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

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Abstract

OBJECTIVES—Angiotensin-converting enzyme (ACE) inhibitor and statin medications may preserve skeletal muscle. We examined associations between each medication class 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 who were aged 65–79 at baseline and had physical performance measures, self-report of health insurance and no prior history of stroke or congestive heart failure were included (n=5777). Women were recruited between 1993 and 1998.

MEASUREMENTS—Medication use was ascertained through a baseline inventory. Physical performance measures (timed 6-meter 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 adjusted for demographic and health characteristics.

RESULTS—ACE inhibitor use was negatively associated with mean grip strength at baseline (22.40 kg, 95% confidence interval [CI] 21.89, 22.91 versus 23.18 kg, 95% CI 23.02, 23.34; $P = .005$) and a greater mean annual change in number of chair stands (−.182, 95% CI −.217, −.147 versus −.145, 95% CI −.156, −.133; $P = .05$) compared to non-use. Statin use was not significantly associated with baseline 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.

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CONCLUSION—These results do not support an association of statin or ACE inhibitor use with 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.

Keywords

ACE inhibitors; statins; physical performance; grip strength

INTRODUCTION

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 for 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, a growing body of evidence suggests a relationship between chronic inflammation and age-related muscle loss, disability, frailty, low physical function, walking speed, and muscle strength.[4–11] Two medication classes, ACE inhibitors and statins, have been identified as potential targets to reduce physical decline with aging.[3–5] Although results from studies have been inconsistent, evidence exists to support a reduced risk of these outcomes with ACE inhibitors and statins, particularly in select samples.[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 benefits that statins may confer by reducing inflammation could be counteracted by the muscle-related adverse events (e.g., myalgia, muscle weakness) that may occur.[21, 22]

Since most studies to date have been conducted in select samples, it is important to examine this issue in large representative samples. Given this background, our objective was to examine the associations between each medication class and baseline and annual change in lower extremity physical performance measures and muscle strength in women ages 65 and older.

METHODS

Study Sample

This study uses data from the Women's Health Initiative (WHI) clinical trials of 68,132 women ages 50 to 79 recruited from 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/retention. Further details regarding the design, recruitment strategy, and data collection methods have been published.[23] The study was reviewed and approved by human subjects review committees at each participating institution.

The study population for this analysis includes the 25% random sample of clinical trial participants ages 65 and older who completed measures of physical performance (n=6025).

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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 analytic sample of 5777 participants.

Outcomes: Physical Performance Measures and Muscle Strength

The three outcomes were assessed at baseline and at follow-up years 1, 3 and 6 by trained and certified staff using standard protocols. Timed walk and repeated chair stands were the measures of lower extremity physical performance assessed which represent two of three items of the Short Portable Performance Battery (SPPB).[24] Slowed gait speed predicts disability and mortality in older adults.[2, 25, 26] The 6 meter 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 the mean number of 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 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 made in the dominant hand with staff coaching for maximal performance and the mean of two trials was used.

ACE Inibitor and Statin Medication Ascertainment

WHI participants were asked to bring all medications taken on a regular basis in the past two 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 either a user or non-user of a statin (lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin) and/or ACE inhibitor (enalapril, benazapril, quinapril, ramipril, fosinopril, trandolapril, captopril) based on the medication inventory at screening. Duration of use was categorized as < 2 years, 2–5 years, or ≥ 5 years. Information was available on tablet strength but not on the prescribed dose.

Other Covariates

Data on demographic and health behavior characteristics (body mass index, smoking, alcohol use, leisure-time physical activity) were obtained at baseline. Body mass index (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, 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 (oral medication or insulin) and hypertension (on hypertensive medication and/or blood pressure > 140/90 mmHg). History of coronary heart disease (CHD) was based on a self-reported physician diagnosis of myocardial infarction, angina, coronary artery bypass graft or percutaneous transluminal coronary angioplasty. Depressive symptoms were assessed by a 6-item short form[29, 30] of the Center for Epidemiologic Studies Depression Scale. Physical function was measured by 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 for women 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 likely not missing at random, values corresponding to the bottom 1% at each visit year for each measure were assigned to participants that attended their annual visit, but could not complete, refused, or did not attempt the task due to safety or health concerns. The percentage of data missing for these reasons was 1.3%, 2.7%, and 7.7% for the timed walk, grip strength, and chair stands, respectively.[32] The models examine whether the mean scores on these outcome measures of exposure groups differ at baseline (*P*-intercept) or differ with respect to mean annual change over time (*P*-slope). The reasonableness of these linear fits was confirmed by comparing these estimates to 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, depressive symptoms, history of CHD and hormone trial participation. Sensitivity analyses also included additional adjustment for baseline activity level by quartiles of MET-hrs/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 and mean annual change in outcomes. Parameter estimates, 95% confidence intervals (CI), and two sided p-values were obtained using SAS PROC MIXED version 9.2 (SAS Institute, Cary, NC). Presentation of these summary statistics was graphed in R (version 2.11; R Development Core Team (2010) - http://www.R-project.org).

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

RESULTS

Women were followed on average for 7.5 years (±SD 1.5) through the planned study closeout in Spring 2005. At that time 3.5% (N=202) of our sample had withdrawn or were lost to follow-up and 7.8% (N=450) of our sample 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 and of these women, 31% were users for a duration of between 2 to 5 years and 15.0% were users for more than 5 years. Likewise, 10.4 % (N=600) of participants were current users of ACE inhibitors and of these women 32.5% were users for a duration of between 2 to 5 years and 33.5% were users for more than 5 years. Concurrent use of both agents was reported by 83 (1.4%) women. Of those using an ACE inhibitor or statin at baseline, 72% and 82% were still using these respective medications at the year 3 visit. Physical performance measures were available at all four visits on 66.1% (N=3818) of participants, three visits on 20.6% (N=1187), two visits 8.9% (N=516), and available on a single visit for 4.4% (N=256) participants.

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Figure 1 shows the trajectory of each outcome according to baseline statin use adjusted for covariates. There were no differences in baseline walking speed, chair stands or grip strength (*P*-intercept .84, .53, .07 respectively) or mean annual change (*P*-slope .58, .28, .52 respectively) between statin users and nonusers. The relationship between the duration of statin use and each outcome were not statistically significant. We next examined the interaction between and age and statin use for physical performance measures and grip strength. 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 among statin users, regardless of age; mean (95% confidence interval [CI]) = 1.09 (1.06, 1.13), 1.09 (1.06, 1.13), and 1.08 (1.04, 1.11) meters/second by increasing age groups (65–67 years, 68–71 years, and 72–79 years respectively). However, baseline walking speed was negatively associated with age in statin nonusers; mean (95% CI) = 1.13 (1.12, 1.14), 1.10 (1.09, 1.11) and 1.05 (1.03, 1.06) meters/second for increasing age groups. 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 (decline) in the number of chairs stands performed was relatively constant across increasing age groups for statin users, with mean (95% CI) values of −0.157 (−0.221, −0.093), −0.124 (−0.182, −0.066), −0.105 (−0.173, −0.037) by increasing age groups. However, the mean annual change in performance among the oldest statin non-users was nearly twice that of youngest non-users; mean (95% CI) = −0.117 (−0.137, −0.098), −0.139 (−0.158, −0.120), and −0.204 (−0.226, −0.183). Age did not modify the association of statin use on 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 among users and nonusers (*P*-intercept= . 61); however, there was suggestion of a greater annual decline in chair stand performance among users (*P*-slope =.05). ACE inhibitor use was associated with a reduced 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 for any outcome. The interactions between age and ACE inhibitor use were not significant for any outcome.

Sensitivity Analyses

Models adjusting for baseline activity level by quartiles of MET-hrs/wk or baseline use of NSAIDs produced similar estimates to those derived from the primary analyses. Results similar to the primary analyses were obtained when statin and ACE inhibitor use were modeled as time-varying exposures by updating exposure at year 3. No significant associations were observed between statin use and each outcome. While 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 non-users experiencing less decline compared with users (*P* value intercept changed from .05 to .006). We examined the interaction between each exposure and physical functioning subgroups as measured by the Rand-36 physical function scale (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* values > .20. For ACE inhibitors, tests of trend for both regression parameters yielded *P* values > .14. There was not a significant interaction between current statin and ACE

inhibitor use with any outcome (all *P* values > .18). Lastly, 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

In this large prospective study in older women with an average of 7.5 years of follow-up, we 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 (i.e. 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, our 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 strength. Of interest, 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. However, this finding should be viewed as preliminary and requires confirmation. Statin users had a slightly better performance on timed chair stands compared to nonusers in a one-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 patients with peripheral arterial disease. In fact, Giri et al. did not find an association between statin use and functional decline in those without peripheral artery disease.[13] Our overall results are consistent with 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 post-menopausal women,[36] self-reported mobility disability,[33] or a decline in lower extremity muscle strength.[37]

Several potential explanations may explain these discrepant findings. First, the positive associations between statins and physical functioning in those with peripheral arterial disease may be due to improved 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] however precise estimates may not be known for older frail adults. When examining the association of statins with 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. However, 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 be captured in our study. Information from on an on-going trial examining the effect of high dose atorvastatin on muscle parameters in adults older than 20 may help clarify some of these unanswered questions.[39]

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ACE inhibitors

To our knowledge, 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 of ACE inhibitor use with 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 to the outcomes of our study (sit to stand test, get up and go).[40] Likewise, a six month randomized controlled trial also did not find that ACE inhibitor treatment improved a well-established measure of physical performance (i.e., 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 with mobility disability, frailty or grip strength.[33, 42–44] Given the mixed findings among 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, we believe that additional research is needed to further clarify these relationships.

Strengths of this study include the prospective design, the range of age in this older well-characterized sample of postmenopausal women, availability of serially obtained standardized physical performance measures, and ability to adjust for a large number of covariates that may be confounders. However this study has certain limitations. Dose of medication 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 decline ranged from −.019 to −.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 we took to control for confounding such as stratification and adjustment, all observational studies of pharmacologic exposures are subject to issues related to confounding by indication. This issue 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 multi-factorial 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 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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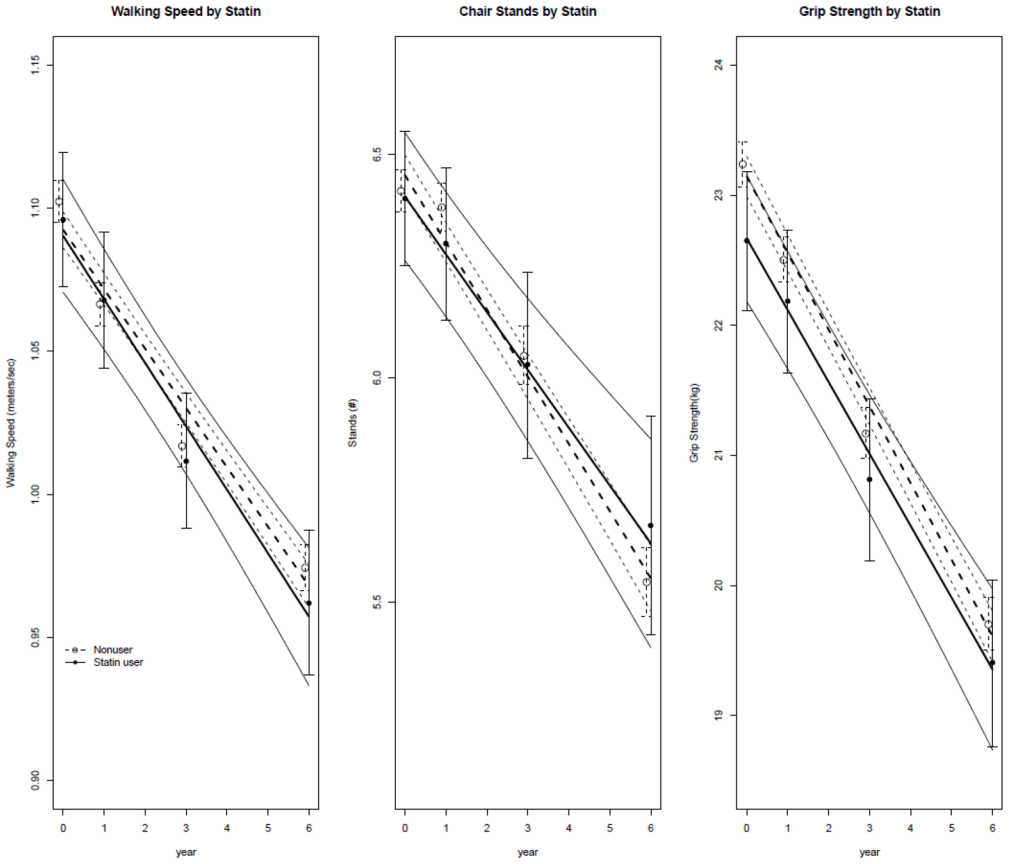
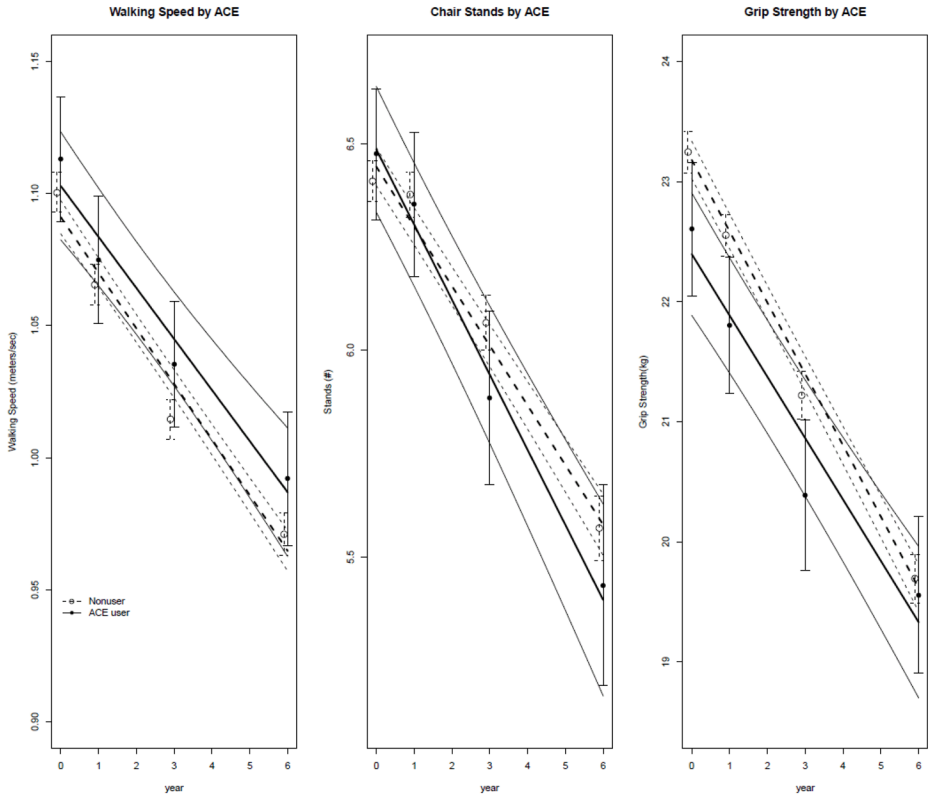


	Walking Speed (m/s)	P value	Chair Stands (#)	P value	Grip Strength (kg)	P value
Mean Baseline Performance, β_0 (95% CI)		0.84		0.53		0.07
Nonusers	1.09 (1.09, 1.10)		6.45 (6.41, 6.50)		23.14 (22.99, 23.30)	
Statin Users	1.09 (1.07, 1.11)		6.41 (6.26, 6.55)		22.67 (22.18, 23.15)	
Mean Annual Performance 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 by Baseline Statin Use

Linear estimate and 95%CI (solid and dashed lines) from a multivariable adjusted linear repeated measures model. Models were adjusted for age, ethnicity, education, BMI, alcohol consumption, systolic blood pressure, diastolic blood pressure, self-reported health, number of antihypertensive medications, diabetes, depressive symptoms, history of CHD, hormone trial randomization, and ACE use. The minimum sample size (baseline, year 1, year 3, year 6) for three outcome measures was n= (496, 436, 419,377) for statin users and n= (4852, 4243, 4189, 3768) for non-users.



	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 estimate and 95%CI (solid and dashed lines) from a multivariable adjusted linear repeated measures model. Models were adjusted for age, ethnicity, education, BMI, alcohol consumption, systolic blood pressure, diastolic blood pressure, self-reported health, number of antihypertensive medications, diabetes, depressive symptoms, history of CHD, hormone trial randomization, and statin use. The minimum sample size (baseline, year 1, year 3, year 6) for the three outcome measures was n= (551, 477, 460, 410) for ACE users and n= (4797, 4201, 4148, 3734) for non-users.

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Table 1

Baseline Characteristics According to Statin and Angiotensin-Converting Enzyme Inhibitor Use[a,b]

	Statin Use				*P* Value	ACE Inhibitor Use				*P* Value
	Yes		No			Yes		No		
Age, mean (±SD)	70.0	(3.6)	69.8	(3.7)	0.21	70.1	(3.7)	69.8	(3.7)	0.04
Education					0.28					0.02
≤ High school/GED or less	138	25.8	1326	25.4		167	28.1	1297	25.2	
School after high school	231	43.3	2105	40.4		256	43.0	2080	40.4	
College degree or higher	165	30.9	1782	34.2		172	28.9	1775	34.5	
Race/ethnicity					0.04					0.25
White	452	83.9	4535	86.6		506	84.3	4481	86.6	
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/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	1579	30.4	0.28	177	29.8	1577	30.7	0.66
BMI, mean (±SD)	28.9	(5.6)	28.5	(5.6)	0.09	30.6	(6.3)	28.3	(5.5)	<0.001
Smoking status					0.12					0.40
Never	268	50.9	2855	55.3		322	54.2	2801	55.0	
Past	231	43.8	2029	39.3		246	41.4	2014	39.5	
Current	28	5.3	279	5.4		26	4.4	281	5.5	
Alcohol consumption					0.71					<0.001
Non drinker	245	45.6	2302	44.1		313	52.2	2234	43.3	
≤ 1 drink/day	233	43.4	2365	45.3		228	38.0	2370	45.9	
> 1 drink/day	59	11.0	557	10.7		59	9.8	557	10.8	
Physical Activity (MET-hours per week), mean (±SD)	11.3	(12.4)	11.4	(12.8)	0.90	9.1	(10.5)	11.6	(13.0)	<0.001
Self-reported health					<0.001					<0.001
Excellent	45	8.4	779	15.0		23	3.8	801	15.6	
Very good	197	36.7	2178	41.8		212	35.5	2163	42.0	
Good	238	44.3	1828	35.1		284	47.5	1782	34.6	

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	Statin Use				*P* Value	ACE Inhibitor Use				*P* Value
	Yes		No			Yes		No		
Fair/poor	57	10.6	424	8.1		79	13.2	402	7.8	
Treated diabetes (pills or shots)	50	9.3	258	4.9	<0.001	70	11.7	238	4.6	<0.001
Hypertension	334	62.3	2730	52.5	<0.001	578	97.6	2486	48.3	<0.001
History of coronary heart disease[c]	106	20.0	377	7.3	<0.001	95	16.4	388	7.6	<0.001
No. of Depressive symptoms					0.73					0.02
0	145	27.3	1307	25.4		135	22.8	1317	25.9	
1–2	197	37.0	2021	39.3		252	42.6	1966	38.7	
3–4	121	22.7	1162	22.6		115	19.5	1168	23.0	
5+	69	13.0	655	12.7		89	15.1	635	12.5	
Blood pressure										
Systolic (mm Hg), mean (±SD)	133.4	(18.1)	132.0	(17.3)	0.07	139.7	(18.1)	131.3	(17.1)	<0.001
Diastolic (mm Hg), mean (±SD)	75.1	(9.6)	74.8	(9.1)	0.49	77.1	(10.1)	74.6	(9.0)	<0.001
HRT use status					0.73					0.18
Never used	297	55.2	2819	53.8		303	50.5	2813	54.4	
Past user	109	20.3	1052	20.1		126	21.0	1035	20.0	
Current user	132	24.5	1365	26.1		171	28.5	1326	25.6	
No. of antihypertensive medications					<0.001					<0.001
0	238	44.2	3437	65.6		0	0.0	3675	71.0	
1	180	33.4	1176	22.5		296	49.3	1060	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	

ACE= Angiotensin-Converting Enzyme

[a]Results expressed as number (percent) unless indicated otherwise

[b]P value based on a chi-squared test of association for categorical variables and t-test for continuous variables.

[c]Myocardial infarction, angina, coronary artery bypass graft, percutaneous transluminal coronary angioplasty

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Appendix A

A Comparison of Minimally[1] and Fully[2] Adjusted Linear Repeated Measures Analyses of Physical Performance Measures and Grip Strength by Baseline Statin Use and Baseline Angiotensin-Converting Enzyme (ACE) Inhibitor Use.

		Walking Speed (m/s)				Chair Stands (#)				Grip Strength (kg)			
		Minimally Adjusted		Fully Adjusted		Minimally Adjusted		Fully Adjusted		Minimally Adjusted		Fully Adjusted	
		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, β_0 (95% CI)**		0.16		0.84		0.08		0.53		0.01		0.07
	Nonusers	1.09 (1.08, 1.10)		1.09 (1.09, 1.10)		6.45 (6.40, 6.49)		6.45 (6.41, 6.50)		23.14 (22.99, 23.30)		23.14 (22.99, 23.30)	
	Statin Users	1.08 (1.06, 1.09)		1.09 (1.07, 1.11)		6.32 (6.17, 6.46)		6.41 (6.26, 6.55)		22.51 (22.04, 22.99)		22.67 (22.18, 23.15)	
	Mean Annual Performance Change, β_1 (95% CI)		0.75		0.58		0.40		0.28		0.46		0.52
	Nonusers	−.020 (−.022, −.019)		−.021 (−.022, −.019)		−.151 (−.162, −.140)		−.150 (−.162, −.139)		−.591 (−.625, −.558)		−.589 (−.623, −.556)	
	Statin Users	−.021 (−.026, −.016)		−.022 (−.027, −.017)		−.135 (−.171, −.098)		−.129 (−.166, −.093)		−.549 (−.655, −.443)		−.552 (−.659, −.446)	
ACE	**Mean Baseline Performance, β_0 (95% CI)**		0.18		0.29		0.15		0.61		<0.001		0.005
	Nonusers	1.09 (1.08, 1.10)		1.09 (1.08, 1.10)		6.45 (6.40, 6.49)		6.45 (6.40, 6.49)		23.17 (23.02, 23.33)		23.18 (23.02, 23.34)	
	ACE 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, β_1 (95% CI)		0.77		0.48		0.01		0.05		0.15		0.13
	Nonusers	−.020 (−.022, −.019)		−.021 (−.023, −.020)		−.145 (−.156, −.133)		−.145 (−.156, −.133)		−.595 (−.629, −.562)		−.594 (−.628, −.560)	
	ACE Users	−.020 (−.024, −.015)		−.019 (−.024, −.015)		−.190 (−.225, −.156)		−.182 (−.217, −.147)		−.518 (−.619, −.416)		−.511 (−.613, −.409)	

[1]Minimally adjusted models included age, race/ethnicity, education, and BMI.

[2]Results from fully adjusted models (shaded portion of the table) were presented earlier in Figures 1 & 2, and 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, depressive symptoms, history of CHD and hormone trial participation.