Statin Use and Leg Functioning in Patients With and Without Lower-Extremity Peripheral Arterial Disease

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Background—We determined whether statin use (versus nonuse) is associated with superior lower-extremity functioning independently of cholesterol levels and other confounders in patients with and without peripheral arterial disease.

Methods and Results—Participants included 392 men and women with an ankle brachial index (ABI) <0.90 and 249 with ABI 0.90 to 1.50. Functional outcomes included 6-minute walk distance and 4-meter walking velocity. A summary performance score combined performance in walking speed, standing balance, and time for 5 repeated chair rises into an ordinal score ranging from 0 to 12 (12 = best). Adjusting for age, sex, ABI, comorbidities, education level, medical insurance status, cholesterol, and other confounders, participants taking statins had better 6-minute walk performance (1276 versus 1218 feet, \( P = 0.045 \)), faster walking velocity (0.93 versus 0.89 m/s, \( P = 0.006 \)), and a higher summary performance score (10.2 versus 9.4, \( P < 0.001 \)) than participants not taking statins. Positive associations were attenuated slightly after additional adjustment for C-reactive protein level but remained statistically significant for walking velocity and the summary performance score. We did not find significant associations between lower-extremity functioning and aspirin, ACE inhibitors, vasodilators, or \( \beta \)-blockers.

Conclusions—Statin use is associated with superior leg functioning compared with no statin use, independent of cholesterol levels and other potential confounders. These data suggest that non–cholesterol-lowering properties of statins may favorably influence functioning in persons with and without peripheral arterial disease. (Circulation. 2003; 107:757-761.)

Key Words: statins • peripheral vascular disease • inflammation

*HMG-Co-A reductase inhibitor drugs (statins) have beneficial effects on atherosclerosis beyond those related to cholesterol lowering.\(^1\)\(^-\)\(^6\) Statins stabilize atherosclerotic plaques, reduce oxidative stress, and decrease vascular inflammation.\(^1\)\(^-\)\(^2\) In vascular endothelium, statins increase concentrations of nitric oxide, which has vasodilator, antithrombotic, and antiproliferative properties.\(^3\) These beneficial properties may contribute to the reduction in cardiac and cerebrovascular events in patients treated with statins.

Men and women with lower-extremity peripheral arterial disease (PAD) have impaired functioning compared with those without PAD.\(^7\) Greater PAD severity, as measured by the ankle brachial index (ABI), is associated with more extensive functional impairment.\(^7\) Although favorable effects of statins, acting on lower-extremity arterial obstruction, may improve PAD-related functional impairment, such associations have not been studied previously to our knowledge. Because of the direct actions of statins on endothelial function, we hypothesized that statin use might improve lower-extremity functioning in patients with and without PAD. We therefore sought to determine whether statin use (versus nonuse) would be associated with better functioning, independent of cholesterol levels and other possible confounding factors in a cohort of patients with and without PAD. Because statin use may be a marker of better health care access or quality, we also assessed relations between \( \beta \)-blocker, aspirin, ACE inhibitors, and vasodilator use with functioning.

Methods

Participant Identification
The protocol was approved by the institutional review boards at Northwestern University’s Feinberg School of Medicine and Catholic Health Partners Hospital. All participants gave informed consent. Participants were age 55 years and older.

PAD was defined as ABI <0.90.\(^7\)\(^-\)\(^9\) Absence of PAD was defined as ABI \( \geq 0.90 \) and \( \leq 1.50 \).\(^7\)\(^-\)\(^9\) PAD participants were identified from consecutive patients with PAD documented in 3 Chicago-area hospitals.
Exclusion Criteria
Individuals with ABI >1.50 were excluded, because this indicates poorly compressible leg arteries and inability to gauge arterial obstruction accurately.2–9 Individuals with an abnormal ABI at the noninvasive vascular laboratory who had a normal ABI at their study visit were excluded. Individuals originally found to have normal lower-extremity arterial studies at the noninvasive vascular laboratory with ABI <0.90 at the study visit were also excluded. The number of participants excluded because their ABI was either >1.50 or not consistent with vascular laboratory test results was 151.

Ankle Brachial Index Measurement
After participants rested supine for 5 minutes, a hand-held Doppler probe (Nicolet Vascular Pocket Dop II) 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. Pressures were measured twice, in the order listed and then in reverse order. ABIs were calculated by dividing average pressures in each leg by the average of the four brachial pressures.9 Average brachial pressures in the arm with 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 >10 mm Hg in at least 1 measurement set. Lowest leg ABI was used in all analyses.

C-Reactive Protein Levels
C-reactive protein (CRP) levels were determined using an immunometric technique on the Behring BN II analyzer (Dade Behring). Monoclonal anti-CRP antibodies, coated on polystyrene beads, agglutinate with CRP in the serum sample. Intensity of the resulting scattered light in the nephelometer was used to determine the CRP content. This assay detects CRP concentrations as low as 0.015 mg/dL.10

Cholesterol Levels
Total cholesterol levels were measured using enzymatic reaction with peroxidase/phenol-4-aminoiphenazone indicator reaction.11 The concentration of HDL-cholesterol was determined using a direct enzymatic colorimetric assay.12

Comorbidities
Algorithms developed for the Women’s Health and Aging Study and the Cardiovascular Health Study were used to document comorbidities.13 These algorithms combine data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire. Criteria developed by the American College of Rheumatology were used to diagnose knee arthritis, hip arthritis, hip fracture, spinal stenosis, and disk disease were combined into an arthritis category. Knee arthritis, hip arthritis, hip fracture, spinal stenosis, and disk disease were combined into an arthritis category.

Statin Use
All prescription and over-the-counter medications were recorded. Doses were not recorded. The principal investigator (M.M.M.) classified medications as follows: statins, aspirin, β-blockers, ACE inhibitors, and vasodilators. The principal investigator was blinded to all other participant data when medications were classified into categories.

Functional Measures
Health interviewers collecting data on lower-extremity performance were trained and certified by the study principal investigator (M.M.M.) before data collection. Recertification occurred every 6 months. Health interviewers were unaware of study hypotheses regarding statin use and leg functioning.

Six-Minute Walk
Following a standardized protocol, participants walk up and down a 100-foot hallway for 6 minutes after instructions to cover as much distance as possible during 6 minutes.17 This test is highly reproducible among individuals with PAD (R=0.94).17

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.18–20 To calculate the summary performance score, a 0 to 4 score is assigned for performance on 4-meter walking velocity, time to rise from a seated position 5 times, and standing balance, respectively.18–20 Individuals receive a zero score for each task they are unable to complete. One to four scores for each task are assigned based on quartiles of performance for >5000 community dwelling men and women participating in the Established Populations for the Epidemiologic Study of the Elderly.19–20 Scores are summed to obtain the summary performance score, ranging from 0 to 12.

Four-Meter Walking Velocity
Walking velocity was measured with a 4-meter walk performed at usual pace.18–20 Each walk was performed twice. The faster walk in each pair was used in analyses. Four-meter walk tests are highly reproducible.21

Other Measurements
Body Mass Index
Height and weight were measured at the study visit. Body mass index was calculated as weight (kg)/height2 (m2).

Education and Health Insurance Category
Education and type of health insurance were used as proxies for socioeconomic status and were obtained by patient interview. Education was categorized as high school graduate or less, some college, and college graduate or higher. Health insurance was categorized as private, Medicare and private, Medicare, and Medicaid/no health insurance.

Leg Symptoms
Leg symptoms were categorized using the San Diego Claudication questionnaire, based on a previous study.8 Leg symptom categories were intermittent claudication, exertional leg pain/carry-on, atypical exertional leg pain/stop, leg pain on exertion and rest, and no exertional leg symptoms.8

Statistical Analyses
We used descriptive statistics to compare characteristics of statin users versus statin nonusers. For continuous variables, statistical significance of differences between statin users and nonusers was evaluated using ANOVA. The statistical significance of differences
in dichotomous variables between statin users versus nonusers was determined using χ² tests.

Differences in lower-extremity functioning between users and nonusers for each drug category were evaluated using ANOVA, adjusting for the known and potential confounders of age, race, sex, educational level, health insurance status, body mass index, ABI, total cholesterol, and comorbidities. Differences in functioning between statin users and nonusers were determined, adjusting for the aforementioned confounders and also CRP. This allowed us to examine whether reduction of CRP levels by statins could mediate the aforementioned relationships between statin use and leg functioning. Analyses were performed among all participants, participants with ABI <0.90, and in the entire cohort (Table 2). There were no significant differences in the prevalence of each leg pain category or in the prevalence of revascularization between statin users versus nonusers.

In unadjusted analyses, the summary performance score was significantly higher in statin users compared with nonusers among participants with ABI <0.90 and in the entire cohort (Table 2). There were no significant differences in other functional measures between statin users and nonusers in unadjusted analyses.

Adjusting for confounders, statin users had significantly better functioning than statin nonusers among the entire cohort for 6-minute walk performance (1276 versus 1218 feet, P<0.005), 4-meter walking velocity (0.93 versus 0.89 m/s, P=0.006), and the summary performance score (10.2 versus 9.4, P<0.001). Significant independent associations between statin use and better lower-extremity functioning were observed among participants with ABI <0.90 for 4-meter walking velocity and the summary performance score, adjusting for confounders. Among participants with ABI 0.90 to 1.49, the summary performance score was significantly higher in statin users than nonusers (10.6 versus 9.9, P=0.046).

Table 1 shows characteristics of participants according to statin use versus nonuse and ABI category. Statin users included higher proportions of men and had a higher prevalence of cardiovascular disease, a higher prevalence of college graduates, lower cholesterol levels, and a lower prevalence of arthritis compared with statin nonusers. Among participants with ABI <0.90, 34.2% had intermittent claudication, 20.4% were asymptomatic, and 45.4% had leg pain on exertion and rest. Among participants with ABI <0.90, 38.0% had a history of lower-extremity revascularization. There were no significant differences in the prevalence of each leg pain category or in the prevalence of revascularization between statin users versus nonusers.

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Table 1. Characteristics Among Men and Women Age 55 Years and Older According to Presence Versus Absence of Statin Use*

<table>
<thead>
<tr>
<th></th>
<th>Taking Statins (n=177)</th>
<th>Not Taking Statins (n=215)</th>
<th>Taking Statins (n=75)</th>
<th>Not Taking Statins (n=174)</th>
<th>Taking Statins (n=252)</th>
<th>Not Taking Statins (n=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.2 (7.8)</td>
<td>72.3 (9.0)</td>
<td>68.5 (7.6)</td>
<td>69.5 (8.2)</td>
<td>70.4 (7.8)</td>
<td>71.1 (8.7)</td>
</tr>
<tr>
<td>Male, %</td>
<td>63.8</td>
<td>60.5</td>
<td>62.7†</td>
<td>48.8†</td>
<td>63.5†</td>
<td>55.3‡</td>
</tr>
<tr>
<td>African-American race, %</td>
<td>13.0</td>
<td>16.3</td>
<td>14.7</td>
<td>16.7</td>
<td>13.5</td>
<td>16.4</td>
</tr>
<tr>
<td>ABI</td>
<td>0.65 (0.14)</td>
<td>0.65 (0.15)</td>
<td>1.07 (0.11)†</td>
<td>1.10 (0.12)†</td>
<td>0.78 (0.23)‡</td>
<td>0.85 (0.26)§</td>
</tr>
<tr>
<td>Walking for exercise, %</td>
<td>56.6</td>
<td>49.3</td>
<td>62.7</td>
<td>63.2</td>
<td>58.3</td>
<td>55.5</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>170 (37.9§)</td>
<td>187 (37.3)</td>
<td>167 (35.9</td>
<td></td>
<td>)</td>
<td>182 (36.7)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>39.7 (13.6)</td>
<td>40.2 (16.3)</td>
<td>42.5 (12.6)</td>
<td>46.2 (17.2)</td>
<td>40.5 (13.3)</td>
<td>42.9 (16.9)</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>39.0 (34.3)</td>
<td>39.5 (35.7)</td>
<td>18.4 (28.7)</td>
<td>21.9 (28.8)</td>
<td>32.9 (34.0)</td>
<td>31.6 (33.9)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29.4</td>
<td>33.9</td>
<td>24.0</td>
<td>17.8</td>
<td>27.8</td>
<td>26.7</td>
</tr>
<tr>
<td>Heart disease and stroke, %</td>
<td>70.6§</td>
<td>51.2$</td>
<td>58.7§</td>
<td>29.3§</td>
<td>67.1§</td>
<td>41.4§</td>
</tr>
<tr>
<td>Arthritis, %</td>
<td>36.2</td>
<td>41.4</td>
<td>53.3</td>
<td>59.8</td>
<td>41.3†</td>
<td>49.6†</td>
</tr>
<tr>
<td>CRP, mg/dL (median [IQR])</td>
<td>0.22 (0.12-0.58¶)</td>
<td>0.35 (0.16-0.73¶)</td>
<td>0.33 (0.13-0.56)</td>
<td>0.24 (0.12-0.65)</td>
<td>0.26 (0.12-0.57)</td>
<td>0.30 (0.13-0.67)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school graduate or less, %</td>
<td>24.9</td>
<td></td>
<td></td>
<td>39.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College graduate or higher, %</td>
<td>45.2†</td>
<td>34.9‡</td>
<td>46.7</td>
<td>39.7</td>
<td>45.6#</td>
<td>37.0#</td>
</tr>
<tr>
<td>Health insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>24.3</td>
<td>20.5</td>
<td>32.0</td>
<td>31.0</td>
<td>26.6</td>
<td>25.2</td>
</tr>
<tr>
<td>Medicare+private, %</td>
<td>46.9</td>
<td>53.9</td>
<td>42.7</td>
<td>36.8</td>
<td>45.6</td>
<td>46.3</td>
</tr>
<tr>
<td>Medicare, %</td>
<td>26.0</td>
<td>19.1</td>
<td>21.3</td>
<td>24.1</td>
<td>24.6</td>
<td>21.3</td>
</tr>
<tr>
<td>Public aid/Medicaid/no health insurance, %</td>
<td>2.8</td>
<td>6.5</td>
<td>4.0</td>
<td>8.0</td>
<td>3.2‡</td>
<td>7.2‡</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD) unless otherwise indicated. IQR indicates interquartile range; HDL, high-density lipoprotein.

†P<0.05; ‡P<0.04; §P<0.001; ¶P<0.002; ¶¶P<0.01; †‖P<0.03.
TABLE 2. Differences in Functional Outcomes Among Participants According to Statin Use*

<table>
<thead>
<tr>
<th>Statin Use</th>
<th>ABI &lt;0.90 (n=392)</th>
<th>ABI 0.90 to 1.50 (n=249)</th>
<th>ABI ≥1.50 (n=641)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin Users</td>
<td>Statin Nonusers</td>
<td>Statin Users</td>
</tr>
<tr>
<td></td>
<td>(n=177)</td>
<td>(n=215)</td>
<td>(n=75)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six-minute walk distance, feet</td>
<td>1159 (369)</td>
<td>1098 (375)</td>
<td>0.109</td>
</tr>
<tr>
<td>Four-meter walking velocity, m/s</td>
<td>0.90 (0.18)</td>
<td>0.86 (0.22)</td>
<td>0.057</td>
</tr>
<tr>
<td>Summary performance score, (range, 0 to 12, 12=best)</td>
<td>10.1 (2.1)</td>
<td>9.0 (2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Adjusted for age, sex, race, educational level, health insurance, BMI, ABI, total cholesterol, heart disease and stroke, pulmonary disease, diabetes, and arthritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six-minute walk distance, feet</td>
<td>1157</td>
<td>1100</td>
<td>0.114</td>
</tr>
<tr>
<td>Four-meter walking velocity, m/s</td>
<td>0.90</td>
<td>0.86</td>
<td>0.028</td>
</tr>
<tr>
<td>Summary performance score, (range, 0 to 12, 12=best)</td>
<td>10.0</td>
<td>9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Adjusted for age, sex, race, educational level, health insurance, BMI, ABI, total cholesterol, heart disease and stroke, pulmonary disease, diabetes, arthritis, and log CRP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six-minute walk distance, feet</td>
<td>1151</td>
<td>1106</td>
<td>0.211</td>
</tr>
<tr>
<td>Four-meter walking velocity, m/s</td>
<td>0.90</td>
<td>0.86</td>
<td>0.051</td>
</tr>
<tr>
<td>Summary performance score, (range, 0 to 12, 12=best)</td>
<td>10.0</td>
<td>9.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Values are expressed as means (SD) for unadjusted analyses and adjusted means for adjusted functional measures.

Adjusting for confounders, aspirin use was associated with faster 4-meter walking speed compared with no aspirin use in patients with ABI <0.90 (0.89 versus 0.85 m/s, P=0.044). There were no other significant associations between aspirin use, β-blocker use, ACE inhibitor use, or vasodilator use and lower-extremity functioning among participants with ABI <0.90, participants with ABI 0.90 to 1.49, or all participants (data not shown).

Adjusting for all previous confounders plus CRP, the association between statin use and better lower-extremity functioning was attenuated among all participants for 6-minute walk distance and 4-meter walking velocity (Table 2). The significant relationship between statin use and higher summary performance score was maintained and not attenuated. Even after adjustment for CRP, relations between statin use and 4-meter walking velocity as well as the summary performance score remained highly statistically significant (Table 2).

Discussion
Among persons with and without PAD, statin users had better performance on objective measures of leg functioning than statin nonusers. Statin users had several characteristics associated with greater impairment in functioning compared with nonusers, including a higher prevalence of heart disease and stroke and a higher proportion of participants with ABI <0.90 compared with nonusers. Nonetheless, statin use was associated with better functioning compared with nonuse after adjustment for these and other confounders.

A large body of literature has established that statins have favorable actions on atherosclerosis and vascular properties other than those attributed to cholesterol lowering.1–6,22,23 Statins increase production of nitric oxide in the endothelium, which has local vasodilatory properties in addition to antithrombogenic, antiproliferative, and leukocyte-adhesion inhibiting effects.22,23 Other mechanisms by which statins favorably influence atherosclerosis include enhancement of endothelium-dependent relaxation,3 inhibition of platelet function,5 and inhibition of endothelin-1, a potent vasoconstrictor and mitogen.4 Therefore, it is biologically plausible that statins might improve lower-extremity functioning in PAD by retarding the deleterious effects of atherosclerosis on leg arteries. Furthermore, the association between statin use and functional performance was attenuated slightly after adding CRP to the fully adjusted model, suggesting that reduction of vascular inflammation may be one mechanism by which statins are associated with better functioning. Statin-associated reduction of inflammatory cytokines could improve blood flow, regress atherosclerosis, or improve end-organ function (such as skeletal muscle).24

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. To test this possibility, we studied relations between aspirin, β-blocker, and ACE inhibitor use with functioning. β-blocker use does not influence treadmill-walking performance in patients with PAD but could reflect better medical care.23 We also studied relationships between vasodila-
tor use and lower-extremity functioning, because vasodilatation could theoretically improve leg functioning in PAD. We found no consistent associations between use of these drugs and functioning, suggesting that the relation between statin use and better leg functioning is not a consequence of better medical care associated with statin use. Although a positive relation between statin dose and better leg functioning would strengthen our findings, we did not have information on statin dose. We also did not have information on duration of statin use. However, recent data indicate that the antiinflammatory actions of statins are immediate, suggesting that the relation between statin use and leg functioning may not be affected by statin use duration.

To our knowledge, only one clinical trial has evaluated the relationship between statins and PAD outcomes. The Scandinavian Simvastatin Survival Study (4S) demonstrated that subjects randomized to simvastatin had a 38% reduction in new or worsening claudication compared with subjects randomized to placebo over a median follow-up of 5.4 years ($P=0.008$). The authors report no previous studies related to statin use and lower-extremity functioning.

The favorable association between statin use and functioning was also observed in participants with ABI 0.90 to 1.49. This beneficial association may relate to a favorable influence of statins on subclinical lower-extremity atherosclerosis. Previous work shows that non-PAD patients with ABI values of 0.90 to 1.10 have poorer functioning than patients with ABI values of 1.1 to 1.50, suggesting that subclinical lower-extremity atherosclerosis impairs leg functioning. Better functioning in the non-PAD group taking statins may additionally relate to beneficial effects of statins on inflammatory-mediated impairments in skeletal muscle function.

In conclusion, statin-associated benefits on endothelial function and vascular inflammation may improve leg functioning in patients with and without PAD. Confirmation of this finding elsewhere, as well as additional study of the mechanisms pertaining to the association between statin use and superior functioning, are indicated. It will also be important to determine whether deliberate statin use improves functioning in patients with optimal cholesterol levels.

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**References**

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