Statins, Angiotensin-Converting Enzyme Inhibitors, and Physical Performance in Older Women

Shelly L. Gray, PharmD, MS, Aaron K. Aragaki, MS,‡ Michael J. LaMonte, PhD, MPH,§ Barbara B. Cochrane, PhD,‡† Charles Kooperberg, PhD,‡ Jennifer G. Robinson, MD, MPH,¶** Nancy F. Woods, PhD,‡† and Andrea Z. LaCroix, PhD‡*

OBJECTIVES: To examine associations between angiotensin-converting enzyme (ACE) inhibitor and statin medications and baseline and mean annual change in physical performance measures and muscle strength in older women.

DESIGN: Prospective cohort study.

PARTICIPANTS: Participants from the Women's Health Initiative Clinical Trials aged 65 to 79 at baseline who had physical performance measures, self-report of health insurance, and no prior history of stroke or congestive heart failure were included (N = 5,777). Women were recruited between 1993 and 1998.

MEASUREMENTS: Medication use was ascertained through a baseline inventory. Physical performance measures (timed 6-m walk, repeated chair stands in 15 seconds) and grip strength were assessed at baseline and follow-up Years 1, 3, and 6. Multivariable-adjusted linear repeated-measures models were adjusted for demographic and health characteristics.

RESULTS: ACE inhibitor use was associated with lower mean grip strength at baseline (22.40 kg, 95% confidence interval (CI) = 21.89–22.91 vs 23.18 kg, 95% CI 23.02–23.34; $P = .005$) and greater mean annual change in number of chair stands (−0.182, 95% CI −0.217 to −0.147 vs −0.145, 95% CI −0.156 to −0.133; $P = .05$) than nonuse. Statin use was not significantly associated with baseline measures or mean annual change for any outcome. A subgroup analysis suggested that statin use was associated with less mean annual change in chair stands ($P = .006$) in the oldest women.

CONCLUSION: These results do not support an association between statin or ACE inhibitor use and slower decline in physical performance or muscle strength and thus do not support the use of these medications for preserving functional status in older adults. **J Am Geriatr Soc 60:2206–2214, 2012.**

Key words: angiotensin-converting enzyme inhibitors; statins; physical performance; grip strength

Maintaining adequate physical function is important for older adults to continue independent living in the community. An objective of Healthy People 2020 is to "reduce the proportion of older adults who have moderate to severe functional limitations."[1] Performance-based measures of functional status, such as timed walk, are useful in identifying individuals at risk of disability.[2]

Multiple factors appear to be involved in the decline in physical function and development of frailty that occurs with aging.[3–5] Of special interest is that a growing body of evidence suggests a relationship between chronic inflammation and age-related muscle changes, disability, frailty, and decline in physical function.[4–11] Two medication classes, angiotensin-converting enzyme (ACE) inhibitors and statins, have been identified as potential ways to reduce physical decline with aging.[3–5] Although results from studies have been inconsistent, there is evidence to support a lower risk of these outcomes with ACE inhibitors and statins, particularly in select samples of individuals.[12–18]

It is biologically plausible that these medications may prevent decline in physical function beyond what might be expected by reducing vascular events. ACE inhibitors may have a direct effect on muscle or may reduce inflammation,[3–5] whereas statins may reduce systemic inflammation, as indicated by specific markers (e.g., C-reactive protein (CRP)).[19,20] However, it is possible that the muscle-related adverse events (e.g., myalgia, muscle weakness) that have

From the *School of Pharmacy, University of Washington, Seattle, Washington; †School of Nursing, University of Washington, Seattle, Washington; ‡Women's Health Initiative Clinical Coordinating Center, Fred Hutchinson Cancer Research Center, Seattle, Washington; §Department of Social and Preventive Medicine, School of Public Health and Health Professions, University at Buffalo, Buffalo, New York; ¶Department of Epidemiology, University of Iowa, Iowa City, Iowa; and **Department of Medicine, University of Iowa, Iowa City, Iowa.

Address correspondence to Shelly L. Gray, School of Pharmacy, University of Washington, Seattle, WA 98195. E-mail: slgray@u.washington.edu

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been described may counteract the benefits that statins may confer by reducing inflammation.[21,22]

Because most studies have been conducted in select samples, it is important to examine this question in large representative samples. Given this background, the objective of the current study was to examine the associations between each medication class and baseline lower extremity physical performance measures and muscle strength and annual change in these measures in women aged 65 and older.

METHODS

Study Sample

This study used data from the Women's Health Initiative (WHI) clinical trials of 68,132 women aged 50 to 79 recruited between 1993 and 1998 from 40 clinical centers in the United States. Women were eligible for study inclusion if they were postmenopausal and unlikely to relocate or die within 3 years. There were additional eligibility criteria specific to each clinical trial for reasons of safety, competing risk, and adherence and retention. Further details regarding the design, recruitment strategy, and data collection methods have been published.[23] Human subjects review committees at each participating institution reviewed and approved the study.

The study population for this analysis included the 25% random sample of clinical trial participants aged 65 and older who completed measures of physical performance (n = 6,025). Women were excluded from this analysis if they reported baseline congestive heart failure (n = 57), history of stroke (n = 98), or no health insurance (n = 100), leaving an analytical sample of 5,777 participants.

Outcomes: Physical Performance Measures and Muscle Strength

Trained, certified staff assessed the three outcomes at baseline and follow-up Years 1, 3, and 6 using standard protocols. Timed walk and repeated chair stands, two of three items of the Short Portable Performance Battery (SPPB),[24] were the measures of lower extremity physical performance assessed. Slow gait speed predicts disability and mortality in older adults.[2,25,26] The 6-m timed walk was performed at usual walking speed, with use of ambulatory aids as needed. The test was repeated for a second trial, and the results were recorded as mean seconds. The chair stand test was conducted if the participant was able to stand at least once without using hands or arms from a straight-backed, nonpadded, flat-seated, armless chair. Two 15-second trials of repeated chair stands were performed with the arms folded across the chest, with a 1- to 2-minute rest in between trials, and results were averaged.

Hand grip strength was measured using a handheld dynamometer (Jamar hand dynamometer, Lafayette Instruments, Lafayette, IN). Low grip strength is a predictor of disability, mortality, and other poor outcomes in older adults.[27] Two measurements were taken in the dominant hand, with staff coaching for maximal performance, and the mean of two trials was used.

ACE Inhibitor and Statin Medication Ascertainment

WHI participants were asked to bring all medications taken on a regular basis in the past 2 weeks to their first screening interview. Trained clinic interviewers entered each medication name and strength from the containers directly into a database that assigned drug codes using Medi-Span software that was updated quarterly (First DataBank, Inc., San Bruno, CA). Women reported duration of use for each current medication. A woman was categorized as a user or nonuser of a statin (lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin) or ACE inhibitor (enalapril, benazepril, quinapril, ramipril, fosinopril, trandolapril, captopril) based on the medication inventory at screening. Duration of use was categorized as less than 2 years, 2 to 5 years, or 5 years or more. Information was available on tablet strength but not on prescribed dose.

Other Covariates

Data on demographic and health behavior characteristics (body mass index (BMI), smoking, alcohol use, leisure-time physical activity) were obtained at baseline. BMI was calculated using measured height and weight as weight (kg) divided by height squared (m^2). Alcohol consumption was estimated from a food-frequency questionnaire. Physical activity energy expenditure was calculated from self-reported recreational physical activity, including walking and mild, moderate, and strenuous physical activity (metabolic equivalent score (MET) hours/wk).[28] Medical conditions at baseline included self-reported physician diagnoses of treated diabetes mellitus (oral medication or insulin) and hypertension (taking hypertensive medication, blood pressure >140/90 mmHg). History of coronary heart disease (CHD) was based on a self-reported physician diagnosis of myocardial infarction, angina pectoris, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty. Depressive symptoms were assessed using a 6-item short form[29,30] of the Center for Epidemiologic Studies Depression Scale. Physical function was measured using the Rand-36 physical function scale (range 0–100), with higher scores indicating better physical function.[31] Baseline medications used for hypertension other than ACE inhibitors (e.g., calcium channel blockers, beta-blockers, and diuretics), nonsteroidal anti-inflammatory drugs (NSAIDs), and menopausal hormone therapy were also ascertained.

Statistical Analysis

Baseline characteristics were compared according to use of statins or ACE inhibitors using chi-square tests for association for categorical variables and *t*-tests for continuous variables. Each exposure was examined in separate analyses. Multivariable-adjusted linear repeated-measures models with an unstructured covariance matrix were used to examine the longitudinal association between each exposure and outcomes (physical performance measures and grip strength). To account for data that were probably not missing at random, values corresponding to the bottom 1% at each visit year for each measure were assigned to participants who attended their annual visit but could not complete, refused, or did not attempt the task because of

safety or health concerns.[32] The percentage of data missing for these reasons was 1.3% for the timed walk, 2.7% for grip strength, and 7.7% for chair stands. The models examined whether mean scores on these outcome measures of exposure groups differed at baseline (*P*-intercept) or with respect to mean annual change over time (*P*-slope). The reasonableness of these linear fits was confirmed by comparing these estimates with results obtained by treating time as a categorical variable. To control for confounding, models were adjusted for age, ethnicity, education, BMI, alcohol consumption, systolic and diastolic blood pressure, self-reported health, number of antihypertensive medications, diabetes mellitus, depressive symptoms, history of CHD, and hormone trial participation. Sensitivity analyses included additional adjustment for baseline activity level according to quartile of MET h/wk and baseline use of NSAIDs. Interactions with each exposure and age at baseline were examined. Additional analyses examined whether duration of medication use at baseline was associated with baseline measures and mean annual change in outcomes. Parameter estimates, 95% confidence intervals (CIs), and two-sided *P*-values were obtained using SAS PROC MIXED version 9.2 (SAS Institute, Inc., Cary, NC). Presentation of these summary statistics was graphed in R (version 2.11, R Development Core Team, http://www.R-project.org).

Several additional sensitivity analyses were conducted to examine the robustness of results and further examine confounding by indication. First, each exposure was examined as a time-varying covariate by updating exposure at Year 3. The interaction between exposure and Rand-36 physical function scale (tertiles <75, 75–90, ≥90) was examined. For the ACE inhibitor analysis, the sample was restricted to participants with hypertension. The interaction between current ACE inhibitor and statin use was also examined by testing the significance of cross-product terms.

RESULTS

Women were followed on average for 7.5 ± 1.5 years through the planned study closeout in spring 2005. At that time, 3.5% (n = 202) of the sample had withdrawn or been lost to follow-up, and 7.8% (n = 450) had died. A description of the study sample at baseline is given in Table 1. At baseline, 9.3% (n = 539) of participants were current users of statins; 31% of these had been users for 2 to 5 years and 15.0% for more than 5 years. Likewise, 10.4% (n = 600) of participants were current users of ACE inhibitors; 32.5% of these had been users for 2 to 5 years and 33.5% for more than 5 years. Eighty-three women (1.4%) reported concurrent use of both agents. Seventy-two percent of those using an ACE inhibitor at baseline and 82% of those using a statin at baseline were still using these medications at the Year 3 visit. Physical performance measures were available at all four visits for 66.1% (n = 3,818) of participants, at three visits for 20.6% (n = 1,187), at two visits for 8.9% (n = 516), and at a single visit for 4.4% (n = 256).

Figure 1 shows the trajectory of each outcome according to baseline statin use adjusted for covariates. There were no differences between statin users and nonusers in baseline walking speed, chair stands or grip strength (*P*-intercept = .84, .53, and .07, respectively) or mean annual change (*P*-slope = .58, .28, and .52, respectively). The relationships between duration of statin use and each outcome were not statistically significant. The effect of the interaction between age and statin use on physical performance measures and grip strength was next examined. At baseline, walking speed was the only outcome in which a significant interaction was found between age and statin use (*P*-trend-intercept = .01). Baseline walking speed was similar in statin users regardless of age (aged 65–67: mean 1.09 m/s, 95% CI = 1.06–1.13 m/s; aged 68–71: mean 1.09 m/s, 95% CI = 1.06–1.13 m/s; aged 72–79: mean 1.08 m/s, 95% CI = 1.04–1.11 m/s), although baseline walking speed was negatively associated with age in statin nonusers (aged 65–67: mean 1.13 m/s, 95% CI = 1.12–1.14 m/s, aged 68–71: mean 1.10 m/s, 95% CI = 1.09–1.11 m/s, aged 72–79: mean 1.05 m/s, 95% CI = 1.03–1.06 m/s). When examining mean annual change, chair stands was the only outcome in which an interaction between age and statin use was found (*P*-trend-slope = .006). The mean annual change in the number of chair stands performed was relatively constant across increasing age groups for statin users (aged 65–67: mean −0.157, 95% CI=−0.221 to −0.093 m/s, aged 68–71: mean −0.124, 95% CI=−0.182 to −0.066, aged 72–79: mean −0.105, 95% CI=−0.173 to −0.037), but the mean annual change in performance in the oldest statin nonusers was nearly twice that of the youngest nonusers (aged 65–67: mean −0.117, 95% CI=−0.137 to −0.098 m/s, aged 68–71: mean −0.139, 95% CI=−0.158 to −0.120, aged 72–79: mean −0.204, 95% CI=−0.226 to −0.183). Age did not modify the association between statin use and baseline or mean annual change in grip strength.

Figure 2 shows the trajectory of each outcome according to baseline ACE inhibitor use adjusted for covariates. There were no differences in baseline walking speed or mean annual change in performance between users and nonusers of ACE inhibitors. For chair stands, there was not a difference in baseline performance between users and nonusers (*P*-intercept = .61), but there was suggestion of a greater annual decline in chair stand performance in users (*P*-slope = .05). ACE inhibitor use was associated with weaker grip strength at baseline (*P*-intercept = .005). Similar results were obtained when linearity was not assumed and year was modeled as a categorical variable (*P* = .03). There was no difference in mean annual change in grip strength over time (*P*-slope = .13). When examining mean annual change according to duration of use, longer duration of ACE inhibitor use was not associated with better performance on any outcome. Interactions between age and ACE inhibitor use were not significant for any outcome.

Sensitivity Analyses

Models adjusting for baseline activity level according to quartile of MET h/wk or baseline use of NSAIDs produced estimates similar to those derived from the primary analyses. Results similar to those from the primary analyses were obtained when statin and ACE inhibitor use were modeled as time-varying exposures by updating exposure

Table 1. Baseline Characteristics According to Statin and Angiotensin-Converting Enzyme (ACE) Inhibitor Use

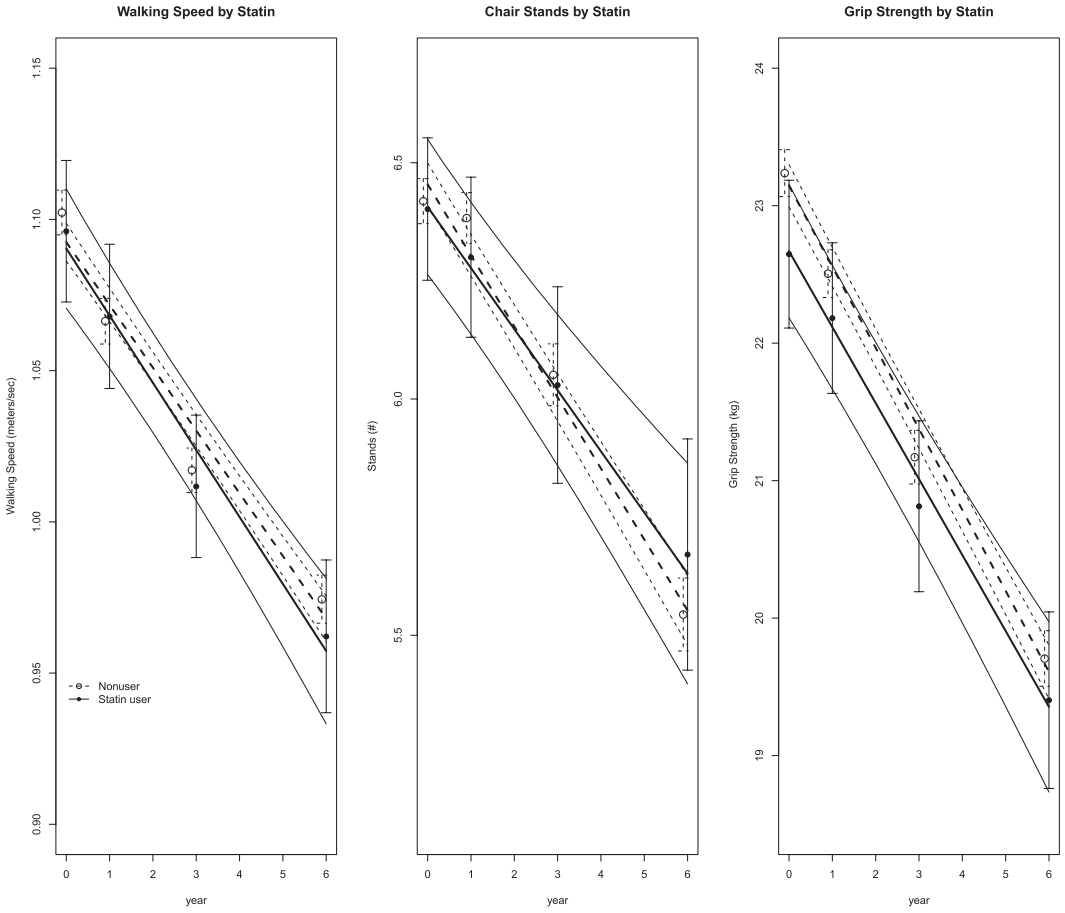
Characteristic	Statin Use			ACE Inhibitor Use		
	Yes	No	*P*-Value	Yes	No	*P*-Value
Age, mean ± SD	70.0 ± 3.6	69.8 ± 3.7	.21	70.1 ± 3.7	69.8 ± 3.7	.04
Education						
≤ High school/GED or less	138 (25.8)	1,326 (25.4)	.28	167 (28.1)	1,297 (25.2)	.02
School after high school	231 (43.3)	2,105 (40.4)		256 (43.0)	2,080 (40.4)	
College degree or higher	165 (30.9)	1,782 (34.2)		172 (28.9)	1,775 (34.5)	
Race or ethnicity						
White	452 (83.9)	4,535 (86.6)	.04	506 (84.3)	4,481 (86.6)	.25
Black	46 (8.5)	387 (7.4)		60 (10.0)	373 (7.2)	
Hispanic	9 (1.7)	133 (2.5)		14 (2.3)	128 (2.5)	
American Indian	1 (0.2)	11 (0.2)		1 (0.2)	11 (0.2)	
Asian or Pacific Islander	21 (3.9)	111 (2.1)		11 (1.8)	121 (2.3)	
Unknown	10 (1.9)	61 (1.2)		8 (1.3)	63 (1.2)	
Living alone	175 (32.6)	1,579 (30.4)	.28	177 (29.8)	1,577 (30.7)	.66
Body mass index kg/m^2, mean ± SD	28.9 ± 5.6	28.5 ± 5.6	.09	30.6 ± 6.3	28.3 ± 5.5	<.001
Smoking status						
Never	268 (50.9)	2,855 (55.3)	.12	322 (54.2)	2,801 (55.0)	.40
Past	231 (43.8)	2,029 (39.3)		246 (41.4)	2,014 (39.5)	
Current	28 (5.3)	279 (5.4)		26 (4.4)	281 (5.5)	
Alcohol consumption, drinks/d						
0	245 (45.6)	2,302 (44.1)	.71	313 (52.2)	2,234 (43.3)	<.001
≤1	233 (43.4)	2,365 (45.3)		228 (38.0)	2,370 (45.9)	
>1	59 (11.0)	557 (10.7)		59 (9.8)	557 (10.8)	
Physical activity, metabolic equivalent hours per week, mean ± SD	11.3 ± 12.4	11.4 ± 12.8	.90	9.1 ± 10.5	11.6 ± 13.0	<.001
Self-reported health						
Excellent	45 (8.4)	779 (15.0)	<.001	23 (3.8)	801 (15.6)	<.001
Very good	197 (36.7)	2,178 (41.8)		212 (35.5)	2,163 (42.0)	
Good	238 (44.3)	1,828 (35.1)		284 (47.5)	1,782 (34.6)	
Fair or poor	57 (10.6)	424 (8.1)		79 (13.2)	402 (7.8)	
Treated diabetes mellitus (oral or injected)	50 (9.3)	258 (4.9)	<.001	70 (11.7)	238 (4.6)	<.001
Hypertension	334 (62.3)	2,730 (52.5)	<.001	578 (97.6)	2,486 (48.3)	<.001
History of coronary heart disease[a]	106 (20.0)	377 (7.3)	<.001	95 (16.4)	388 (7.6)	<.001
Number of depressive symptoms						
0	145 (27.3)	1,307 (25.4)	.73	135 (22.8)	1,317 (25.9)	.02
1–2	197 (37.0)	2,021 (39.3)		252 (42.6)	1,966 (38.7)	
3–4	121 (22.7)	1,162 (22.6)		115 (19.5)	1,168 (23.0)	
≥5	69 (13.0)	655 (12.7)		89 (15.1)	635 (12.5)	
Blood pressure, mmHg, mean ± SD						
Systolic	133.4 ± 18.1	132.0 ± 17.3	.07	139.7 ± 18.1	131.3 ± 17.1	<.001
Diastolic	75.1 ± 9.6	74.8 ± 9.1	.49	77.1 ± 10.1	74.6 ± 9.0	<.001
Hormone replacement therapy						
Never used	297 (55.2)	2,819 (53.8)	.73	303 (50.5)	2,813 (54.4)	.18
Past user	109 (20.3)	1,052 (20.1)		126 (21.0)	1,035 (20.0)	
Current user	132 (24.5)	1,365 (26.1)		171 (28.5)	1,326 (25.6)	
Number of antihypertensive medications						
0	238 (44.2)	3,437 (65.6)	<.001	0 (0.0)	3,675 (71.0)	<.001
1	180 (33.4)	1,176 (22.5)		296 (49.3)	1,060 (20.5)	
2	97 (18.0)	522 (10.0)		229 (38.2)	390 (7.5)	
≥3	24 (4.5)	103 (2.0)		75 (12.5)	52 (1.0)	

P-values based on chi-square test of association for categorical variables and *t*-test for continuous variables.

SD = standard deviation; GED = general education degree.

[a] Myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous transluminal coronary angioplasty.

at Year 3. No significant associations were observed between statin use and each outcome. Although the strength of the association between ACE inhibitor use and baseline grip strength was attenuated, the result was still statistically significant (*P*-value intercept changed from .005 to .04). The association between ACE inhibitor use and mean annual change in chair stand performance was strengthened, with nonusers experiencing less decline than users (*P*-value intercept changed from .05 to .006). The interaction between each exposure and physical functioning subgroups as measured using the Rand-36 physical function scale was examined (tertiles: <75, 75–90, ≥90). Neither statin nor ACE inhibitor use interacted with baseline physical functioning. For statins, tests of trend for both regression parameters yielded $P > .20$. For ACE inhibitors, tests of trend for both regression parameters



	Walking Speed (m/s)	P value	Chair Stands (#)	P value	Grip Strength (kg)	P value
Mean Baseline Performance, β_0 (95% CI)		0.84		0.53		0.07
Nonusers	1.09 (1.09, 1.10)		6.45 (6.41, 6.50)		23.14 (22.99, 23.30)	
Statin Users	1.09 (1.07, 1.11)		6.41 (6.26, 6.55)		22.67 (22.18, 23.15)	
Mean Annual Performance Change, β_1 (95% CI)		0.58		0.28		0.52
Nonusers	-.021 (-.022, -.019)		-.150 (-.162, -.139)		-.589 (-.623, -.556)	
Statin Users	-.022 (-.027, -.017)		-.129 (-.166, -.093)		-.552 (-.659, -.446)	

Figure 1. Multivariable-adjusted linear repeated measures analyses of physical performance measures and grip strength according to baseline statin use. Linear estimates and 95% confidence intervals (CIs; solid and dashed lines) from a multivariable-adjusted linear repeated-measures model. Models were adjusted for age, ethnicity, education, body mass index, alcohol consumption, systolic blood pressure, diastolic blood pressure, self-reported health, number of antihypertensive medications, diabetes mellitus, depressive symptoms, history of coronary heart disease, hormone trial randomization, and angiotensin-converting enzyme use. The minimum sample sizes (baseline, Years 1, 3, 6) for three outcome measures were 496, 436, 419, and 377 for statin users and 4,852, 4,243, 4,189, and 3,768 for nonusers.

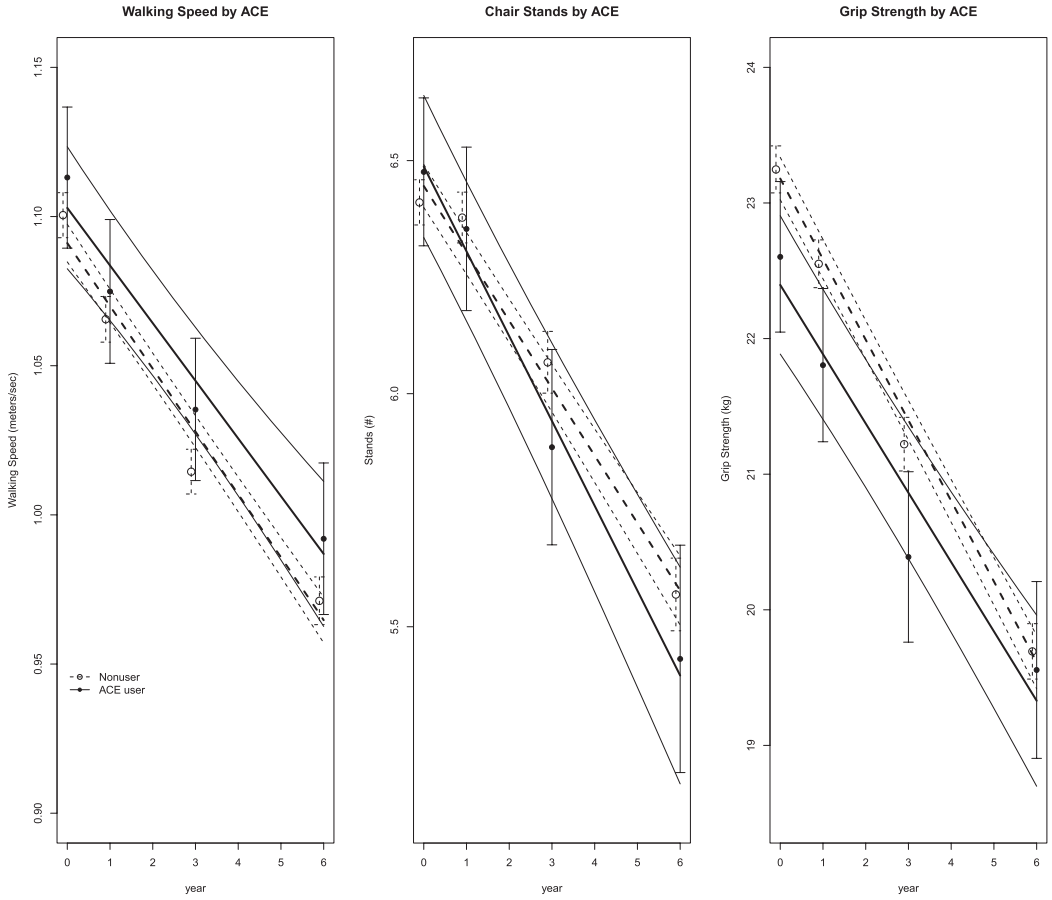
yielded $P > .14$. There was not a significant interaction between current statin and ACE inhibitor use with any outcome (all $P > .18$). Similar results were obtained with ACE inhibitor use and each outcome when restricting the sample to those with hypertension—an attempt to examine confounding by indication.

DISCUSSION

This large prospective study in older women with an average of 7.5 years of follow-up did not find a consistent association between statin or ACE inhibitor use and two measures of lower extremity physical performance or grip strength. A major contribution of this study is the examination of a clinically relevant performance-based measure of physical function (gait speed) in a large representative sample of older women. An advantage of performance-based measures over self-reported functional status (e.g., mobility disability[33]) is the ability to examine relationships between medication use and physical function earlier on the disablement continuum. Thus, these results provide additional information to a growing body of literature suggesting that these medications may not be beneficial for slowing age-related decline in physical performance.

Statins

Statin use was not associated with baseline or mean annual change in physical performance measures or grip



	Walking Speed (m/s)	P value	Chair Stands (#)	P value	Grip Strength (kg)	P value
Mean Baseline Performance, β_0 (95% CI)		0.29		0.61		0.005
Nonusers	1.09 (1.08, 1.10)		6.45 (6.40, 6.49)		23.18 (23.02, 23.34)	
ACE Users	1.10 (1.08, 1.12)		6.49 (6.34, 6.64)		22.40 (21.89, 22.91)	
Mean Annual Performance Change, β_1 (95% CI)		0.48		0.05		0.13
Nonusers	-.021 (-.023, -.020)		-.145 (-.156, -.133)		-.594 (-.628, -.560)	
ACE Users	-.019 (-.024, -.015)		-.182 (-.217, -.147)		-.511 (-.613, -.409)	

Figure 2. Multivariable-adjusted linear repeated measures analyses of physical performance measures and grip strength by baseline angiotensin-converting enzyme (ACE) inhibitor use. Linear estimates and 95% confidence intervals (CIs; solid and dashed lines) from a multivariable-adjusted linear repeated-measures model. Models were adjusted for age, ethnicity, education, body mass index, alcohol consumption, systolic blood pressure, diastolic blood pressure, self-reported health, number of antihypertensive medications, diabetes mellitus, depressive symptoms, history of coronary heart disease, hormone trial randomization, and statin use. The minimum sample size (baseline, Years 1, 3, 6) for the three outcome measures were 551, 477, 460, and 410 for ACE inhibitor users and 4,797, 4,201, 4,148, and 3,734 for nonusers.

strength. Statin use was associated with less decline in performance on chair stands in the oldest women, suggesting that some aspect of health status or exposure in this group is overshadowing the influence of age, but this finding should be viewed as preliminary and requires confirmation. Statin users had a slightly better performance on timed chair stands than nonusers in a 1-year longitudinal study in older men (−0.5 seconds, $P = .04$).[18] Additional data supporting statin medications and positive function-related outcomes have come from small randomized trials[15,34] and a longitudinal study[13] in individuals with peripheral arterial disease. No association was found between statin use and functional decline in those without peripheral arterial disease.[13] The overall results of the current study are consistent with those of studies conducted in more-representative sample.[33,35–37] Large observational studies found that statin use was not related to lower incidence of frailty in postmenopausal women,[36] self-reported mobility disability,[33] or a decline in lower extremity muscle strength.[37]

Several potential factors may explain these discrepant findings. First, the positive associations between statins and physical functioning in those with peripheral arterial disease may be due to better endothelial function resulting in enhanced lower extremity blood flow[13] rather than a reduction in inflammation-mediated sarcopenia. Second, use of statin medications is associated with dose-related muscle complaints; these adverse events could negate any positive association with physical performance due to reduction in inflammation. Muscle adverse events may occur in up to 10% of those receiving high-dose treatment,[38] but precise estimates may not be known for older

frail adults. When examining the association between statins and physical performance measures in a population study, such as ours, average population estimates are obtained, and potential beneficial associations in subgroups could be masked. It is encouraging that there is no evidence from this study that statin use is associated with deteriorating performance, but it is possible that those who experience statin-related muscle adverse events discontinue therapy before the long-term consequence of functional limitations develop, which would not have been captured in the current study. Information from an ongoing trial examining the effect of high-dose atorvastatin on muscle parameters in adults aged 20 and older may help clarify some of these unanswered questions.[39]

ACE Inhibitors

To the knowledge of the authors, this is the first study to report a negative association between ACE inhibitor use and physical performance (e.g., chair stand performance) or muscle strength (e.g., baseline grip strength). Prior studies have reported positive or neutral associations between ACE inhibitor use and physical function measures. The studies most relevant for comparison are those that used performance measures similar to those in the present study, which include two randomized controlled trials and one longitudinal study. A randomized controlled trial in older adults with self-reported functional impairment without heart failure reported that ACE inhibitors increased 6-minute walking distance, a measure of exercise capacity, but had no effect on secondary measures of physical performance that are comparable with the outcomes of the current study (sit to stand test, get up and go).[40] Likewise, a 6-month randomized controlled trial did not find that ACE inhibitor treatment improved a well-established measure of physical performance (the SPPB) and hand grip strength in older adults.[41] In contrast to these, ACE inhibitor use was related to less decline in muscle strength and walking speed in older disabled women with hypertension in a longitudinal study.[12] Studies conducted in small select samples found that ACE inhibitor use improved walking distance in those with heart failure and peripheral arterial disease,[16,17] improvements speculated to be related to improvements in cardiovascular function. In contrast, results from longitudinal studies in more-representative samples have not found associations between ACE inhibitor use and mobility disability, frailty, or grip strength.[33,42–44] Given the mixed findings in available studies on the association between ACE inhibitors and physical functioning, and because of the greater decline observed on one performance measure in the present study, additional research is needed to further clarify these relationships.

Strengths of this study include the prospective design, the age range in this older well-characterized sample of postmenopausal women, the availability of serially obtained standardized physical performance measures, and the ability to adjust for a large number of covariates that may be confounders, but this study has certain limitations. Medication dose was not available, and medication adherence was unknown. Lack of dose information is particularly relevant when examining the association between statins and physical performance, where one might expect that the benefit would be limited to lower doses. Furthermore, these healthy women had small average annual declines in gait speed (adjusted average annual change ranged from −0.019 to −0.022 m/s), perhaps making it difficult to observe differences according to medication use. To put these findings in perspective, a change in gait speed of 0.05 m/s has been proposed as a small clinically meaningful change.[45] Finally, despite the measures taken to control for confounding, such as stratification and adjustment, all observational studies of pharmacological exposures are subject to problems related to confounding by indication. This may be particularly relevant for the negative association found for some outcomes and ACE inhibitor use.

CONCLUSION

In summary, in this prospective study of well-functioning older women, ACE inhibitor or statin medication use was not related to less decline in physical performance or grip strength. Given the multifactorial nature of age- and disease-related functional decline, modification of one potential factor may not be sufficient to delay decline. Taken together with the existing conflicting results from other investigators, there is a paucity of evidence to support using these medications for preserving functional status. Randomized controlled trials in older adults would provide much-needed information regarding the potential differential effect of statin dose on measures of muscle strength or physical performance.

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APPENDIX A: Comparison of Minimally and Fully Adjusted Linear Repeated-Measures Analyses of Physical Performance Measures and Grip Strength According to Baseline Statin and Angiotensin-Converting Enzyme (ACE) Inhibitor Use

	Walking Speed, m/s				Chair Stands, n				Grip Strength, kg			
	Minimally Adjusted		Fully Adjusted		Minimally Adjusted		Fully Adjusted		Minimally Adjusted		Fully Adjusted	
Medication use	Estimate (95% CI)	*P*-Value	Estimate (95% CI)	*P*-Value	Estimate (95% CI)	*P*-Value	Estimate (95% CI)	*P*-Value	Estimate (95% CI)	*P*-Value	Estimate (95% CI)	*P*-Value
Statin												
Mean baseline performance												
Nonusers	1.09 (1.08–1.10)	.16	1.09 (1.09–1.10)	.84	6.45 (6.40–6.49)	.08	6.45 (6.41–6.50)	.53	23.14 (22.99–23.30)	.01	23.14 (22.99–23.30)	.07
Statin users	1.08 (1.06–1.09)	1.09	6.32 (1.07–1.11)	6.41	22.51 (6.17–6.46)	22.67	(6.26–6.55)		(22.01–22.99)		(22.18–23.15)	
Mean annual performance change												
Nonusers	−0.020 (−0.022 to −0.019)	.75	−0.021 (−0.022 to −0.019)	.58	−0.151 (−0.162 to −0.140)	.40	−0.150 (−0.162 to −0.139)	.28	−0.591 (−0.625 to −0.558)	.46	−0.589 (−0.623 to −0.556)	.52
Statin users	−0.021 (−0.026 to −0.016)		0.022 (−0.027 to −0.017)		−0.135 (−0.171 to −0.098)		−0.129 (−0.166 to −0.093)		−0.549 (−0.655 to −0.443)		−0.552 (−0.659 to −0.446)	
ACE inhibitor												
Mean baseline performance												
Nonusers	1.09 (1.08–1.10)	.18	1.09 (1.08–1.10)	.29	6.45 (6.40–6.49)	.15	6.45 (6.40–6.49)	.61	23.17 (23.02–23.33)	<.001	23.18 (23.02–23.34)	.005
ACE inhibitor users	1.08 (1.06–1.10)		1.10 (1.08–1.12)		6.34 (6.21–6.48)		6.49 (6.34–6.64)		22.32 (21.87–22.78)		22.40 (21.89–22.91)	
Mean annual performance change												
Nonusers	−0.020 (−0.022 to −0.019)	.77	−0.021 (−0.023 to −0.020)	.48	−0.145 (−0.156 to −0.133)	.01	−0.145 (−0.156 to −0.133)	.05	−0.595 (−0.629 to −0.562)	.15	−0.594 (−0.628 to −0.560)	.13
ACE inhibitor users	−0.020 (−0.024 to −0.015)		−0.019 (−0.024 to −0.015)		−0.190 (−0.225 to −0.156)		−0.182 (−0.217 to −0.147)		−0.518 (−0.619 to −0.416)		−0.511 (−0.613 to −0.409)	

Minimally adjusted models included age, race and ethnicity, education, and body mass index (BMI).

Results from fully adjusted models were presented earlier in Figures 1 and 2 and are presented again for ease of comparison. Full covariates adjustment included age, ethnicity, education, BMI, alcohol consumption, systolic and diastolic blood pressure, self-reported health, number of antihypertensive medications, diabetes mellitus, depressive symptoms, history of coronary heart disease, and hormone trial participation.

CI = confidence interval.