Drugs Aging (2016) 33:829–837
DOI 10.1007/s40266-016-0396-8

ORIGINAL RESEARCH ARTICLE

Angiotensin-Converting Enzyme Inhibitors and Parameters of Sarcopenia: Relation to Muscle Mass, Strength and Function: Data from the Berlin Aging Study-II (BASE-II)

Dominik Spira[1] · Jeremy Walston[2] · Nikolaus Buchmann[1] · Jivko Nikolov[1] · Ilja Demuth[1,3] · Elisabeth Steinhagen-Thiessen[1] · Rahel Eckardt[1] · Kristina Norman[1]

Published online: 24 September 2016

Abstract

Background Pharmacological options for the treatment of sarcopenia currently do not exist. However, off-label treatment options of some established drugs have been suggested.

Objectives The aim of this study was to assess differences in various muscle and physical performance parameters in relation to the intake of angiotensin-converting enzyme (ACE) inhibitors in a cohort of community-dwelling older people.

Methods Eight hundred and thirty-eight participants from the Berlin Aging Study-II (BASE-II) were included. Appendicular lean mass was assessed with dual-energy X-ray absorptiometry and related to height and body mass index. Muscle strength was measured by grip strength and related to muscle mass (arm muscle quality) and functional status was assessed via the timed "Up and Go" test.

Results Users of ACE inhibitors had higher lean mass related to height but significantly lower lean mass related to body mass index ($p = 0.001$ for women and $p < 0.0001$ for men). Moreover, they exhibited lower arm muscle quality ($p = 0.032$ for women and $p = 0.031$ for men) and reported difficulties in climbing stairs more often than non-users ($p = 0.014$ for women and $p = 0.004$ for men). After adjustment for confounders, there were no significant differences regarding lean mass, arm muscle quality and the timed "Up and Go" test according to the use of ACE inhibitors.

Conclusions In BASE-II, no positive relationship was found between the intake of ACE inhibitors and lean mass, strength, muscle quality or function. Moreover, remarkable differences between parameters of absolute and relative lean mass in relation to the use of ACE inhibitors became evident. Fat mass proved to be an important confounder and therefore muscle mass cannot be viewed irrespectively of whole body composition.

Key Points

No positive association was found between the intake of angiotensin-converting enzyme (ACE) inhibitors and muscle strength, muscle quality or function.

Striking differences between parameters of absolute and relative lean mass in relation to the use of ACE inhibitors became evident. Users of ACE inhibitors had significantly lower relative muscle mass but higher absolute muscle mass.

Studies investigating the effects of drugs on lean mass should have carefully selected target parameters, taking into account the need to correct for factors contributing to lean mass such as height, weight and body mass index.

✉ Kristina Norman
kristina.norman@charite.de

[1] Charité Research Group on Geriatrics, Charité-Universitätsmedizin Berlin, Reinickendorfer Str. 61, Berlin 13347, Germany

[2] Johns Hopkins University School of Medicine, Baltimore, MD, USA

[3] Institute of Medical and Human Genetics, Charité-Universitätsmedizin Berlin, Berlin, Germany

1 Introduction

Sarcopenia, the age-related loss of muscle mass, muscle strength and muscle function, has been linked to falls, disability, loss of independence, and increased morbidity and mortality [1–3]. Considering that all basic activities of daily life require a certain amount of intact muscle function, it is clear that the search for pharmaceutical agents and ideal treatment strategies to prevent or treat sarcopenia is an important healthcare topic and part of constant efforts in medical research. To date, exercise, e.g. resistance training, nutritional intervention such as adequate protein and energy intake, and correcting vitamin D deficiency are the most appropriate strategies in terms of a risk-benefit balance. However, recently, owing to the beneficial impact of some drugs on muscle tissue, alternative off-label pharmacological options for sarcopenia have been proposed [4]. Angiotensin-converting enzyme (ACE) inhibitors are prescribed mainly for patients with arterial hypertension, chronic heart failure and post-myocardial infarction where they yield considerable therapeutic benefits in reducing mortality and hospitalisation rates [5, 6]. Increased skeletal muscle blood flow mediated by enhanced endothelial function and anti-inflammatory effects via reduced production of proinflammatory cytokine levels have been suggested as possible mechanisms for preserving or improving muscular function [7, 8]. Effects on skeletal muscle have been observed both in cross-sectional analyses as well as in longitudinal studies, but results have been conflicting.

In the Health, Aging and Body Composition (Health ABC) Study, participants using ACE inhibitors had a larger lower extremity muscle mass than those using other antihypertensive drugs. Additionally, the time of exposure to ACE inhibitors tended to be associated with a larger muscle mass [9]. Moreover, in a cohort of the Women's Health and Aging Study, continued users of ACE inhibitors showed a significantly lower decline in muscle strength after 3 years of follow-up compared with other groups [10]. In patients with chronic heart failure, treatment with the ACE inhibitor enalapril led to increased muscle fibre areas and lactate dehydrogenase activity in a small observational study. The authors concluded, however, that the extent to which this may also have been caused by increased physical activity remains unclear [11]. Randomised controlled trials investigating the effect of ACE inhibitors on physical function have to date led to inconsistent results [12–14].

The aim of this cross-sectional analysis in a large sample of community-dwelling older adults was (1) to assess differences in various established muscle mass parameters including the criteria for low lean mass recently defined by the Foundation for the National Institutes of Health Sarcopenia Project [15]; (2) to assess differences in functional parameters between participants with and without ACE inhibitor intake; and (3) to adjust all our analyses concerning lean mass for fat mass, to account for the effect of body composition.

2 Methods

2.1 Participants

All participants gave written informed consent and the Ethics Committee of the Charité-Universitätsmedizin Berlin approved the study (Approval No. EA2/029/09). Eight hundred and thirty-eight community-dwelling participants from the Berlin Aging Study-II (BASE-II) recruited as volunteers between 2009 and 2014 were included in this analysis. The eligibility criteria of BASE-II at the time of recruitment have been described previously in detail [16]. Briefly, participants were community dwelling, comparably healthy and independently living older subjects aged between 60 and 80 years. Exclusion criteria were: (1) reported difficulty in walking one-quarter of a mile without assistance, (2) known Parkinson's disease, stroke or myocardial infarction, (3) previous head, heart or vascular surgery, or (4) known dementia or malignant disease. For this analysis, we also excluded participants using angiotensin receptor blockers to avoid potential confounding due to the similar mechanism of action.

Participants were examined by a study physician on the first study day and were excluded if showing signs of acute illness. No participants with possibly confounding conditions such as fever or oedema were included.

2.2 Angiotensin-Converting Enzyme Inhibitors

All individual types of ACE inhibitors were recorded and the duration of intake of ACE inhibitors was listed in years. Participants were divided into the two groups of non-users of ACE inhibitors and users of ACE inhibitors.

2.3 Anthropometric Measurements

Body weight was measured to the nearest 0.1 kg and height was determined to the nearest 0.1 cm using an electronic weighting and measuring station (seca 764; seca GmbH & Co. KG, Hamburg, Germany). Weight and height were used to calculate body mass index (BMI) (weight [kg]/height $[m]^2$).

2.4 Body Composition

Body composition was assessed with dual-energy X-ray absorptiometry (Hologic® QDR® Discovery™; Hologic, Inc., Bedford, MA, USA). Participants wore light clothes and a trained technician performed the dual-energy X-ray absorptiometry measurement protocol. The system software (APEX version 3.0.1., Hologic Inc. Bedford, MA,USA) provided the mass of lean soft tissue, fat and bone mineral content. Absolute appendicular lean mass (ALM) in kilograms was calculated as the sum of the regional lean mass of the four limbs and the skeletal muscle mass index (SMI) as ALM/height^2 (kg/m^2) was derived [17]. For comparison, the ALM adjusted to BMI (ALM/BMI) was calculated as the sum of the regional lean mass in kilograms divided by BMI in kg/m^2 [18]. Further analyses were performed using established cut-points for sarcopenia defined by sex-specific low SMI and low ALM/BMI [1, 15, 17, 18]. The muscle mass of the lower extremity (LEMM) was calculated by summing the lean mass of right and left leg [9]. For relative leg muscle mass, LEMM in percentage (LEMM%) was calculated as the sum of the lean mass of both legs in kilograms divided by body mass in kilograms $\times$ 100.

2.5 Hand Grip Strength

Maximal isometric hand grip strength was measured in both hands using a Smedley Dynamometer (Scandidact, Odder, Denmark). While performing the test, the participants were standing and the shoulder was adducted and neutrally rotated on the tested side, the elbow was flexed to 90°, and the forearm and wrist were in a neutral position. The participants were then asked to perform a maximal isometric contraction, and the highest value was recorded after performing the test three times on each side. The cut-off values suggested by Fried et al. were used to identify reduced grip strength [19]. Further hand grip strength was corrected for arm lean mass to form an additional parameter reflecting arm muscle quality (AMQ) [20].

2.6 Timed "Up and Go" Test

To assess lower extremity muscle function, we used the timed "Up and Go" test (TUG) [21]. The participants were instructed to stand up from a standard chair, walk a distance of 3 m (marked by a line on the floor), turn and walk back to the chair and sit down again. The time was taken in seconds using a stop watch. Participants unable to complete the test in less than 10 s were considered to have impaired function [21].

2.7 Self-Reported Physical Performance

Participants were asked whether they had difficulties performing physical tasks such as climbing several flights of stairs or performing strenuous activities such as lifting or carrying heavy objects, walking fast or running (severe/moderate/no difficulties).

2.8 Co-Variables

Systolic and diastolic blood pressures were measured with an electronic sphygmomanometer (boso-medicus memory; Jung, Willingen, Germany) after a 5-min rest period in a sitting position on both arms and the mean value between both arms was chosen. Diseases were taken from the medical history recorded by a study physician. Furthermore, a morbidity index was computed based on participant-reported and physician-assessed medical diagnosis of diseases representing most of the Charlson Comorbidity Index [22] categories that have been described previously in detail [23]. The regression analysis was adjusted for arterial hypertension as the main indication for the use of ACE inhibitors and the morbidity index including cardiovascular disease.

2.9 Statistics

Statistical analyses were carried out using the software package IBM Statistics SPSS 21 (IBM, Armonk, NY). Data are given as median and interquartile distribution. A one-sample Kolmogorov–Smirnov test was performed to test variables for Gaussian distribution and Levene's test was performed to test for homogeneity of variances. The bivariate relationship between the duration of intake of ACE inhibitors and muscle parameters was analysed using Spearman's correlation. To compare means between users and non-users of ACE inhibitors, the Student's t test was employed, provided that variables were normally distributed and showed homogeneity of variance. If these requirements were not given, a Mann–Whitney U test was employed to compare those groups. The chi-squared test was used to compare percentages between those groups in relation to categorical variables. Differences between the different types of ACE inhibitors and muscle parameters were assessed by either analysis of variance in the case of normally distributed variables or by the Kruskal–Wallis test in the case of non-parametric variables.

To assess the association between the intake of ACE inhibitors, muscle parameters, strength and function, a regression analysis for significant confounders was performed with the general linear model, allowing adjustment for both continuous and categorical variables. An acceptable level of statistical significance was established a priori at $p < 0.05$.

3 Results

3.1 Characteristics of the Study Population

Eight hundred and thirty-eight participants were included in this analysis. The median age was 68 years and ranged from 60 to 82 years. Table 1 shows the characteristics of the study population according to the use of ACE inhibitors and stratified by sex. Overall prevalence of self-reported arterial hypertension was 38.1 % and the prevalence of self-reported congestive heart failure as well as that of coronary artery disease was 2.7 %. Of all 838 participants, 169 (20.2 %) were using ACE inhibitors. The most frequently taken ACE inhibitor was ramipril, which accounted for 65.7 % of prescribed ACE inhibitors, followed by enalapril (17.8 %), lisinopril (8.3 %), quinapril (2.4 %), captopril (1.8 %), fosinopril (1.8 %) and spirapril (1.2 %). At the other end, perindopril and benazepril were taken by only one participant each (0.6 %).

The duration of ACE inhibitor intake ranged between 1 and 30 years with a median intake of 3 years. As can be seen in Table 1, users of ACE inhibitors significantly more often had a history of arterial hypertension, whereas there were no significant differences regarding blood pressure, congestive heart failure and coronary artery disease except for coronary artery disease in women. Although morbidity was overall low, users of ACE inhibitors exhibited a higher morbidity as measured by the morbidity index. Users of ACE inhibitors also had a significantly higher BMI and higher total body fat percentage and significantly lower lean/fat mass ratio. Comparing the groups of users of ACE inhibitors vs. non-users of ACE inhibitors, we found that significantly more men (30.4 %) than women (22.1 %) were using ACE inhibitors ($p = 0.041$). Therefore, all analyses regarding parameters of muscle mass and strength were stratified according to sex.

3.2 Differences in Absolute Muscle Mass and Skeletal Muscle Mass Index

As shown in Table 1, both ALM and SMI were significantly higher in men using ACE inhibitors. Although statistical significance was not reached, women using ACE inhibitors tended to have higher ALM and SMI than those not using ACE inhibitors. LEMM showed no significant difference between users and non-users. Significantly fewer male participants with the intake of ACE inhibitors showed a SMI below the sex-specific cut-off for sarcopenia (Table 1).

3.3 Differences in Relative Muscle Mass and Appendicular Lean Muscle Mass/Body Mass Index

When analysing the relative amount of leg lean mass (LEMM%) and lean mass adjusted for BMI (ALM/BMI), we obtained contrasting results as LEMM% and ALM/BMI were significantly lower in both male and female users of ACE inhibitors (Table 1).

3.4 Muscle Strength, Muscle Quality and Muscle Function

Whereas no overall differences were found in hand grip strength between users and non-users of ACE inhibitors, arm muscle quality was significantly lower in male and female ACE inhibitor users (Table 1). Moreover, significantly more female participants taking ACE inhibitors showed grip strength below established cut-off values. The TUG time as a functional parameter did not differ significantly in participants with an intake of ACE inhibitors.

3.5 Self-Reported Physical Performance

Participants taking ACE inhibitors reported severe difficulties in climbing several flights of stairs and performing strenuous activities (only women) significantly more often than non-ACE inhibitor users (Table 1).

After adjusting for age, total fat mass, indication of drug use (arterial hypertension) and morbidity (morbidity index), we found no significant effect of ACE inhibitor use on SMI, ALM/BMI, AMQ and TUG time (Table 2). As anticipated, age showed a significant influence on ALM/BMI and TUG time in both sexes and on grip strength corrected by arm muscle mass (AMQ) in men only and total fat mass showed a significant influence on SMI and ALM/BMI as well. Moreover, TUG time was influenced by total fat mass and comorbidity in women (Table 2).

There was no correlation between the duration of intake of ACE inhibitors and LEMM, LEMM%, SMI, ALM/BMI, grip strength, arm muscle quality and TUG time. Likewise, no differences between those parameters were observed with regard to different types of ACE inhibitors. These results remained stable after ruling out those types with the lowest group size, e.g. perindopril.

4 Discussion

Previous studies have suggested a positive impact of ACE inhibitor use on skeletal muscle. In this study, we analysed the association between the use of ACE inhibitors

Table 1 Differences in parameters of body composition, hand grip strength and arm muscle quality according to the use of ACE inhibitors

Sex/parameter	No use of ACE inhibitors	Use of ACE inhibitors	*p*-value
Women			
n	412	91	
Age (years)	67.0 (65.0–69.0)	69.0 (65.0–71.0)	0.003
BMI (kg/m^2)	25.0 (22.9–28.1)	27.8 (25.5–31.2)	<0.0001
ALM (kg)	15.85 (14.53–17.47)	16.26 (14.47–17.82)	0.389
Lean/fat mass ratio (g/g)	1.5 (1.3–1.8)	1.4 (1.1–1.6)	<0.0001
Total body fat percentage	39.4 (34.8–43.1)	42.5 (38.8–47.4)	<0.0001
LEMM (kg)	12.2 (11.0–13.4)	12.6 (11.2–13.7)	0.214
LEMM%	18.6 (17.0–19.9)	17.0 (16.1–18.1)	<0.0001
SMI (kg/m^2)	6.0 (5.5–6.5)	6.2 (5.6–6.7)	0.119
ALM/BMI	0.624 (0.565–0.691)	0.570 (0.520–0.649)	0.001
Hand grip strength (kgF)	26.5 (23.5–29.5)	25.5 (22.0–30.0)	0.096
Arm muscle quality (kgF/kg)	12.3 (10.8–14.1)	11.7 (9.9–13.5)	0.032
TUG (s)	7.1 (6.2–8.2)	7.5 (6.5–8.5)	0.054
<Sex-specific SMI cut-off[a]	87 (21.1)	18 (19.8)	0.451
<Sex-specific ALM/BMI cut-off[b]	32 (7.8)	20 (22.0)	<0.0001
<Sex-specific hand grip strength cut-off[c]	45 (10.9)	22 (24.2)	0.001
>TUG cut-off[d]	25 (6.1)	10 (11.1)	0.078
Performing strenuous activities	58 (14.6)	12 (13.5)	0.048
Climbing several flights of stairs	24 (6.1)	12 (13.5)	0.014
Systolic blood pressure (mmHg)	142.0 (128.1–156.5)	148.0 (133.8–164.3)	0.103
Diastolic blood pressure (mmHg)	80.5 (14.5–88.4)	84.0 (77.6–93.5)	0.332
Comorbidities			
Congestive heart failure	8 (2.0)	4 (4.4)	0.153
Coronary artery disease	3 (0.7)	7 (8.0)	<0.0001
Arterial hypertension	98 (24.0)	86 (95.6)	<0.0001
Morbidity index	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.006
Men			
n	257	78	
Age (years)	69.0 (66.0–71.0)	69.0 (67.0–71.0)	0.690
BMI (kg/m^2)	25.8 (24.2–28.0)	28.0 (25.9–30.8)	<0.0001
ALM (kg)	23.48 (21.77–25.47)	24.65 (22.70–25.67)	0.022
Lean/fat mass ratio (g/g)	2.5 (2.1–2.9)	2.1 (1.9–2.6)	0.001
Total body fat percentage	28.9 (25.8–32.0)	32.0 (27.8–34.5)	<0.0001
LEMM (kg)	17.3 (16.1–18.7)	17.9 (16.6–18.8)	0.122
LEMM%	22.0 (20.7–23.5)	20.3 (19.6–22.5)	<0.0001
SMI (kg/m^2)	7.6 (7.2–8.1)	7.8 (7.4–8.4)	0.007
ALM/BMI	0.908 (0.831–0.983)	0.852 (0.797–0.929)	<0.0001
Hand grip strength (kgF)	42.0 (37.5–46.0)	42.5 (37.5–46.0)	0.740
Arm muscle quality (kgF/kg)	12.2 (10.8–13.8)	11.6 (10.2–13.0)	0.031
TUG (s)	7.4 (6.3–8.4)	7.8 (6.8–9.0)	0.072
<Sex-specific SMI cut-off[a]	78 (30.4)	11 (14.1)	0.003
<Sex-specific ALM/BMI cut-off[b]	35 (13.6)	17 (21.8)	0.061
<Sex-specific hand grip strength cut-off[c]	37 (14.4)	8 (10.3)	0.230
>TUG cut-off[d]	22 (8.7)	11 (14.5)	0.110
Performing strenuous activities	29 (12.7)	12 (17.6)	0.115
Climbing several flights of stairs	7 (3.1)	5 (7.4)	0.004
Systolic blood pressure (mmHg)	145.5 (133.5–158.0)	143.5 (128.5–155.5)	0.115

Table 1 continued

Sex/parameter	No use of ACE inhibitors	Use of ACE inhibitors	*p*-value
Diastolic blood pressure (mmHg)	85.0 (78.0–90.5)	80.5 (75.3–89.8)	0.216
Comorbidities			
Congestive heart failure	5 (2.0)	5 (6.5)	0.057
Coronary artery disease	7 (2.8)	5 (6.4)	0.128
Arterial hypertension	60 (23.6)	72 (92.3)	<0.0001
Morbidity index	1.0 (0.0–1.0)	1.0 (1.0–2.0)	0.004

Variables are presented as median and interquartile range or *n* (%)

ACE angiotensin-converting enzyme, *ALM* appendicular lean mass, *ALM/BMI* appendicular skeletal muscle mass/body mass index, *BMI* body mass index, *LEMM* lower extremity muscle mass, *LEMM%* lower extremity muscle mass/whole body mass × 100, *SMI* skeletal muscle mass index, *TUG* Timed "Up and Go" test

[a] According to Cruz-Jentoft et al. [1], Baumgartner et al. [17]

[b] According to McLean et al. [15], Cawthon et al. [18]

[c] According to Cruz-Jentoft et al. [1], Fried et al. [19]

[d] According to Cruz-Jentoft et al. [1], Podsiadlo and Richardson [21]

Table 2 Regression analysis for differences in relative and absolute muscle mass, grip strength, AMQ and TUG time according to the use of ACE inhibitors

Determinants	Dependent variables							
	SMI[a]		ALM/BMI[b]		Arm muscle quality[c]		TUG[d]	
	β	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value
Women								
Use of ACE inhibitors	0.049	0.627	0.008	0.482	0.052	0.887	0.132	0.572
Age (years)	−0.016	0.084	−0.003	0.012	0.017	0.619	0.088	<0.0001
Total fat mass (kg)	0.044	<0.0001	−0.061	<0.0001	−0.014	0.352	0.046	<0.0001
Hypertension[e]	−0.047	0.627	−0.015	0.111	−0.577	0.059	0.051	0.793
Morbidity index	−0.017	0.525	−0.001	0.845	−0.085	0.406	0.215	<0.0001
Men								
Use of ACE inhibitors	−0.067	0.617	0.002	0.890	0.013	0.974	−0.301	0.312
Age (years)	−0.022	0.055	−0.003	0.022	−0.100	0.003	0.136	<0.0001
Total fat mass (kg)	0.035	<0.0001	−0.084	<0.0001	−0.043	0.020	0.015	0.304
Hypertension[e]	0.112	0.326	−0.004	0.746	−0.510	0.119	0.082	0.747
Morbidity index	−0.064	0.049	−0.009	0.029	−0.044	0.638	0.067	0.351

ACE angiotensin-converting enzyme, *ALM* appendicular lean mass, *ALM/BMI* appendicular lean muscle mass/body mass index, *AMQ* arm muscle quality, *BMI* body mass index, *SMI* skeletal muscle mass index, *TUG* Timed "Up and Go" test

[a] Women: R^2 0.219 (adjusted 0.210); men R^2 0.138 (adjusted 0.123)

[b] Women and men: R^2 0.334 (adjusted 0.323)

[c] Women: R^2 0.023 (adjusted 0.012); men R^2 0.072 (adjusted 0.056)

[d] Women: R^2 0.129 (adjusted 0.112); men R^2 0.104 (adjusted 0.089)

[e] Compared with condition not present

and several functional and muscle mass-related parameters, taking whole body composition as a potential confounder into account. The main finding in our study was that whereas absolute muscle mass (SMI) was indeed higher in male participants using ACE inhibitors, ACE inhibitor treatment was associated with significantly lower, relative BMI-adjusted muscle mass (ALM/BMI) in both men and women. Grip strength did not differ significantly between users and non-users of ACE inhibitors, whereas arm muscle quality (grip strength corrected for arm muscle mass) was significantly lower in those taking ACE inhibitors. After adjustment for the most notable potential confounders such as age, fat mass, indication of drug use and other morbidities, no

significant differences in SMI, ALM/BMI, arm muscle quality and TUG time remained.

In our study, users of ACE inhibitors had a significantly higher BMI and greater fat mass, accounting for their lower relative muscle mass and unfavourable ratio of muscle to fat. Relative muscle mass has previously been shown to be a better predictor of physical performance and mobility than absolute muscle mass [24–26] because higher fat mass and fat-to-lean mass ratio are associated with impaired physical performance and functional limitation [27, 28].

Prior studies have all used different methodology, which hampers comparisons. As mentioned in Sect. 1, the Health ABC study participants using ACE inhibitors had a larger LEMM than those using other antihypertensive drugs but not than those with no drug intake in a cross-sectional analysis [9]. In our study, we found significantly lower values in the users of ACE inhibitors even after correcting LEMM for weight.

Results from longitudinal studies on changes in muscle mass, strength or function after treatment with ACE inhibitors have hitherto been conflicting. Enalapril seems to be able to ameliorate weight loss associated with cachexia and linked to impaired survival as was shown retrospectively in a study investigating 1929 patients with chronic heart failure from the Studies of Left Ventricular Dysfunction (SOLVD) [29]. However, the extent to which this is attributable to preservation of muscle tissue in particular and applicable to sarcopenic patients without heart failure is unclear. ACE inhibitor intake was associated with weaker grip strength at baseline in the Women's Health Initiative Clinical Trial (WHICT), but showed no significant effect on the mean annual change over time [30]. Similarly, in the Hertfordshire Cohort Study (HCS), use of ACE inhibitors was not associated with differences in grip strength at baseline nor after follow-up [31]. In the Women's Health and Aging Study (WHAS), however, no differences between ACE inhibitor users and non-users were seen at baseline, but the mean 3-year decline in knee extension strength and walking speed was significantly lower in those using ACE inhibitors continuously compared with those taking other antihypertensive drugs and those with no drug use at all [10]. However, the participants in the WHAS were frail and disabled, which may have led to greater effect sizes than in comparably healthier and younger cohorts as in the WHICT and HCS. Finally, in randomised controlled trials in older patients with (1) a high cardiovascular risk profile or (2) functional impairment without heart failure, ACE inhibitor treatment had no impact on physical performance or muscle strength over a period of 20–24 weeks [12, 14]. In a meta-analysis of three randomised controlled trials, although with a limited number of participants, grip strength was not significantly different between users of ACE inhibitors and those taking placebo or other antihypertensives [32].

Although the duration of ACE inhibitor intake would likely influence any muscle-related outcome, we found no difference when analysing the time of exposure to ACE inhibitors. This finding must, however, be interpreted with caution because it has been shown that a gradual reactivation of the conversion of angiotensin I to angiotensin II occurs under long-term therapy with lisinopril [33]. It is therefore tempting to speculate that possible benefits of ACE inhibitor therapy in skeletal muscle decrease over time as negative effects of angiotensin II on muscle tissue, which have been demonstrated in animal models, become more prominent [34–36].

The cross-sectional study design of our study obviously limits interpretation of causality. Furthermore, because ACE inhibitor treatment was prescribed on medical indication, we were not able to compare ACE inhibitor users in our study with a control group of healthy ACE inhibitor users. Likewise, it was not possible to compare subgroups of participants taking ACE inhibitors but no other antihypertensive drugs with those who were not taking ACE inhibitors but were taking other antihypertensive agents (e.g. β-blockers) because the small sample sizes involved were not sufficient to allow useful statistical analysis. The sample size of participants with coronary heart disease and heart failure was, moreover, too small for sub-group analyses. We might postulate that ACE inhibitors would have better effects on muscle tissue in more severe cardiovascular diseases or in adults aged over 75 years, where loss of weight and strength is more pronounced.

5 Conclusions

In summary, we found no positive relationship between the intake of ACE inhibitors and skeletal muscle mass, strength, muscle quality or function. Taking body composition into account, we even found lower relative muscle mass and strength in ACE inhibitor users. This finding may in part be owing to the chronic medical conditions that underlie the need for ACE inhibitor use. Given these results, previous studies demonstrating improvement in muscle mass with ACE inhibitor use should be interpreted with caution because muscle mass was not adjusted for body composition in most studies. As a result of the above-mentioned limitations, and the relative lack of clinical trials that extend over several years in older adults, we cannot however preclude a positive effect of ACE inhibitor treatment on muscle in the very old or in severe disease states. Future studies, especially interventional trials in which muscle mass is determined as an outcome parameter,

should take into account the contrasting results concerning parameters of absolute and relative muscle mass.

Compliance with Ethical Standards

Funding This study was supported by the German Federal Ministry of Education and Research under Grant No. 16SV5536 K. Responsibility for the contents of this publication lies with the authors.

Conflict of interest Dominik Spira, Jeremy Walston, Nikolaus Buchmann, Jivko Nikolov, Ilja Demuth, Elisabeth Steinhagen-Thiessen, Rahel Eckardt and Kristina Norman declare they have no conflicts of interest with the content of this study.

Ethical Approval This study was approved by the Ethics Committee of the Charité-Universitätsmedizin Berlin (Approval No. EA2/029/09) and registered with the clinical trial registry Deutsches Register Klinischer Studien (DRKS00009277).

References

1. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European Consensus on Definition and Diagnosis. Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412–23.
2. Janssen HC, Emmelot-Vonk MH, Verhaar HJ, et al. Determinants of vitamin D status in healthy men and women aged 40–80 years. Maturitas. 2013;74:79–83.
3. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International Working Group on Sarcopenia. J Am Med Dir Assoc. 2011;12(4):249–56.
4. Rolland Y, Onder G, Morley JE, et al. Current and future pharmacologic treatment of sarcopenia. Clin Geriatr Med. 2011;27(3):423–47.
5. Garg R, Yusuf S, Bussmann WD. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA. 1995;273(18):1450–6.
6. Parmley WW. Evolution of angiotensin-converting enzyme inhibition in hypertension, heart failure, and vascular protection. Am J Med. 1998;105(1A):27S–31S.
7. Onder G, Vedova CD, Pahor M. Effects of ACE inhibitors on skeletal muscle. Curr Pharm Des. 2006;12(16):2057–64.
8. Sumukadas D, Witham MD, Struthers AD, et al. ACE inhibitors as a therapy for sarcopenia: evidence and possible mechanisms. J Nutr Health Aging. 2008;12(7):480–5.
9. Di Bari M, van de Poll-Franse LV, Onder G, et al. Antihypertensive medications and differences in muscle mass in older persons: the Health, Aging and Body Composition Study. J Am Geriatr Soc. 2004;52(6):961–6.
10. Onder G, Penninx BW, Balkrishnan R, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet. 2002;359(9310):926–30.
11. Schaufelberger M, Andersson G, Eriksson BO, et al. Skeletal muscle changes in patients with chronic heart failure before and after treatment with enalapril. Eur Heart J. 1996;17(11):1678–85.
12. Cesari M, Pedone C, Incalci RA, et al. ACE-inhibition and physical function: results from the Trial of Angiotensin-Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (TRAIN) study. J Am Med Dir Assoc. 2010;11(1):26–32.
13. Sumukadas D, Witham MD, Struthers AD, et al. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. Can Med Assoc J. 2007;177(8):867–74.
14. Sumukadas D, Band M, Miller S, et al. Do ACE inhibitors improve the response to exercise training in functionally impaired older adults? A randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2014;69(6):736–43.
15. McLean RR, Shardell MD, Alley DE, et al. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project. J Gerontol A Biol Sci Med Sci. 2014;69(5):576–83.
16. Bertram L, Böckenhoff A, Demuth I, et al. Cohort profile: the Berlin Aging Study II (BASE-II). Int J Epidemiol. 2014;43(3):703–12.
17. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755–63.
18. Cawthon PM, Peters KW, Shardell MD, et al. Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. J Gerontol A Biol Sci Med Sci. 2014;69(5):567–75.
19. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–57.
20. Park SW, Goodpaster BH, Strotmeyer ES, et al. Decreased muscle strength and quality in older adults with type 2 diabetes: the Health, Aging, and Body Composition Study. Diabetes. 2006;55(6):1813–8.
21. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142–8.
22. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
23. Gerstorf D, Hulur G, Drewelies J, et al. Secular changes in late-life cognition and well-being: towards a long bright future with a short brisk ending? Psychol Aging. 2015;30(2):301–10.
24. Estrada M, Kleppinger A, Judge JO, et al. Functional impact of relative versus absolute sarcopenia in healthy older women. J Am Geriatr Soc. 2007;55(11):1712–9.
25. Bijlsma AY, Meskers CGM, van den Eshof N, et al. Diagnostic criteria for sarcopenia and physical performance. Age. 2014;36(1):275–85.
26. Spira D, Buchmann N, Nikolov J, et al. Association of low lean mass with frailty and physical performance: a comparison between two operational definitions of sarcopenia. Data from the Berlin Aging Study II (BASE-II). J Gerontol A Biol Sci Med Sci. 2015;70(6):779–84.
27. Sternfeld B, Ngo L, Satariano WA, et al. Associations of body composition with physical performance and self-reported functional limitation in elderly men and women. Am J Epidemiol. 2002;156(2):110–21.
28. Dufour AB, Hannan MT, Murabito JM, et al. Sarcopenia definitions considering body size and fat mass are associated with mobility limitations: the Framingham Study. J Gerontol A Biol Sci Med Sci. 2013;68(2):168–74.
29. Anker SD, Negassa A, Coats AJ, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting enzyme inhibitors: an observational study. Lancet. 2003;361(9363):1077–83.
30. Gray SL, Aragaki AK, LaMonte MJ, et al. Statins, angiotensin-converting enzyme inhibitors, and physical performance in older women. J Am Geriatr Soc. 2012;60(12):2206–14.

31. Witham MD, Syddall HE, Dennison E, et al. ACE inhibitors, statins and thiazides: no association with change in grip strength among community dwelling older men and women from the Hertfordshire Cohort Study. Age Ageing. 2014;43(5):661–6.
32. Zhou Ls Xu, Lj Wang XQ, et al. Effect of angiotensin-converting enzyme inhibitors on physical function in elderly subjects: a systematic review and meta-analysis. Drugs Aging. 2015;32(9): 727–35.
33. Farquharson CAJ, Struthers AD. Gradual reactivation over time of vascular tissue angiotensin I to angiotensin II conversion during chronic lisinopril therapy in chronic heart failure. J Am Coll Cardiol. 2002;39(5):767–75.
34. Cichello SA, Weisinger RS, Schuijers J, et al. 1-Sarcosine-angiotensin II infusion effects on food intake, weight loss, energy expenditure, and skeletal muscle UCP3 gene expression in a rat model. J Cachexia Sarcopenia Muscle. 2014;5(3):239–46.
35. Brink M, Price SR, Chrast J, et al. Angiotensin II induces skeletal muscle wasting through enhanced protein degradation and down-regulates autocrine insulin-like growth factor I. Endocrinology. 2001;142(4):1489–96.
36. Sumukadas D, Struthers AD, McMurdo MET. Sarcopenia: a potential target for angiotensin-converting enzyme inhibition? Gerontology. 2006;52(4):237–42.