ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS USE AND INCIDENT FRAILTY: A LONGITUDINAL COHORT STUDY

Short title: ACEI and frailty

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ABSTRACT

Introduction: Angiotensin-converting-enzyme inhibitors (ACEI) may have several pleiotropic effects, but the literature regarding a possible relationship between ACEI use and frailty is limited. We investigated whether ACEI use is associated with lower risk of frailty in a cohort of North American individuals.

Methods: Data from the Osteoarthritis Initiative, a cohort study with 8 years of follow-up including community-dwelling adults with knee osteoarthritis or at high risk for this condition, were analyzed. ACEI use was defined through self-reported information and confirmed by a trained interviewer. Frailty was defined using the Study of Osteoporotic Fracture (SOF) index as the presence of at least two of the following criteria: (i) weight loss ≥5% between baseline and any subsequent follow-up visit; (ii) inability to do five chair stands; and (iii) low energy level according to the SOF definition. A multivariable Poisson regression analysis was used to assess the association between ACEI use at baseline and incident frailty. The data were reported as relative risks (RRs) with their 95% confidence intervals (CIs).

Results: The final sample consisted of 4,295 adults (mean age 61.2 years, females=58.1%). At baseline, 551 participants (12.8%) used ACEI. After adjusting for 15 potential confounders, the use of ACEI was associated with a lower risk of frailty (RR=0.72; 95%CI: 0.53-0.99). The adjustment for the propensity score substantially confirmed these findings (RR=0.75; 95%CI: 0.54-0.996).

Conclusion: ACEI use may be associated with a reduced risk of frailty in individuals with/at risk of knee osteoarthritis, suggesting a potential role for ACI in the prevention of frailty.

Keywords: angiotensin-converting-enzyme inhibitors; aged; Osteoarthritis Initiative; frailty.

KEY POINTS

- Angiotensin-converting-enzyme inhibitors (ACEI) may decrease the risk of frailty, but the literature is still limited.
- In our study, after adjusting for 15 potential confounders, the use of ACEI was associated with a lower risk of frailty, particularly in older individuals.
- Using the propensity score did not change our results.

1. INTRODUCTION

Angiotensin-converting-enzyme inhibitors (ACEI) are pharmaceutical preparations used primarily for the treatment of hypertension and congestive heart failure through the inhibition of the angiotensin-converting enzyme, an important component of the renin–angiotensin system.[1] ACEI cause relaxation of blood vessels as well as a decrease in blood volume, which further leads to lower blood pressure and decreased oxygen demand from the heart, justifying their use for high blood pressure and heart failure. However, increasing research has shown that ACEI can be used for other medical conditions, including acute myocardial infarction [2] and diabetic kidney failure. [3]

There is currently burgeoning evidence that ACEI can also have other pleiotropic effects (e.g. for improving muscular function), particularly in older individuals. [4] In an observational study, frailty was less prevalent in the participants who were taking diuretics and ACEI. [5] In a randomized controlled trial, perindopril, one of the most common ACEI, significantly improved the exercise capacity and prevented declines in health-related quality of life among functionally impaired older individuals. [6] Similarly, ACEI seem to improve aerobic capacity in individuals affected by heart failure. [7] These findings suggest a potential role of ACEI in preventing frailty, a state of increased vulnerability to stressor events usually associated with poor muscle function [8] that is common in older individuals [9, 10] and seems to be associated with higher risk of mortality, cardiovascular diseases [11] and poor quality of life. [12] The concept of frailty is debated and different theories exist regarding its definition. [13]

Despite this, to the best of our knowledge, only one study has addressed the association between ACEI use and frailty. Specifically, a large cohort study involving more than 25,000 older women with a three-year follow-up period did not report any significant association between the use of ACEI and incident frailty, after controlling for important confounding variables including physical activity [14]. However, this study had a short follow-up period, only included women, and its

findings conflict with other studies reporting potential beneficial effects of ACEI on muscle function [15]. Given the scant evidence base and the potential to substantially improve the health and quality of life of older individuals if such benefits of ACEI use on frailty can be identified, further research is warranted.

The present study therefore aimed to investigate the association between the use of ACEI and incident frailty in a large cohort of North American individuals followed up for 8 years, accounting for relevant confounders.

2. MATERIALS AND METHODS

2.1 Data source and subjects

Data were obtained from the Osteoarthritis Initiative (OAI) database. Participants were recruited across four clinical sites in the United States of America (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. In the OAI, participants were included if they: (1) had knee OA with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA (e.g. overweight/obese (body mass index, BMI ≥25kg/m²), family history of knee OA).[16] The data of this longitudinal cohort study were collected at baseline and during subsequent evaluations, with a follow-up of 8 years. All participants provided written informed consent. The OAI study was given full ethics approval by the institutional review board of the OAI Coordinating Center, at the University of California in San Francisco.

2.2 Exposure: use of ACEI

ACEI use was assessed at baseline using a specific questionnaire assessing past 30-day use of medications. Trained interviewers checked the medications used by each participant, through an interview with the participant and dispensing records. The ACEI included in the interview were: quinapril, captopril, perindopril, enalapril, lisinopril, ramipril, benapril, fosinopril, trandopril, and moexipril.

2.3 Outcome: incident frailty

The main outcome of interest was incident frailty. In accordance with the Study of Osteoporotic Fracture (SOF) index [17-20], frailty was defined as the presence of at least 2 of the following 3 criteria: (i) weight loss $\geq$5% taking place between baseline and the follow-up examinations (at the baseline examination, a BMI of less than 20 Kg/m^2, a common cut-off for identifying underweight

in older individuals [21] was used, since no information regarding weight changes were recorded); (ii) the inability to rise from a chair five times without arm support (hereafter referred to as inability to carry out chair stands); and (iii) poor energy based on the SF12 questionnaire [22]: response of "little of the time" or "none of the time" to the question "in the past 4 weeks, did you have a lot of energy?" The assessment of the outcome was made at baseline and during the V01 (12 months), V03 (24 months), V05 (36 months), V06 (48 months), V08 (72 months) and V10 (96 months) follow-up assessments.

2.4 Covariates

Several covariates at baseline (other than age and sex) were identified as potential confounding factors based on previous literature.[23] These included: systolic and diastolic blood pressure, recorded by a trained nurse, at the right arm once; race (white vs. other); education (college or higher vs. other); BMI; yearly income ($< \text{vs} \geq \$50{,}000$ or missing data); depressive symptoms assessed using the Center for Epidemiologic Studies Depression Scale (CES-D)[24]; smoking habits (never vs. previous/actual); physical activity evaluated using the total score for the Physical Activity Scale for the Elderly scale (PASE) [25]; Charlson Comorbidity Index score [26]; the number of medications used; daily energy intake; the presence of frailty items at the baseline; the presence of radiographical OA on fixed flexion radiograph and based on the presence of tibiofemoral osteophytes (correspondent to Osteoarthritis Research Society International atlas grades 1-3, clinical center reading). [27]

2.5 Statistical analyses

Data on continuous variables were normally distributed according to the Kolmogorov-Smirnov test. Data were presented as means and standard deviation values (SD) for quantitative measures, and percentages for all categorical variables by the use or non-use of ACEI at baseline. P values were

calculated using an independent T test for continuous variables and a chi-square test for categorical parameters.

To assess the relationship between ACEI use and incident frailty, a multivariable Poisson regression analysis with robust variance estimators was applied. Individuals who were already frail at baseline were excluded from the analysis. The fully adjusted model included baseline values of the covariates mentioned before. Multi-collinearity among covariates was assessed through variance inflation factor (VIF) [28], taking a cut-off of 2 as the criterion for exclusion. However, no covariates were excluded using this criterion. Moreover, we used the propensity score which is a statistical matching technique that attempts to estimate the effect of a treatment by accounting for the covariates that predict receiving the treatment.[29] The propensity score, divided into quartiles, was estimated by using a logistic regression model regressing baseline ACEI use on the above-mentioned covariates. Adjusted relative risks (RRs) and 95% confidence intervals (CI) were calculated to estimate the strength of the associations between ACEI use and incident frailty.

We also ran some additional analyses testing moderation by the presence of high blood pressure (defined as the use of medication or a blood pressure value $\geq$140/90 mmHg), or the presence of congestive heart failure (n=85), but the interaction of ACEI use by these factors in predicting frailty was not significant (p-values>0.05). However, age (i.e., $\leq$65 vs. >65 years) was a significant moderator of our findings (p=0.0001 for fully adjusted and propensity score models) where the association was stronger among older individuals.

A $p<0.05$ was deemed statistically significant. Analyses were performed using STATA® software version 14.1 (Stata Corp LP, College station, Texas).

3. RESULTS

3.1 Sample selection

The OAI dataset initially included a total of 4,796 individuals. At the baseline, 17 individuals were already frail and no information regarding ACEI were recorded for 113 participants. Finally, 388 individuals were lost at follow-up. Accordingly, 4,295 participants were included in the present analyses.

3.2 Descriptive characteristics

The cohort included 2,494 females (58.1%). Mean age was 61.2 years (±9.3 years; range: 45-79 years). At the baseline, 551 participants (12.8%) used ACEI, with lisinopril being the most commonly reported (n=310).

Table 1 illustrates the baseline characteristics in relation to use of ACEI. Individuals using ACEI (n=551) were significantly older, more frequently male, more sedentary, and less frequently white than those not using these medications (n=3,744). Individuals using ACEI were less educated, poorer and more frequently obese than those not using ACEI. ACEI users consumed a larger number of medications than controls. Also, individuals using ACEI had a significantly higher prevalence of knee OA at baseline than non-users. No significant differences in baseline frailty items were detected, except for a higher prevalence of BMI <20 Kg/m^2 in people not using ACEI (2.4 vs. 0.5%, p=0.005) (**Table 1**).

3.3 Angiotensin-converting-enzyme inhibitors and incident frailty

Over a mean follow-up of 8 years, 341 individuals (7.9% of the baseline population) became frail, corresponding to a global incidence of 12 (95%CI: 10-13) cases for 1,000 persons-years. The incidence rate of new cases of frailty was similar between ACEI users and controls (p=1.00; **Table 2**).

After adjusting for 15 potential confounders at baseline, with ACEI non-use as the reference category, baseline ACEI use was associated with a significantly lower risk of frailty in both the fully adjusted model (RR=0.72; 95%CI: 0.53-0.99; p=0.04) and the propensity score-adjusted model (RR=0.75; 95%CI: 0.54-0.996; p=0.046) (**Table 2**).

The association between ACEI use and the onset of frailty was significant only in people older than 65 years (fully-adjusted model, RR=0.49; 95%CI: 0.30-0.80; p=0.004; propensity score-adjusted model, RR=0.54; 95%CI: 0.34-0.87; p=0.01) (p-value for interaction by age=0.001 in both models).

4. DISCUSSION

In this large longitudinal study, over an 8-year follow-up period, our results suggest that ACEI use is associated with a lower risk of frailty, showing a reduction of its incidence by 28% in the fully-adjusted model and by 25% when using the propensity score. These findings were particularly evident in individuals older than 65 years.

The topic of the association between medications commonly used in older individuals and frailty is of great interest in geriatric medicine. Frailty is a very common condition in older people, affecting one in every ten community-dwelling older adults [9], but reaching higher proportions in other settings, such as nursing homes. [10] Several works have reported that a higher number of medications (polypharmacy) is associated with a higher risk of frailty [30, 31], but, on the contrary, some evidence suggests that ACEI can be associated with a lower risk of frailty and better muscle function. However, the evidence is limited to a few studies. Some observational studies, including older patients with hypertension and with normal cardiac function, in fact, have reported significantly slower declines in muscle strength and improved physical performance among patients taking ACEI. [15] However, another longitudinal study failed to find any significant association between the use of ACEI and incident frailty. [14] It is likely that differences between studies in terms of inclusion/exclusion criteria, the type of the analyses and the covariates used, length of follow-up, and definitions of frailty and ACEI use may partly explain these discrepant results, but further research is needed in this sense.

Several mechanisms have been hypothesized for explaining the potential association between ACEI and frailty. First, ACEI may lead to an improvement of cardiac and vascular function [1] that, consequently, is associated with an improvement in physical function and a lower risk of frailty. Second, ACEI increases nitric oxide production [32], which may improve skeletal muscle function. [33] Moreover, ACEI, in animal models, seem to increase the number of sarcomeres through a

reduction in the degradation of bradykinin. [34] Third, ACEI can lower inflammatory levels [35] and inflammation seems to play an important role in the development of frailty and poor muscle function. [36-38] Finally, ACEI can prevent age-related mitochondrial dysfunction further contributing to better muscle function. [39] At the same time, there are novel findings supporting the possibility that ACEI can have adverse effects on health. For example, in a large population based study with over 6.4 years of follow-up, people taking ACEI had a significantly higher risk of lung cancer than controls. [40] These findings suggest that more robust data are needed before recommendations can be made regarding the utility of ACEI in the prevention of frailty. [40]

Finally, our results were statistically significant only in those greater than 65 years of age. Although the reason for this is unknown, it may be that older people had used ACEI for a longer time than younger individuals, making the results significant only in older people. However, other studies are needed to confirm this age-difference.

The strengths of our study are the long duration of follow-up and the large sample size included. However, our findings should be interpreted within some limitations. First, the OAI includes only participants who already have or are at high risk of knee OA. Thus, our results are not generalizable to the general population. Second, the observational nature of our findings can introduce another bias in our results, although we tried to correct this limitation using analyses adjusted for potential confounders and for the propensity score. Third, we did not have any information (at baseline nor during follow-up) on cognitive function and this could have introduced an important bias in our findings. Specifically, even if the risk of physical frailty might be positively influenced by ACEI, the protective effect of ACEI can be nullified in the presence of cognitive frailty. Finally, the record of medications was self-reported (although confirmed by a trained interview) and therefore subject to recall bias. Furthermore, information regarding duration of ACEI use, and the use of ACEI during follow-up were missing.

In conclusion, our data suggest that ACEI use is associated with a lower risk of frailty in this large cohort of North American individuals. Future interventional studies are however needed to confirm/refute our observational findings.

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Conflict of interest: Veronese, Stubbs, Smith, Maggi, Jackson, Soysal, Demurtas, Celotto, Koyanagi declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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