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Angiotensin-converting Enzyme Inhibitor and Statin Medication Use and Incident Mobility Limitation in Community Older Adults. The Health, Aging and Body Composition Study

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Abstract

Objective—Angiotensin-converting enzyme (ACE) inhibitors and statin medications have been proposed as potential agents to prevent or delay physical disability; yet limited research has evaluated whether such use in older community dwelling adults is associated with a lower risk of incident mobility limitation.

Design—Longitudinal cohort study

Setting—Health, Aging and Body Composition (Health ABC)

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Conflict of Interest

Author Contributions: Dr. Gray conceived of and designed the study and the analyses, interpreted the data, and drafted the manuscript. Dr. Boudreau assisted in the study design, acquisition of the data, and preparation of the manuscript, and performed the analyses. Dr. Newman contributed to the conception and design of the study, assisted in the acquisition of the data, and assisted in drafting the manuscript. Dr. Studenski contributed to the study design and data interpretation, and assisted in the preparation of the manuscript. Drs. Simonsick, Shorr and Bauer contributed to the design, analyses, and interpretation of data for this study and assisted in preparing the manuscript. Dr. Hanlon contributed to the study design, participated in the analyses and interpretation of the data, and assisted in manuscript preparation. We would like to acknowledge Yazan Roumani, MS, MBA, for his assistance with the data variable creating and analyses.

Participants—3055 participants who were well functioning at baseline (e.g., no mobility limitations).

Measurements—Summated standardized daily doses (low, medium and high) and duration of ACE inhibitor and statin use was computed. Mobility limitation (two consecutive self-reports of having any difficulty walking 1/4 mile or climbing 10 steps without resting) was assessed every 6 months after baseline. Multivariable Cox proportional hazard analyses were conducted adjusting for demographics, health status, and health behaviors.

Results—At baseline, ACE inhibitors and statins were used by 15.2% and 12.9%, respectively and both increased to over 25% by year 6. Over 6.5 years of follow-up, 49.8% had developed mobility limitation. In separate multivariable models, neither ACE inhibitor (multivariate hazard ratio [HR] 0.95; 95% confidence interval [CI] 0.82–1.09) nor statin use (multivariate HR 1.02; 95% CI 0.87–1.17) was associated with a lower risk for mobility limitation. Similar findings were seen in analyses examining dose- and duration-response relationships and sensitivity analyses restricted to those with hypertension.

Conclusions—These findings indicate that ACE inhibitors and statins widely prescribed to treat hypertension and hypercholesterolemia, respectively do not lower risk of mobility limitation, an important life quality indicator.

INTRODUCTION

Impairment in mobility, a type of functional status measure, is pervasive in older adults. In 2005, 15% of older men and 23% of older women were unable to walk 2 to 3 blocks. (Federal Interagency Forum) Adequate mobility is important to successfully continue living independently in the community. Mobility problems are associated with increased use of health services use and mortality. {Guralnik, 1994 #605} {Guralnik, 1995 #498} Thus, maintaining mobility is an important public health priority for older adults.

Chronic inflammation has been identified as contributing to several comorbidities and age-related muscle loss (e.g., sarcopenia), with the end result leading to decline in functional status (including mobility). {Walston, 2006 #385} {Corsonello, #616} {Burton, #613} Chronic inflammation and/or sarcopenia may be amenable to pharmacotherapy such as angiotensin converting enzyme (ACE) inhibitors and statins; medications which may reduce the risk of mobility loss. Statins may reduce physical disability by decreasing systemic inflammation as indicated by specific markers (e.g., C-reactive protein [CRP]). {Albert, 2001 #55} {Ridker, 1999 #104} ACE inhibitors may have direct effect on muscle in addition to reducing inflammation through reduction in angiotensin II. {Burton, #613} {Walston, 2006 #385} {Sumukadas, 2006 #350; Onder, 2007 #303} {Corsonello, #616}

Indeed, one observational study showed that the use of ACE inhibitors in older adults with hypertension resulted in positive effects on mobility limitation as measured by gait speed. {Onder, 2002 #2}. However subsequent short-term randomized trials have produced mixed results regarding the effects of ACE inhibitors on measures of functional status (e.g., mobility) {Sumukadas, 2007 #384} {Cesari, 2010 #603} Evidence for statin use being potentially beneficial is improved walking speed in patients with peripheral arterial or vascular disease. {Giri, 2006 #273} {McDermott, 2003 #25} {Mondillo, 2003 #22} What is not known is whether these potential beneficial effects will be offset by the muscle-related adverse events that may occur with statin use including myalgia, muscle weakness/cramps. Given this background, the objective of this study is to evaluate whether the time-varying use of ACE inhibitor or/and statin medications was related to a lower risk for incident mobility limitation among community dwelling older adults. In addition, dose and duration response relationships were also examined.

METHODS

Study Design, Sample and Source of Data

Longitudinal data used in the study were collected from 3,075 black and white men and women aged 70–79 residing in specified zip code areas surrounding Pittsburgh, PA and Memphis, TN with no reported difficulty walking for ¼ mile, climbing 10 steps, or performing basic activities of daily living enrolled between 1997 and 1998 in the Health, Aging and Body Composition (Health ABC) study and followed for 6.5 years. {Newman, 2003 #416} Twenty participants were excluded due to insufficient medication use information at baseline, leaving a sample of 3055 participants in the analysis. This study was approved by the University of Pittsburgh and University of Tennessee Memphis Institutional Review Boards and informed consent was obtained from each participant prior to data collection.

Data Collection and Management

The information collected annually during clinic visits included a battery of detailed physiologic measurements and questionnaire material regarding sociodemographic characteristics, multiple aspects of health status, and medication use. For medications, at baseline (year 1) and annually through year 6 (except year 4), participants were asked to bring to clinic all medications they had taken in the previous two weeks. Medication information was also collected during home visits. Highly trained interviewers transcribed from the medication containers information on medication name, strength, dosage form, and whether the medication was taken as needed. Respondents were asked the number of times they took each product the previous day, week, or month, and when they started the medication. The medication data was coded using the Iowa Drug Information System (IDIS) and then entered into a computerized database. {Pahor, 1994 #417}

ACE Inhibitor and Statin Medication Exposure

The primary exposure variables included ACE inhibitor and/or statin medication use derived from the computerized files of participants' coded prescription medication data. For ACE inhibitor exposure, IDIS class codes 24080202-24080232 were included. For current users of ACE inhibitor medication at baseline (year 1) and years 2, 3, 5, and 6 we calculated the daily dose by multiplying the number of dosage forms taken the previous day by medication strength. The daily dose was then converted to a standardized daily dose (SDD) by dividing it by the minimum effective dose per day recommended for older adults according to a well respected geriatric pharmacotherapy reference. {Semla, 2010 #590} Thus, a person taking 1.0 standardized ACE inhibitor medication unit will have taken the minimum recommended effective daily dose for elders for one agent. {Boudreau, 2009 #597} For ACE inhibitors the minimum effective geriatric dose per day for individual agents is: quinapril (10 mg), captopril (50 mg), perindopril (4 mg), enalapril (5 mg), lisinopril (10 mg), ramipril (2.5 mg), benazepril (10 mg), fosinopril (10 mg), trandolapril (1 mg), moexipril (7.5 mg).

For statin exposure, IDIS class codes 24060202-24060208 were included. Little information is available regarding the relative effect of statins on inflammatory markers. Some studies suggest that effects on C-reactive protein (CRP), an acute phase protein, may be independent of degree of lipid lowering (Ridker, 2005; Albert, 2001), but comparative metrics are not available for anti-inflammatory effects. In order to compare across statins, we converted to units of equivalent dose indicating potency for lipid lowering effect from comparative clinical trials. {Jones, 1998 #271; Jones, 2003 #272} For statins, one unit of SDD was based on lipid lowering effect of 10 mg of atorvastatin (fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20 mg, rosuvastatin 5 mg).

Standardized daily dosage was operationally defined based on the data distribution and clinical relevance into three categories. ACE inhibitors were defined as low dose (SDD < 1.0), medium dose (1.0 ≤ SDD ≤ 2.0) and high dose (SDD > 2.0). Statins were defined as low dose (SDD < 1.0), medium dose (SDD = 1.0) and high dose (SDD > 1.0). We also operationally defined, based on the data distribution, time-varying independent categorical variables for the duration of each exposure (2+ years versus less).

Outcome Variable

Based on annual clinic visits and semi-annual phone or proxy contacts, incident mobility limitation was operationally defined as two consecutive self-reports of having any difficulty walking 1/4 mile or climbing 10 steps without resting. {Newman, 2006 #418} A single report of difficulty followed by death or prior to the next scheduled contact was also classified as an event if an adjudicated decedent proxy interview report indicated that the difficulty had been present for more than 6 months. The time to incident mobility limitation was defined as the time from baseline to the first of the two successive reports of difficulty with the same activity. Follow-up was through year 7.5 after baseline (year 1) with a mean (SD) of 4.2 (2.4) years.

Covariates

We adjusted for potential confounding variables that may influence the relationship between ACE inhibitor or statin medication use and mobility decline. {Guralnik, 1993 #611; Guralnik, 1994 #605} {Onder, 2002 #2} {Giri, 2006 #273; McDermott, 2003 #25} Demographic factors were represented by categorical variables for race (black, white), sex, study site, education (post secondary education, high school graduate and less than high school graduate), and living status (alone, not alone). Age was modeled as a continuous variable. Health-related behaviors were characterized as categorical variables for smoking (current, past, never) and for alcohol use (current, past, never).

Health status factors were represented by dichotomous measures (present/absent) for self-reported health conditions including heart failure, coronary heart disease (CHD), stroke, diabetes, hypertension, pulmonary disease, and peripheral arterial disease. CHD was defined as myocardial infarction, angina, or history of coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. Information regarding incident myocardial infarction (MI) was captured over study follow-up. Categorical variables were created for cognitive impairment (Modified Mini-Mental Status score < 80), {Teng, 1987 #420} high depressive symptoms (Center for Epidemiologic Studies depression scale > 15), {Radloff, 1977 #353} urinary problems (frequent leakage, some, never) {Jackson, 2004 #419}, and vision problems (excellent/good sight, fair sight, poor to completely blind). Participants were asked about self-rated health (poor/fair versus good, very good or excellent). Measured weight and height were used to calculate body mass index (BMI) (weight [kg]/height [m²]) which was categorized as: under/normal (BMI < 25.0); overweight (BMI: 25.0 to 29.9) and obese (BMI: 30.0 & above). {, #598} Medications associated with falls and mobility were included (e.g. diuretics, digoxin, anticholinergic medications and central nervous system medications) {Leipzig, 1999 #362; Boudreau, 2009 #597} as well as a continuous variable representing the number of overall prescription medications (excluding those mentioned above).

Statistical Analyses

Categorical variables were summarized by percentages and continuous variables were summarized by means (standard deviations). At baseline, 9.9% of participants had one or more missing values for covariates. For the multivariable analyses, missing covariate values were replaced with those generated using the multiple imputation procedure in SAS®

software (Cary, NC). The results from the five data sets were combined to obtain regression coefficient estimates and confidence intervals. ACE inhibitors and statins were examined in separately. First age- and sex- adjusted hazard ratios (HR) were determined. Then, multivariable Cox Proportional Hazard analyses was used to model the time to event for the binomial outcome (i.e., incident mobility limitation or not) over 6.5 years using time-varying medication exposures. Heart failure, stroke, MI, diabetes, high depressive symptoms and cognitive impairment were entered as time-varying variables. All other variables were fixed. Tests for duration and dose-response were performed by chi-square test for trend and multiple comparisons between multivariate adjusted hazard ratios. The interaction between time-varying ACE inhibitor and statin use was explored by testing the significance of cross-product terms. For ease of interpretation, we have presented the model that includes participants as users of both medications, ACE-inhibitor use only, statin use only and use of neither. Underlying statistical assumptions were evaluated and verified. All statistical analyses were conducted using SAS[®] Version 9.1.

Sensitivity Analysis for ACE inhibitor exposure—We performed a sensitivity analysis to further address confounding by indication by restricting the sample to those with incident or prevalent treated hypertension without prevalent or incident CHF. Treated hypertension was defined as self report of hypertension or measured blood pressure over 140/90 mmHg, and self report of any antihypertensive medication.

RESULTS

The baseline characteristics of the cohort are shown in Table 1. The mean age was 74 years, 52% were female and 41% were African American. Most individuals rated their health as good to excellent (84%) and 45% had hypertension.

Table 2 provides information on ACE inhibitor and statin use over the study period. At baseline, 465 (15%) of subjects used an ACE inhibitor, with most using medium doses (66%) and more than half (58%) had been taking these medications for two or more years. At baseline, 395 (12.9%) subjects used a statin, with most using low doses (60%) and more than half taking (54 %) for less than 2 years. Only 89 (3.0%) were using both an ACE inhibitor and statin at baseline. Both ACE inhibitor and statin use increased steadily over the course of the study to 26% and 29%, respectively.

Over 6.5 years of follow-up, 49.8% of participants reported incident mobility limitation. Table 3 shows the multivariable relationship between ACE inhibitor use and incident persistent mobility limitation adjusted for demographic, health-related behaviors, and health status. ACE inhibitor use was associated with a 26% increased hazard of incident mobility in the age and sex adjusted model, which was no longer increased in the fully adjusted model (adjusted hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.82–1.09). Neither dose or duration of ACE inhibitor use were associated with incident mobility limitation. When the sample was restricted to participants with hypertension, the HR were not appreciably changed (data not shown)

Table 4 shows the multivariable relationship between statin medication use and incident mobility limitation adjusted for demographic, health related behaviors, and health status. Statin use was not associated with reduced hazard of incident mobility limitation (adjusted HR 1.04, 95% CI 0.89–1.20); nor was a relationship noted with dose or duration of use. Lastly, in the model which considered the potential joint effect of statin and ACE inhibitors, those taking both had a 23% lower risk of incident mobility disability, however this finding was not statistically significant (Table 5; adjusted HR 0.77, 95% CI 0.59–1.01). A statistically significant interaction was not found between the two medication classes.

DISCUSSION

In this prospective study in 3055 well functioning older adults with an average of 4.2 years of follow-up, we did not find that ACE inhibitor or statin medication use was associated with a reduced risk of mobility limitation. A reduced risk was also not noted when examining higher doses or longer duration of use with each agent. A synergistic effect was also not noted with combined use of statins and ACE inhibitors. Our results add to a growing body of studies that have produced mixed results for both medication classes and functional status measures. It should be noted that a key difference of our study was that it was conducted in a sample of community dwelling older adults not restricted to specific diseases; many of the previous studies occurred in select samples (e.g heart failure, peripheral arterial disease, prevalent mobility difficulties).

ACE Inhibitors

Two randomized controlled trials conducted in small select samples found that ACE inhibitor use improved walking distance (a measure of mobility) in those with heart failure and peripheral arterial disease; (Hutcheon, 2002 #617) {Ahimastos, 2006 #614} improvements speculated to be related to improvements in cardiovascular function. ACE inhibitor use in a placebo controlled trial increased exercise time in older hypertensive men. {Leonetti, 1991 #601} In an epidemiological study, ACE inhibitor use was related to less decline in muscle strength and walking speed in older disabled women with hypertension compared to nonuse. {Onder, 2002 #2}, In contrast, ACE-inhibitor use was not associated with a lower risk for incident frailty, a construct which is characterized in part by mobility problems, in healthy postmenopausal women. {Gray, 2009 #615}. A randomized controlled trial in older adults with self-reported mobility or functional impairment without heart failure reported that ACE inhibitors increased 6-minute walking distance to a degree comparable to that achieved after 6 months of exercise training, but had no effect on secondary measures of physical performance (sit to stand test, get up and go). {Sumukadas, 2007 #384} Subsequently, a six month study found that fosinopril treatment resulted in no improvement in a well-established measure of physical performance (ie, the Short Physical Performance Battery) and hand grip strength in older adults at risk for cardiovascular disease. {Cesari, 2010 #603}

Statins

The data supporting statin medications and improvement in physical performance, walking distance or physical activity have come from smaller trials and epidemiologic evaluations in patients with vascular disease. {Giri, 2006 #273} {McDermott, 2003 #25} {Mondillo, 2003 #22} {Mohler, 2003 #150} Data from the PROSPER trial found that pravastatin in older adults at risk for cardiovascular disease had a neutral effect on self-reported functional status, a tertiary outcome. {Shepherd, 2002 #10} Likewise, a large observational study found that statin use was not related to lower incidence of frailty in post-menopausal women. {LaCroix, 2007 #355} One possible explanation for these findings, including ours, is that use of statin medications is associated with various muscle complaints including myalgia, weakness, and cramps, which could be expected to negate any positive impact on mobility due to reduction in inflammation. However, it is likely that those who experience statin induced muscle adverse events discontinue therapy before the long-term consequence of mobility difficulties would manifest.

The strengths of the current study include its size and duration of follow up, the well-collected medication information, the well defined measure of incident mobility limitations and the availability of data on numerous important confounders. We required that the reported difficulty had to be persistent over a minimum of 6 months to be counted as

mobility limitation. An advantage of our self-report evaluations is that they reflect what individuals believe to be their functional capacity. A limitation is that self-reported mobility measures as used in this study may not be sensitive enough to detect an earlier stage of mobility problems as timed performance measures. Nonetheless, even studies using physical performance measures have not consistently reported an inverse association. As with any epidemiologic study, unmeasured factors may have confounded the findings. To address potential bias we adjusted for several variables thought to be confounders, included time varying MI and stroke. We also performed an analysis restricted to those with hypertension which yielded similar results.

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Table 6

Elements of Financial/ Personal Conflicts	Author 1 Shelly L. Gray		Author 3 Robert Boudreau		Author 4 Anne B. Newman		Author 5 Stephanie A. Studenski		Author 6 Ronald I. Shorr		Author 7 Douglas C. Bauer		Author 8 Eleanor Simonsick		Author 9 Joseph T. Hanlon	
	Yes*	No	Yes*	No	Yes*	No	Yes*	No	Yes*	No	Yes*	No	Yes*	No	Yes*	No
Employment or Affiliation		x		x		x		x		x		x		x		x
Grants/Funds		x		x		x	x			x		x		x		x
Honoraria		x		x		x		x		x		x		x		x
Speaker Forum		x		x		x		x		x		x		x		x
Consultant		x		x		x	x			x		x		x		x
Stocks		x		x		x		x		x		x		x		x
Royalties		x		x		x	x			x		x		x		x
Expert Testimony		x		x		x		x		x		x		x		x
Board Member		x		x		x		x		x		x		x		x
Patents		x		x		x		x		x		x		x		x
Personal Relationship		x		x		x		x		x		x		x		x

* For "yes", provide a brief explanation: Dr. Studenski reported receiving institutional grant support, travel expenses, and consultancy fees from Merck; consultancy fees from Novartis and GTX; and royalties from Hazzard Text McGraw Hill.

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Table 1

Baseline Characteristics of the Sample According to ACE inhibitor or Statin Medication Use*

Variables	
<u>Sociodemographics</u>	
Black race†	1266 (41.4)
Female gender	1574 (51.5)
Age, mean (SD)	73.6 (2.9)
Site (Pittsburgh)	1516 (49.6)
Education	
Post secondary	1293 (42.3)
High school graduate	998 (32.7)
< High school graduate	769 (25.2)
Living alone	930 (30.4)
<u>Health-related behaviors</u>	
Smoking status	
Current	320 (10.5)
Past	1398 (45.8)
Never	1341 (43.9)
Alcohol use	
Current	1515 (49.6)
Past	679 (22.2)
Never	861 (28.2)
<u>Health Status</u>	
Heart failure	40 (1.3)
Coronary heart disease	521 (17.1)
Stroke	284 (9.3)
Diabetes	470 (15.4)
Hypertension	1364 (44.7)
Pulmonary disease	127 (4.2)
Peripheral arterial disease	239 (7.8)
Cognitive impairment (Modified MMSE <80)	318 (10.4)
High depressive symptoms (CES-D>15)	145 (4.8)
Urinary problems	
No leak	1871 (61.2)
Some leak	631 (20.7)
Frequent leak	520 (17.0)
Vision problems	
Excellent/good sight	2424 (79.4)
Fair sight	545 (17.8)
Poor sight to completely blind	84 (2.8)
Fair/Poor self-rated health	494 (16.2)
Body mass index	

Variables	
Under/normal	921 (30.2)
Overweight	1302 (42.6)
Obese	780 (25.5)
Diuretic use	787 (25.8)
Digoxin use	207 (6.8)
Anticholinergic use	389 (12.7)
CNS use	424 (13.8)
Number of prescription medications, mean (SD)	6.4 (3.7)

Abbreviations: CES-D= Center for Epidemiologic Studies-Depression scale; CNS= central nervous system; SD= standard deviation; MMSE Mini-Mental Status

* Data represented as N (%), unless otherwise stated

Table 2

Prevalence of ACE inhibitor and Statin Medication Use, Dose and Duration Over Time

Medication Use	Year 1 n=3055 %	Year 2 n=2911 %	Year 3 n=2693 %	Year 5 n=2480 %	Year 6 n=2327 %
Any ACEI use	15.2	16.7	18.3	23.5	25.6
High dose (> 2 SDD)	2.4	2.7	3.5	5.0	6.4
Medium dose (1–2 SDD)	10.0	11.4	11.7	15.2	16.1
Low dose (<1.0 SDD)	2.8	2.7	3.0	3.3	3.1
Long term use (≥ 2 years)	8.8	12.7	14.3	15.0	20.7
Short term use (<2 years)	6.4	4.0	3.9	8.5	5.0
Any Statin use	12.9	15.8	19.9	25.2	28.6
High dose (> 1 SDD)	1.2	2.4	3.6	6.5	8.3
Medium dose (1 SDD)	4.0	5.7	7.8	11.7	12.9
Low dose (<1.0 SDD)	7.8	7.8	8.5	7.0	7.5
Long term use (≥ 2 years)	5.9	11.3	14.6	17.3	23.5
Short term use (<2 years)	7.0	4.5	5.3	7.9	5.2

Abbreviations: ACE=angiotensin-converting enzyme; SDD=standardized daily dose

Table 3

Multivariate Hazard Ratios for Self-Reported Incident Mobility Limitation by Time-varying ACE inhibitor Exposure

Variables	Age- & Sex- Adjusted HR (95%CI)	Fully Adjusted* HR (95%CI)
Any ACE inhibitor use	1.26 (1.10, 1.43)	0.95 (0.82, 1.09)
Non- use	1.00 (reference)	1.00 (reference)
Dose		
> 2 SDD	1.30 (0.99, 1.71)	0.80 (0.60, 1.07)
1–2 SDD	1.34 (1.14, 1.56)	1.06 (0.90, 1.25)
< 1 SDD	0.93 (0.67, 1.30)	0.73 (0.52, 1.01)
Non-use	1.00 (reference)	1.00 (reference)
Duration		
Long term use (> 2 yrs)	1.25 (1.07, 1.45)	0.94 (0.80, 1.11)
Short term use (< 2 yrs)	1.28 (1.03, 1.60)	0.97 (0.77, 1.21)
Non-use	1.00 (reference)	1.00 (reference)

* Model adjusted for baseline sociodemographics (race, age, gender, education, living status), health behaviors (smoking, alcohol), and health status (hypertension, pulmonary disease, peripheral arterial disease, urinary problems, vision problems, fair/poor self-related health, body mass index, use of diuretics, digoxin, CNS medications, statins and total number of medications). Models included time-varying ACE-inhibitor use, stroke, MI, heart failure, diabetes, depressive symptoms and cognitive impairment.

SDD=standardized daily dose

Table 4

Multivariate Hazard Ratios for Self-Reported Incident Mobility Limitation by Time-Varying Statin Exposure

Variables	Age- & Sex- Adjusted HR (95%CI)	Fully Adjusted* HR (95%CI)
Any statin use	1.08 (0.94, 1.24)	1.02 (0.87, 1.17)
Non- use	1.00 (reference)	1.00 (reference)
Dose		
> 1 SDD	1.13 (0.84, 1.52)	0.97 (0.71, 1.32)
1 SDD	1.10 (0.89, 1.35)	1.08 (0.87, 1.33)
< 1 SDD	1.06 (0.87, 1.28)	0.98 (0.80, 1.20)
Non- use	1.00 (reference)	1.00 (reference)
Duration		
Long term use (> 2 yrs)	1.00 (0.85, 1.18)	0.94 (0.79, 1.12)
Short term use (< 2 yrs)	1.25 (1.01, 1.54)	1.15 (0.93, 1.42)
Non- use	1.00 (reference)	1.00 (reference)

* Model adjusted for baseline sociodemographics (race, age, gender, education, living status), health behaviors (smoking, alcohol), and health status (hypertension, pulmonary disease, peripheral arterial disease, urinary problems, vision problems, fair/poor self-related health, body mass index, use of diuretics, digoxin, CNS medications, ACE-inhibitors and total number of medications). Models included time-varying statin use, stroke, MI, heart failure, diabetes, depressive symptoms and cognitive impairment.

SDD=standardized daily dose

Table 5

Multivariate Hazard Ratios for Self-Reported Incident Mobility Limitation by Time-Varying ACE Inhibitor and Statin Exposure

Variables	Age- & Sex- Adjusted HR (95%CI)	Fully Adjusted* HR (95%CI)
ACE use only	1.38 (1.18, 1.60)	1.02 (0.87, 1.19)
Statin use only	1.18 (1.01, 1.38)	1.23 (0.96, 1.33)
ACE and statin Use	1.05 (0.81, 1.37)	0.77 (0.59, 1.01)
No ACE or statin use	1.00 (reference)	1.00 (reference)

* Model adjusted for baseline sociodemographics (race, age, gender, education, living status), health behaviors (smoking, alcohol), and health status (hypertension, pulmonary disease, peripheral arterial disease, urinary problems, vision problems, fair/poor self-related health, body mass index, use of diuretics, digoxin, CNS medications and total number of medications). Models included time-varying ACE-inhibitor use, statin use, stroke, MI, heart failure, diabetes, depressive symptoms and cognitive impairment.

SDD=standardized daily dose