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

Short title: ACEI and frailty

Nicola Veronese[1], MD, Brendon Stubbs[2,3,4], PhD, Lee Smith[5], PhD, Stefania Maggi[1], Sarah E. Jackson[6], PhD, MD, Pinar Soysal[7], MD, Jacopo Demurtas[8], MD, Stefano Celotto[9], MD, Ai Koyanagi[10,11], MD

[1] National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy.

[2] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, UK.

[3] Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience King's College London, De Crespigny Park, London Box SE5 8AF, UK.

[4] Faculty of Health, Social Care and Education, Anglia Ruskin University, Bishop Hall Lane, Chelmsford CM1 1SQ, UK.

[5] The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK.

[6] Department of Behavioural Science and Health, University College London, London UK.

[7] Department of Geriatric Medicine, Bezmialem Vakif University, Faculty of Medicine, Istanbul, Turkey.

[8] Primary Care Department, Azienda USL Toscana Sud Est, Grosseto, Italy

[9] Primary Care Department, Aziendale AAS3 Alto Friuli - Collinare - Medio Friuli, Udine, Italy.

[10] Research and Development Unit, Parc Sanitari Sant Joan de Déu, Universitat de Barcelona, Fundació Sant Joan de Déu, Barcelona, Spain.

[11] Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain.

Corresponding Author:

Nicola Veronese, MD

National Research Council, Neuroscience Institute, Aging Branch

Via Giustiniani, 2 35128 Padova, Italy

Phone: +390498211746; Fax: +390498211218

Email: ilmannato@gmail.com

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.

ACKNOWLEDGEMENTS

Funding: This study was funded by five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript was prepared using an OAI public use data set and does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners.

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.

REFERENCES

1. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation. 1998;97(14):1411-20.

2. Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting–enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. New England Journal of Medicine. 1995;333(25):1670-6.

3. Parving H-H, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. New England Journal of Medicine. 2001;345(12):870-8.

4. Cranney A. Is there a new role for angiotensin-converting-enzyme inhibitors in elderly patients? CMAJ : Canadian Medical Association Journal. 2007;177(8):891-2.

5. Ashdown-Franks G, Stubbs B, Koyanagi A, Schuch F, Firth J, Veronese N, et al. Handgrip strength and depression among 34,129 adults aged 50 years and older in six low- and middle-income countries. J Affect Disord. 2019 Jan 15;243:448-54.

6. Sumukadas D, Witham MD, Struthers AD, McMurdo ME. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. Canadian Medical Association Journal. 2007;177(8):867-74.

7. Hutcheon S, Gillespie N, Crombie I, Struthers A, McMurdo M. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomised double blind placebo controlled trial. Heart (British Cardiac Society). 2002;88(4):373-7.

8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet (London, England). 2013;381(9868):752-62.

9. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. Journal of the American Geriatrics Society. 2012;60(8):1487-92.

10. Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association. 2015;16(11):940-5.

11. Veronese N, Cereda E, Stubbs B, Solmi M, Luchini C, Manzato E, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: results from a meta-analysis and exploratory meta-regression analysis. Ageing research reviews. 2017 Jan 28;35:63-73.

12. Rizzoli R, Reginster JY, Arnal JF, Bautmans I, Beaudart C, Bischoff-Ferrari H, et al. Quality of life in sarcopenia and frailty. Calcified tissue international. 2013 Aug;93(2):101-20.

13. Robine J-M, Michel J-P. Looking forward to a general theory on population aging. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2004;59(6):M590-M7.

14. Gray SL, LaCroix AZ, Aragaki AK, McDermott M, Cochrane BB, Kooperberg CL, et al. Angiotensin-converting enzyme inhibitor use and incident frailty in women aged 65 and older: prospective findings from the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society. 2009 Feb;57(2):297-303.

15. Onder G, Penninx BW, Balkrishnan R, Fried LP, Chaves PH, Williamson J, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet (London, England). 2002 Mar 16;359(9310):926-30.

16. Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. Medical Hypotheses. 2006 //;67(2):362-70.

17. Veronese N, Stubbs B, Noale M, Solmi M, Pilotto A, Vaona A, et al. Polypharmacy Is Associated With Higher Frailty Risk in Older People: An 8-Year Longitudinal Cohort Study. Journal of the American Medical Directors Association. 2017 Apr 07.

18. Bolzetta F, Wetle T, Besdine R, Noale M, Cester A, Crepaldi G, et al. The relationship between different settings of medical service and incident frailty. Experimental gerontology. 2018 Jul 15;108:209-14.

19. Veronese N, Stubbs B, Maggi S, Notarnicola M, Barbagallo M, Firth J, et al. Dietary Magnesium and Incident Frailty in Older People at Risk for Knee Osteoarthritis: An Eight-Year Longitudinal Study. Nutrients. 2017 Nov 16;9(11).

20. Misra D, Felson DT, Silliman RA, Nevitt M, Lewis CE, Torner J, et al. Knee osteoarthritis and frailty: findings from the Multicenter Osteoarthritis Study and Osteoarthritis Initiative. The journals of gerontology Series A, Biological sciences and medical sciences. 2015;70(3):339-44.

21. Veronese N, Cereda E, Solmi M, Fowler SA, Manzato E, Maggi S, et al. Inverse relationship between body mass index and mortality in older nursing home residents: a meta-analysis of 19,538 elderly subjects. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2015 Nov;16(11):1001-15.

22. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical care. 1996;34(3):220-33.

23. Allen KD, Golightly YM. Epidemiology of osteoarthritis: state of the evidence. Current opinion in rheumatology. 2015;27(3):276-83.

24. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychology and aging. 1997;12(2):277-87.

25. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. Journal of clinical epidemiology. 1999;52(7):643-51.

26. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? Medical care. 1996;34(1):73-84.

27. Veronese N, Koyanagi A, Stubbs B, Cooper C, Guglielmi G, Rizzoli R, et al. Statin use and knee osteoarthritis outcomes: A longitudinal cohort study. Arthritis care & research. 2018 Aug 24.

28. Miles J. Tolerance and variance inflation factor. Wiley StatsRef: Statistics Reference Online. 2009.

29. Haukoos JS, Lewis RJ. The Propensity Score. Jama. 2015;314(15):1637-8.

30. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. British journal of clinical pharmacology. 2018;84(7):1432-44.

31. Veronese N, Stubbs B, Noale M, Solmi M, Pilotto A, Vaona A, et al. Polypharmacy Is Associated With Higher Frailty Risk in Older People: An 8-Year Longitudinal Cohort Study. Journal of the American Medical Directors Association. 2017 Jul 1;18(7):624-8.

32. Kitakaze M, Node K, Minamino T, Asanuma H, Ueda Y, Kosaka H, et al. Inhibition of Angiotensin-converting Enzyme Increases the Nitric Oxide Levels in Canine Ischemic Myocardium. Journal of Molecular and Cellular Cardiology. 1998 1998/11/01/;30(11):2461-6.

33. Stamler JS, Meissner G. Physiology of nitric oxide in skeletal muscle. Physiological reviews. 2001 Jan;81(1):209-37.

34. Koh TJ, Tidball JG. Nitric oxide synthase inhibitors reduce sarcomere addition in rat skeletal muscle. The Journal of physiology. 1999;519(1):189-96.

35. Kortekaas KE, Meijer CA, Hinnen JW, Dalman RL, Xu B, Hamming JF, et al. ACE Inhibitors Potently Reduce Vascular Inflammation, Results of an Open Proof-Of-Concept Study in the Abdominal Aortic Aneurysm. PloS one. 2014 12/04
07/01/received
09/29/accepted;9(12):e111952.

36. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing research reviews. 2016 Nov;31:1-8.

37. Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B, et al. Inflammation and sarcopenia: A systematic review and meta-analysis. Maturitas. 2017 Feb;96:10-5.

38. Barberi L, Scicchitano BM, Musarò A. Molecular and cellular mechanisms of muscle aging and sarcopenia and effects of electrical stimulation in seniors. European journal of translational myology. 2015;25(4).

39. Ferder L, Inserra F, Romano L, Ercole L, Pszenny V. Effects of angiotensin-converting enzyme inhibition on mitochondrial number in the aging mouse. The American journal of physiology. 1993 Jul;265(1 Pt 1):C15-8.

40. Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. Bmj. 2018;363:k4209.

Table 1. Characteristics of the participants classified according to their baseline use of angiotensin-converting-enzyme inhibitors (ACEI).

	ACEI users (n=551)	Non-ACEI users (n=3744)	p-value
General characteristics			
Age (years)	64.0 (8.7)	60.8 (9.1)	<0.0001
Females (%)	51.7	59.0	0.001
PASE (points)	147 (73)	162 (83)	<0.0001
White race (%)	75.5	81.3	0.001
Smoking (previous/current) (%)	48.6	46.5	0.35
Graduate degree (%)	23.8	31.7	<0.0001
Yearly income (≥ $50,000) (%)	52.5	60.8	<0.0001
Daily energy intake (Kcal/die)	1400 (553)	1414 (569)	0.30
Medical conditions			
BMI (Kg/m^2)	30.3 (4.9)	28.5 (4.8)	<0.0001
CES-D (points)	6.6 (7.0)	6.4 (6.8)	0.77
Charlson co-morbidity index (points)	0.4 (0.8)	0.6 (1.0)	1.00
Presence of knee OA (%)	63.9	55.8	<0.0001
Number of medications	4.8 (2.6)	2.7 (2.6)	<0.0001
Systolic blood pressure (mmHg)	129 (17)	123 (16)	<0.0001
Diastolic blood pressure (mmHg)	76 (11)	75 (10)	0.66
Frailty items (at baseline)			
BMI <20 Kg/m^2 (%)	0.5	2.4	0.005
Poor physical performance (%)	1.0	0.6	0.24

	ACEI users (n=551)	Non-ACEI users (n=3744)	p-value
Poor chair stands time (%)	10.7	10.8	0.95

Notes: The data are presented as means (with standard deviations) for continuous variables and percentages for categorical variables.

Abbreviations: CES-D: Center for Epidemiologic Studies Depression Scale; PASE: Physical Activity Scale for the Elderly; BMI: body mass index; OA: osteoarthritis.

Table 2. Association between baseline use of statins and incident frailty.

	Events/participants at baseline	Incidence rate (per 1,000 persons-year)	Fully-adjusted model[1] (RR, 95%CI)	p-value	Propensity-score model[2] (RR, 95%CI)	p-value
Non-ACEI users	290/3744	12 (10-13)	1 [reference]	-	1 [reference]	-
ACEI users	44/551	12 (9-17)	0.72 (0.53-0.99)	0.04	0.75 (0.54-0.996)	0.046

Notes:

All the data are presented as relative ratios (RRs) with their 95% confidence intervals (CIs).

[1] Fully adjusted model included as covariates: age (as continuous); sex; race (whites vs. others); education (degree vs. others); body mass index (as continuous); yearly income (categorized as $\geq$ or < 50,000$ and missing data); CES-D: Center for Epidemiologic Studies Depression Scale; smoking habits (current and previous vs. others); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index; number of medications used; daily energy intake; presence at the baseline of any frailty item; diastolic and systolic blood pressure; presence of knee osteoarthritis. [2] Propensity score model included as covariate the propensity score divided into quartiles.