.
26. Ostir GV, Markides KS, Black SA, Goodwin JS. Lower body functioning as a predictor of subsequent disability among older Mexican Americans. J Gerontol A Biol Sci Med Sci 1998;53A:M491–5.
27. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000;55A:M221–31.
28. Laird N, Ware J. Random-effects models for longitudinal data. Biometrics 1982;38:963–74.
29. Little RJ, Wang Y. Pattern-mixture models for multivariate incomplete data with covariates. Biometrics 1996;52:98–111.
30. Fitzmaurice GM, Laird NM, Shneyer L. An alternative parameterization of the general linear mixture model for longitudinal data with non-ignorable drop-outs. Stat Med 2001;20:1009–21.
31. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA 2001;286:1599–606.
32. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317–24.
33. Swerts PMJ, Mostert R, Wouters EFM. Comparison of corridor and treadmill walking in patients with severe chronic obstructive pulmonary disease. Phys Ther 1990;70:439–42.
34. Simonsick EM, Gardner AW, Poehlman ET. Assessment of physical function and exercise tolerance in older adults: reproducibility and comparability of five measures. Aging Clin Exp Res 2000;12:274–80.
35. Greig C, Butler F, Skelton D, Mahmud S, Young A. Treadmill walking in old age may not reproduce the real life situation. J Am Geriatr Soc 1993;41:15–8.
36. Peeters P, Mets T. The six-minute walk as an appropriate exercise test in elderly patients with chronic heart failure. J Gerontol A Biol Sci Med Sci 1996;51A:M147–51.
37. Rezaie-Majd A, Maca T, Bucek RA, et al. Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. Arterioscler Thromb Vasc Biol 2002;22:1194–9.
38. Rezaie-Majd A, Prager GW, Bucek RA, et al. Simvastatin reduces the expression of adhesion molecules in circulating monocytes from hypercholesterolemic patients. Arterioscler Thromb Vasc Biol 2003; 23:397–403.
39. Ross SD, Allen IE, Connelly JE, et al. Clinical outcomes in statin treatment trials: a meta-analysis. Arch Intern Med 1999;159: 1793–802.
40. Mitch WE, Goldberg AL. Mechanism of muscle wasting: the role of ubiquitin-proteasome pathway. N Engl J Med 1997;335:1897–905.
41. Goodman MN. Tumor necrosis factor induces skeletal muscle protein breakdown in rats. Am J Physiol 1991;260:E727–30.
42. Ferrucci L, Penninx BW, Volpato S, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. J Am Geriatr Soc 2002;12:1947–54.
43. Tousoulis D, Charalambos A, Bosinakou E, et al. Effects of atorvastatin on reactive hyperemia and inflammatory process in patients with congestive heart failure. Atherosclerosis 2005;178:359–63.