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Angiotensin-Converting Enzyme Inhibitor Use and Incident Frailty in Women Ages 65 and Older: Prospective Findings from the Women's Health Initiative Observational Study

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Abstract

OBJECTIVES: Angiotensin-converting enzyme (ACE) inhibitor medications have the potential to preserve skeletal muscle and thus may be targets to prevent frailty in older adults. Our objective was to examine the associations between current use, duration, and potency of ACE inhibitors and incident frailty in women ages 65 and older who are not frail at baseline.

DESIGN: Data are from the Women's Health Initiative Observational Study (WHI-OS), a prospective study conducted at 40 United States clinical centers.

PARTICIPANTS: Women between the ages of 65-79 years at baseline who were not frail (n=27,378).

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MEASUREMENTS: Current ACE inhibitor use was ascertained through direct inspection of medicine containers at baseline. Components of frailty included: self-reported low physical function/impaired walking; exhaustion; low physical activity; and unintended weight loss between baseline and 3 years of follow-up. Frailty was ascertained through self-reported and physical measurements data at baseline and 3-year clinic contacts.

RESULTS: By the three year follow-up, 3950 (14.4%) women had developed frailty. Current ACE inhibitor use had no association with incident frailty (multivariate-adjusted odds ratio (OR)=0.96; 95% confidence interval (CI), 0.82-1.13). Duration and potency of ACE inhibitor use were also not significantly associated with incident frailty. A similar pattern of results was observed when incident cardiovascular disease events were studied as a separate outcome or when the sample was restricted to those with hypertension.

CONCLUSION: Overall, incidence of frailty was similar in current ACE inhibitor users and non-users.

Keywords

ACE inhibitor use; frailty; disability; Women's Health Initiative

INTRODUCTION

In geriatric medicine, the term “frailty” has been used loosely to describe a condition characterized by increased vulnerability to stressors because of impairment in physiological reserve, leading to increased risk for adverse health outcomes.1 The past several years have witnessed progress in moving towards a standard and measurable conceptualization of the frailty syndrome. Definitions have varied, but frailty phenotypes in recent epidemiologic studies have typically included muscle weakness, fatigue, slowness, low physical activity and unintended weight loss.2, 3 Increasing evidence suggests a relationship between inflammation and risk of disability, frailty, walking speed and muscle strength.4-6

The renin angiotensin system (RAS) is involved in skeletal muscle structure and function and may play a role in the development of physical disability.7 Angiotensin-converting enzyme (ACE) inhibitors are medications that inhibit the conversion of angiotensin I to angiotensin II, components of the RAS. It is well known that ACE inhibitor use improves morbidity and mortality in patients with heart failure. In addition, ACE inhibitor use reduces physical disability in patients with heart failure,8 most likely because of improvements in cardiovascular function. Even more intriguing is data from epidemiological studies that suggest that ACE inhibitor use is associated with beneficial effects on physical performance and components of the frailty syndrome in those without heart failure. Use of ACE inhibitors in older adults with hypertension resulted in positive effects on muscle strength, walking speed, and lower extremity muscle mass. 9,10 A recent randomized controlled trial found that 6 months of treatment with perindopril in older adults who had mobility or functional impairments had improved walking capacity at 6 months.11

Evidence suggests that ACE inhibitors may have anti-inflammatory effects,12, 13 which may in part mediate these beneficial effects. ACE inhibitors were listed as potential targets for prevention of frailty in a recent Research Agenda on Frailty in Older Adults developed by the American Geriatrics Society/National Institute on Aging.14 The objective of this paper was to examine whether use of ACE inhibitors at baseline was associated with less incident frailty over three years in non-frail women over the age of 65 years in the Women's Health Initiative Observational Study (WHI-OS).

METHODS

Study Sample

This study uses data from the WHI-OS, a prospective study of 93,676 women ages 50-79 recruited from 1993-1998 from 40 clinical centers in the United States. Women were eligible for study inclusion if they were postmenopausal, unlikely to relocate or die within 3 years, and not enrolled in any of the WHI clinical trials. Further details regarding the design, recruitment strategy, and data collection methods have been published.15 The study was reviewed and approved by human subjects review committees at each participating institution.

This analysis includes women ages 65-79 years who were not frail at baseline (*n*=35,902). Women were excluded if they reported at baseline a diagnosis or disease that manifests as frailty (Parkinson's disease, congestive heart failure, stroke, or use of antidepressant medications; N =2710) or did not have health insurance (N =374). Women were also excluded if they died prior to the three year follow-up visit (N=799) or if information was missing on one of the frailty components (N=4641), as described below, leaving a sample of 27,378.

Measurement and Classification of Frailty

The frailty phenotype developed in the WHI cohort was based on the criteria used by Fried and colleagues2 and has been found to be strongly associated with future mortality, disability, hospitalization and hip fracture among older women in the WHI-OS.3 The components are as follows:

1. Muscle weakness/slowness was measured by the Rand-36 physical function scale (range 0-100). A score in the lowest quartile of this scale was highly associated with measured slow walking speed and low grip strength in the WHI Clinical Trial. 3 To align the scoring with Fried's frailty measure, if a participant met the threshold for frailty on this criteria (e.g. had poor physical function) they received two points because both the muscle strength and walking speed components were measured by this scale.
2. Exhaustion was measured by the Rand-36 Vitality Scale (range 0-100) using four items pertaining to the past four weeks: “Did you feel….worn out?; tired?; full of pep?; have a lot of energy?”
3. Low physical activity was classified using a questionnaire that assessed the frequency and duration of four speeds of walking and activities in the prior week. 16،17 Kilocalories of energy expended in a week on leisure time activity was calculated (MET score=kcal/week*kg).18
4. Shrinking, or unintentional weight loss, was defined as *unintentional* weight loss of >5% of body weight in the past two years, based on measured weight at the baseline and three-year clinic visits in combination with a self-reported item on whether recent weight loss was intentional at the three-year follow-up.

A frailty component was classified as present if the participant had a score in the lowest quartile of the distribution for that component or had unintentional weight loss. Participants were classified as frail (three or more points), prefrail (one or two points), or not frail (0 points). 2، 3

ACE Inhibitor Exposure

WHI participants were asked to bring all current medications taken on a regular basis to their first screening interview. Clinic interviewers entered each medication name and strength directly from the containers into a database that assigned drug codes using Medi-Span software (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 an ACE inhibitor based on the medication inventory at screening. Participants could be taking other antihypertensives. Duration of use was categorized as < 2 years, 2-5 years, or ≥ 5 years. Information on tablet strength, but not prescribed dose, was available.

In order to examine dose effect we used strength of the tablet as a proxy to define an equivalent "dose" for the ACE inhibitors. One unit of equivalent dose was based on lisinopril 10 mg (enalapril 10 mg, benazapril 10 mg, quinapril 10 mg, ramipril 2.5 mg, fosinopril 10 mg, trandolapril 2 mg, captopril 50 mg). Low equivalent dose was defined as less than 1 standardized unit, medium equivalent dose as 1 standardized unit, and high equivalent dose as greater than 1 standardized unit.

Other Covariates

Data on demographic (race or ethnicity, age, family income, education, living arrangement), health behavior characteristics, and medical history were obtained by self-report at baseline. Alcohol consumption was estimated from a food-frequency questionnaire. Smoking was classified as current, past, or never. Level of physical activity (above the range indicating frailty) was measured in kcal of energy expenditure. Body mass index (BMI) was defined using measured height and weight at baseline as weight (kg) divided by height (m^2). Current use of calcium channel blockers, beta-blockers, diuretics, and statins was ascertained at baseline. Information was collected on duration of previous use of postmenopausal hormone therapy (HRT) which was defined as current, past, or never use of any estrogen with or without progestin.

Medical conditions at baseline included self-reported physician diagnosis of arthritis, treated diabetes (oral medication or insulin), hypertension (on hypertensive medication and/or blood pressure > 140/90 mmHg), and cancer. A participant was considered to have a history of coronary heart disease (CHD) if they self reported a physician diagnosis of myocardial infarction (MI), angina, coronary artery bypass graft or percutaneous transluminal coronary angioplasty procedures (CABG/PTCA). Incident cardiovascular outcomes included clinical MI, definite and possible CHD death, angina, CABG/PTCA, carotid artery disease, heart failure, and stroke. These events were ascertained initially by annual self-report and confirmed through medical records that were reviewed and adjudicated first by local clinic physicians and then a panel of central adjudicators.19 Depressive symptoms were assessed by a 6-item short form20 of the Center for Epidemiologic Studies Depression Scale.

Statistical Analysis

Baseline characteristics were compared for women according to baseline ACE inhibitor use using chi-square tests for heterogeneity for categorical variables and t-test for continuous variables. Multinomial logistic regression models were used to examine associations between ACE inhibitor use (current use, duration, equivalent dose) and incident frailty adjusting for important confounding factors. The models adjusted for independent predictors of incident frailty identified in our previous report3 and variables significantly associated with exposure in the bivariate analyses including age, income, education, ethnicity, whether a participant lived alone, BMI, smoking, alcohol, physical activity, HRT use, self-reported health, treated diabetes, depressive symptoms, arthritis, history of cancer, history of CHD (MI, angina, CABG/PTCA), systolic blood pressure, diastolic blood pressure, number of

antihypertensive medications, and statin use. Interactions between current ACE inhibitor use and age, BMI, diabetes, smoking, baseline frailty score and statin use were explored by testing the significance of cross-product terms. At the design stage, we estimated that this analysis had 80% power to detect odds ratios in the range of 0.80-0.85.

ACE inhibitor use is more common in those with hypertension, diabetes and history of CHD, which place users at inherently higher risk of future cardiovascular disease (CVD) events than non-users. Because incident CVD events could lead to frailty, a protective effect of ACE inhibitor use with frailty could be masked and the odds ratio would appear biased toward the null. Additional analyses were conducted to reduce confounding by indication. Multinomial logistic models were constructed to examine ACE inhibitor use in relation to non-CVD frailty by separating out women who experienced an intervening CVD event. In these analyses, frailty and incident CVD were modeled as separate outcomes. In addition, we conducted additional analyses restricting to sample to those with hypertension, and to those with hypertension taking one or less antihypertensive medication. The latter restriction was applied in order to select a more homogenous group of participants with hypertension (e.g. similar risk for CVD events).

RESULTS

At baseline, 8.0 percent of women (N=2192) were current users of ACE inhibitors and 66.9% of these women were current users for a duration of two or more years (N=1467). For women who had strength information (N=2173), 2.3%, 3.3% and 2.3% were using a low, medium and high equivalent dose respectively.

ACE inhibitor use at baseline was associated with lower income, lower education, minority race/ethnicity, living alone, higher body mass index, lower alcohol consumption, use of multiple antihypertensives, statin use, lower self-rated health status, higher levels of co-morbidity, and prevalence of several health conditions (e.g. treated diabetes, hypertension, arthritis, history of CHD, Table 1). The average diastolic (76.6 ± 10.3 vs. 73.8±9.2, $p < .0001$) and systolic blood pressures (138.5 ±18.9 vs. 130.0 ±17.7, $p < .0001$) were higher in the participants using ACE inhibitors compared to non-users.

By the three-year follow-up contact, 3950 women had developed frailty (14.4%). Current ACE inhibitor use had no association with incident frailty (odds ratio [OR] =0.96, 95% confidence interval [CI], 0.82-1.13; table 2). Duration and equivalent dose of ACE inhibitor use were also not significantly associated with incident frailty. There were no significant interactions between current ACE inhibitor use and age, BMI, diabetes, smoking, baseline frailty score and statin use. A similar pattern of results was observed when incident frailty was studied in the absence of intervening cardiovascular disease events (data not shown).

When restricting the sample to those with hypertension, the association of ACE inhibitor use with frailty was similar to the analysis in the entire sample (OR=0.96 95% CI, 0.81-1.13). When restricting the sample to those with hypertension using 1 or less antihypertensive medication, there was a moderate association between equivalent dose of ACE inhibitor and reduced risk of frailty (table 3). Odds ratios were reduced for women who used low dose (OR=0.76, 95% CI, 0.53-1.11) and for medium dose (OR=0.71, 95% CI, 0.52-0.98) but not for high dose (OR=1.15, 95% CI, 0.78-1.71; $p = .04$).

DISCUSSION

In this prospective study of more than 25,000 women aged 65 years and older, current use of ACE inhibitors was not significantly related to the development of frailty at three years of follow-up. Risk of frailty was not related to duration or equivalent dose of ACE inhibitor

exposure. Results were similar when we restricted the sample to those with hypertension or when frailty outcomes in the absence of intervening cardiovascular events were examined. However, when restricting the sample to those with hypertension taking one or less antihypertensive medication, we did find a reduced risk for frailty in those using low and medium equivalent doses.

To our knowledge, this is the first large prospective study to examine ACE inhibitor use in relation to incident frailty. Other studies that have reported beneficial effects of ACE inhibitor use in older adults beyond the known benefits in heart failure have examined related outcomes such as walking speed, muscle mass or weight loss. In an observational study of 641 disabled older women without heart failure, continuous users of ACE inhibitors over the three-year observation period had a slower decline of muscle strength and walking speed compared to users of other antihypertensive medications.9 In a cross sectional analysis of data from the Health, Aging and Body Composition study, use of ACE inhibitors was associated with larger lower extremity muscle mass compared with use of other antihypertensive agents.10 Data from the Cardiovascular Health Study suggest that in older individuals with hypertension, use of an ACE inhibitor was associated with less annual weight loss.21 However, these investigators did not find an association with ACE inhibitor use and upper extremity muscle strength as measured by grip strength. A recent randomized controlled trial in older adults with mobility or functional impairments without heart failure found that individuals receiving perindopril for 6 months were able to walk on average 30 meters longer in 6 minutes compared with placebo. Improvements were not found in secondary outcome measures that are more akin to the components of the frailty measure, such as timed up-and-go or repeated chair stands, although the study was not powered for these secondary outcomes.11 The authors commented that improvements in walking may have been in part due to improved cardiovascular function, rather than muscle strength. Furthermore, a cross-sectional analysis found no association between ACE-inhibitor use and walking speed or grip strength.22 Taken together, these studies suggest that ACE inhibitor use is not consistently associated with any particular component of the frailty construct, or the composite phenotype.

Confounding by indication is a source of bias that could obscure or mask completely any protective association between ACE inhibitor use and development of frailty. In the present study, we employed several strategies to address confounding by indication including multivariate adjustment, multinomial logistic regression, interaction testing, and restriction to address the problem that ACE inhibitors are disproportionately prescribed to older women with a greater risk of CVD events. In fact, when restricting the sample to those with hypertension using monotherapy or no medication for hypertension, the most homogenous group in terms of CVD risk, a reduced risk was found for those using for two years or more and for those using low or medium equivalent doses, with only the latter reaching statistical significance. These results should be interpreted with caution and require replication in other cohorts or randomized trials, since the analysis by dose was exploratory and the use of tablet strength as a proxy for dose.

ACE inhibitors may preserve skeletal muscle function through direct and indirect effects on skeletal muscle, involving inflammatory and metabolic pathways.7 ACE inhibitors may decrease inflammation by inhibiting interleukin-6 and TNF-α production,12, 13 factors that have been associated with lower muscle mass and strength.23 Treatment with ACE inhibitors improve metabolic efficiency by increased insulin sensitivity and glucose uptake by skeletal muscle 24, 25 and may delay or prevent muscle loss by modulation of the insulin-like growth factor (IGF) system.26,27 However, data are conflicting regarding whether the IGF system contributes to declining muscle strength and functional disability in older adults.28-30

Strengths of this study include its prospective design, objective assessment of ACE inhibitor use, inclusion of over 2000 current ACE inhibitor users, consideration of a large number of covariates related to the development of frailty, and the ability to separate out adjudicated, intervening CVD events. However a few limitations should be noted. Information was only available on the prescription strength and not actual dose of ACE inhibitor medication and medication adherence was unknown. The timing of initiation and discontinuation of ACE inhibitor use in relation to the onset of frailty during follow-up was not measured. Lack of physical performance measurements is another weakness. 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.

CONCLUSION

In conclusion, this large prospective study of generally healthy older women showed no association between current ACE inhibitor use and the development of frailty over three years of follow-up. A reduced risk of frailty was noted in women on one or less antihypertensive agent using low and medium doses. However, clinicians should not assume that older adults treated with ace-inhibitors have a reduced risk of developing frailty. Whether ACE inhibitor use has a beneficial effect on physical performance and other components of frailty warrants further study, especially in sufficiently powered randomized controlled trials.

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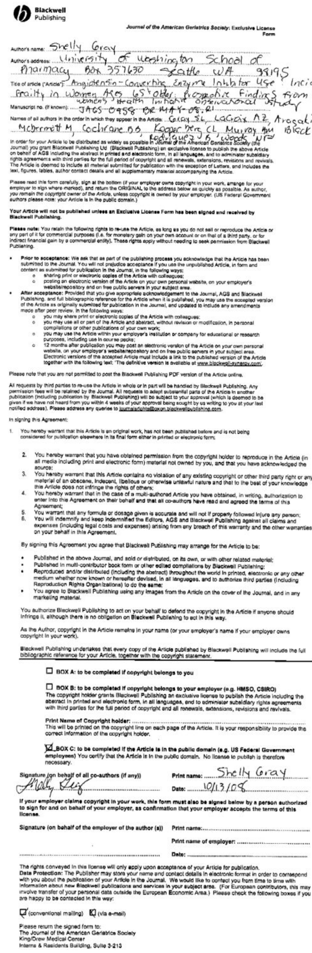

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Table 1

Baseline Characteristics versus Baseline ACE Inhibitor Exposure (N=27,378)

	ACE Inhibitor User		Non-user		
	N	**%**	**N**	**%**	***P* Value**
Age, years					.07
65-69	1076	49.1	12876	51.1	
70-79	1116	50.9	12310	48.9	
Family income					< .001
<$20K	408	20.3	3821	16.5	
$20K - $35K	578	28.7	6701	28.9	
$35K - $50K	442	21.9	5096	21.9	
$50K - $75K	348	17.3	4234	18.2	
≥$75K	238	11.8	3371	14.5	
Education					< .001
High school/GED or less	488	22.4	5238	20.9	
School after high school	861	39.6	9216	36.8	
College degree or higher	826	38.0	10615	42.3	
Ethnicity					.003
White	1920	87.6	22407	89.0	
Black	131	6.0	1064	4.2	
Hispanic	43	2.0	485	1.9	
American Indian	7	0.3	53	0.2	
Asian/Pacific Islander	69	3.1	824	3.3	
Unknown	22	1.0	353	1.4	
Living alone at baseline	731	33.7	7924	31.7	.05
Body mass index					< .001
Underweight	17	0.8	363	1.5	
Normal	749	34.4	11405	45.7	
Overweight	827	38.0	8925	35.8	
Obese	584	26.8	4262	17.1	
Smoking					.73
Never smoked	1170	54.2	13487	54.3	

	ACE Inhibitor User		Non-user		
	N	%	N	%	*P* Value
Past smoker	909	42.1	10348	41.7	
Current smoker	79	3.7	990	4.0	
Alcohol intake					< .001
Non/past drinker	691	31.8	6712	26.8	
<1 drink/week	647	29.7	7682	30.7	
1-14 drinks/week	730	33.6	9446	37.7	
> 14 drinks/week	107	4.9	1197	4.8	
Hormone therapy use					.96
Never used	1019	46.5	11644	46.3	
Past use	366	16.7	4257	16.9	
Current use	806	36.8	9258	36.8	
Calcium channel blocker use	337	15.4	2509	10.0	< .001
Beta-blocker use	270	12.3	2312	9.2	< .001
Diuretic use	604	27.6	2713	10.8	< .001
Other antihypertensive use	59	2.7	567	2.3	.19
Number of antihypertensive medications					< .001
0	0	0.0	18856	74.9	
1	1156	52.7	4612	18.3	
2	803	36.6	1509	6.0	
3+	233	10.6	209	0.8	
Statin use	372	17.0	2324	9.2	< .001
Self-reported health					< .001
Excellent	154	7.1	4918	19.7	
Very Good	886	40.8	11902	47.6	
Good	974	44.9	7330	29.3	
Fair/Poor	156	7.2	855	3.4	
ADL disability (≥ limitation)	22	1.0	255	1.0	.97
Treated diabetes	188	8.6	581	2.3	< .001
Hypertension	2122	98.0	10867	43.7	< .001
Depressive symptoms					

	ACE Inhibitor User		Non-user		
	N	%	N	%	*P* Value
0	621	28.9	7391	29.8	.54
1-2	869	40.4	9907	40.0	
3-4	419	19.5	4900	19.8	
5+	243	11.3	2587	10.4	
History of arthritis	1198	55.1	12874	51.5	.001
History of cancer	315	14.5	3602	14.4	.96
History of CHD	249	11.6	1720	7.0	< .001
Any comorbid condition	1630	74.4	12524	49.7	< .001

ACE=angiotensin-converting enzyme inhibitor

Table 2

Adjusted* Odds Ratios Relating ACE Inhibitor Use to Risk of Frailty at Three-Year Follow-Up: Women's Health Initiative Observational Study (N=27,378)

	Not Frail	Pre-Frail		Frail		*P* Value†
	N	N	OR (95% CI)	N	OR (95% CI)	
Current ACE inhibitor use						
Non-user	14155	7527	1.00	3504	1.00	.88
User	1030	716	1.00 (0.88-1.14)	446	0.96 (0.82-1.13)	
Years of ACE inhibitor use						
Non-users	14155	7527	1.00	3504	1.00	.59
<2	321	262	1.16 (0.95-1.42)	142	0.96 (0.75-1.24)	
2-5	337	215	0.91 (0.74-1.12)	146	0.96 (0.74-1.24)	
>5	372	239	0.95 (0.78-1.16)	158	0.97 (0.76-1.24)	
Potency of ACE inhibitor use‡						
Non-users	14155	7527	1.00	3504	1.00	.73
Low	300	221	1.09 (0.88-1.35)	112	0.88 (0.67-1.16)	
Medium	429	287	0.95 (0.78-1.14)	187	0.95 (0.75-1.19)	
High	292	203	1.00 (0.80-1.25)	142	1.08 (0.83-1.41)	

ACE=angiotensin-converting enzyme inhibitor; OR=odds ratio; CI=confidence interval

*Odds ratios derived from multivariate multiple logistic regression analysis adjusting age, income, education, ethnicity, BMI, smoking, alcohol, physical activity, HRT use, whether a participant lived alone, self-reported health, diabetes, depressive symptoms, arthritis, history of cancer, history of CHD, systolic blood pressure (tertiles and linear), diastolic blood pressure (tertiles and linear), number of antihypertensive medications, and statin use.

†P-value from the aforementioned regression model, where significance corresponds to the overall effect of ACE inhibitor exposure variable and frailty.

‡19 were missing strength of information.

Table 3

Adjusted* Odds Ratios Relating ACE Inhibitor Use to Risk of Frailty Among Hypertensive Participants on 1 or No Antihypertensive Medications: Women's Health Initiative Observational Study (N=10330).

	Not Frail	Pre-Frail		Frail		*P* Value†
	N	N	OR (95% CI)	N	OR (95% CI)	
Current ACE inhibitor use						
Non-user	4783	2917	1.00	1515	1.00	.25
User	559	360	0.97 (0.82-1.16)	196	0.83 (0.66-1.04)	
Years of ACE inhibitor use						
Non-users	4783	2917	1.00	1515	1.00	.26
<2	174	137	1.14 (0.87-1.50)	73	0.97 (0.69-1.38)	
2-5	184	101	0.77 (0.57-1.03)	59	0.76 (0.53-1.10)	
≥5	201	122	1.01 (0.77-1.33)	64	0.76 (0.53-1.09)	
Potency of ACE inhibitor use						
Non-users	4783	2917	1.00	1515	1.00	.04
Low	175	135	1.18 (0.90-1.55)	55	0.76 (0.53-1.11)	
Medium	249	136	0.76 (0.58-0.98)	87	0.71 (0.52-0.98)	
High	132	87	1.11 (0.80-1.53)	53	1.15 (0.78-1.71)	

ACE=angiotensin-converting enzyme inhibitor; OR=odds ratio; CI=confidence interval

*Odds ratios derived from multivariate multinomial logistic regression analysis adjusting age, income, education, ethnicity, body mass index, smoking, alcohol, physical activity, HRT use, whether a participant lives alone, self-reported health, diabetes, depressive symptoms, arthritis, history of cancer, history of CHD, systolic blood pressure (tertiles and linear), diastolic blood pressure (tertiles and linear), number of antihypertensive medications, and statin use.

†P-value from the aforementioned regression model, where significance corresponds to the overall effect of ACE inhibitor exposure variable and frailty.

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