**Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study**


**Summary**

**Background** Angiotensin-converting enzyme (ACE) inhibitors prevent decline in physical function in patients with congestive heart failure (CHF). We aimed to see whether ACE inhibitors also prevent reduction in physical performance and in muscle strength in older women who do not have CHF.

**Methods** We assessed 3-year rates of decline in both knee extensor muscle strength and walking speed in 641 women with hypertension who had participated in the Women’s Health and Aging Study. Women were stratified into four groups according to type and duration of antihypertensive drug treatment. 61 had used ACE inhibitors continuously, 133 intermittently, 146 never, and 301 had used other hypertensive drugs either continuously or intermittently.

**Findings** Participants who had taken ACE inhibitors continuously had a lower mean 3-year decline in muscle strength of –1·0 kg (SE 1·1) compared with –3·7 (0·5) kg in continuous/intermittent users of other antihypertensive drugs (p=0·016) and with –3·9 kg in those who had never used antihypertensives (p=0·026). Muscle strength fell by 3·0 kg in 3 years in both continuous and intermittent users of ACE inhibitors (p=0·096). Mean 3-year decline in walking speed in continuous ACE inhibitor users was –1·7 cm/s compared with –13·6 cm/s in intermittent users of ACE inhibitors (p=0·015), –15·7 cm/s in continuous/intermittent users of other antihypertensive drugs (p=0·002), and –17·9 cm/s in never users of antihypertensive drugs (p=0·001).

**Interpretation** ACE inhibitor treatment may halt or slow decline in muscle strength in elderly women with hypertension and without CHF.

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**Introduction**

Age-related physical disability and loss of physical function are becoming priorities in public health.1 Many disabilities are directly caused by or associated with acute events, such as stroke and hip fracture; or chronic conditions, such as congestive heart failure, coronary heart disease, diabetes, and osteoarthritis.2 Progressive decline in physical function and physical disability in elderly people, however, does not always relate to disease. Although diverse mechanisms of action might account for physical disability in this population, gradual loss of muscle mass and muscle strength have frequently been associated with onset and progression of these disabilities.3

There is little evidence about the efficacy of pharmacological interventions that prevent decline in physical function in elderly people. Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity, mortality, number of admissions, and decline in physical function and exercise capacity in patients with congestive heart failure (CHF).4 These therapeutic effects have been mainly attributed to inhibition of the renin-angiotensin system, which prevents ventricular remodelling, modulates myocardial oxygen consumption, and improves peripheral vasodilatation.5

Improvements in physical function from ACE inhibitors could also be mediated by direct effects of these agents on skeletal muscle.6 In particular, activation of the renin-angiotensin system has been associated with mechanical, metabolic, and biochemical changes in skeletal muscle.7

We postulate that ACE inhibitors can prevent physical decline in elderly people who do not have CHF, and aimed to assess whether treatment with ACE inhibitors is associated with less decline in muscle strength and decline in walking speed in older women with hypertension when compared with those on other hypertensives or no drugs.

**Methods**

**Patients**

We selected 755 participants from the Women’s Health and Aging Study (WHAS) who had a history of self-reported hypertension or who presented with a systolic blood pressure of 140 mm Hg or greater, or a diastolic blood pressure of 90 mm Hg or greater. 46 (6%) patients had no follow-up data, and 68 (9%) with CHF were excluded from the analysis. WHAS is a 5-year longitudinal observational study done by the National Institute on Aging and Johns Hopkins University. In this study, the causes and course of disability were assessed in women from Baltimore, Maryland, USA who were moderately to severely disabled. The 1002 women enrolled in this observational study had difficulty in doing at least two of four functional domains (mobility and exercise tolerance, arm function, basic self-care, and higher functioning tasks of independent living), and scored higher than 17 on the mini mental state examination. These women account for about a third of...
older women who are disabled living in Maryland. Patients were examined at home at baseline and every 6 months for 3 years, and then contacted by telephone yearly for 2 further years to obtain information on disability, morbidity, and mortality. Thus, data on muscle strength and walking speed were obtained for 3 years of follow-up. The study was approved by the ethical committee of Johns Hopkins University and all participants provided written informed consent at enrolment. The study design and methods for recruitment and screening of patients have been reported previously.

Measurement of variables
We assessed maximum isometric strength of the knee extensor muscles at baseline, after 1 year, and then every 6 months for the next 2 years of the study using a handheld dynamometer (Nicholas manual muscle tester; Model BK-7745, Fred Sammons Inc, Burr Ridge, IL, USA). Participants were seated in a chair and asked to extend the knee, pushing as hard as they could against the dynamometer, which was positioned a few inches above the ankle. Strength was measured as the peak force that the examiner had to apply to break the isometric contraction. Two trials were done on each leg. The best result of the stronger leg was used in the analyses. This measure has been inversely related to decline in physical function, disability, and mortality, and is highly reliable when done by well trained examiners.

We measured walking speed by having the participant walk at her usual pace over a 4-m course. The faster of two walks was used. This measure is predictive of onset of incident disability, mortality, and nursing home and hospital admission in older participants, and has shown a high test-retest reliability.

Baseline presence of CHF, angina, myocardial infarction, stroke, and diabetes were based on algorithms that combined information including self reports, reports from the primary care physician, present and past medical treatments, review of medical records, and medical signs and symptoms. Participants were judged to be hypertensive on the basis of self-report, or if they had a baseline systolic blood pressure of 140 mm Hg or greater, or a diastolic blood pressure of 90 mm Hg or greater. Cardiovascular events (myocardial infarction, stroke, CHF) were self-reported twice yearly.

We assessed baseline physical activity by summarising responses to several common activities in older women: number of blocks walked (0=0, 1–5=1, >6=2) and the number of flights of stairs climbed (0=0, 2–21=1, >22=2) in the week before the interview; and whether participants had done heavy household chores (no=0, yes=1), heavy outdoor work chores (no=0, yes=1), regular exercise (no=0, yes=1), danced (no=0, yes=1), or bowled (no=0, yes=1) in the 2 weeks before the interview. We then combined these categories to give a total (range 0–9), and created three categories in which 0 was very physically inactive, 1–3 were slightly physically active, and 4 or more were moderately physically active. This index has previously been used in this sample and showed a direct association with muscle strength.

Antihypertensive drugs
Information on use of drugs was obtained regularly throughout the study. Participants were asked to display all current and non-prescription drugs taken in the past 2 weeks. The interviewer transcribed the name and strength of the drug from the container label. If the label was not seen, the interviewer asked the participant the name of the drug. This method of drug ascertainment is similar to that used in other epidemiological studies and is valid and reliable. Analytical variables were created for use of ACE inhibitors, β-blockers, calcium-channel blockers, thiazides, and central and peripheral α-blockers.

Statistical analysis
Continuous users included patients who had reported use of ACE inhibitors at each twice yearly follow-up visit in which they participated and patients with missing data for drug use at one or more follow-up visits who had reported use of ACE inhibitors at all other visits. Intermittent users included those who discontinued ACE inhibitor drugs during the study, or those who started taking ACE inhibitors at any follow-up visit. Continuous/intermittent users of other drugs were defined as those who reported use of β-blockers, calcium-channel blockers, thiazides, or α-blockers, but not of ACE inhibitors, in one or more follow-up visit.

We also compared the effect of any use of ACE inhibitors (n=194), with no use of ACE inhibitors (n=447) over the 3 years of the study. Furthermore, among continued ACE inhibitor users we investigated a possible dose-effect. For analysis of dose effect, we calculated the baseline median daily dose for each ACE inhibitor (fosinopril=10 mg [n=1], captopril=50 mg [IQR 50–75], lisinopril=10 mg [10–20], enalapril=10 mg [5–10], ramipril=5·0 mg [2·5–7·5], benazepril=10·0 mg [10–62·5], quinapril=10 mg [10–30]). At each follow-up, a variable was calculated on the basis of use of a dose of ACE inhibitors equal to or below median dose, or above median dose. Continuous users of ACE inhibitors were then divided into those with dose above the median (high dose; n=12) and others (low dose or change of dose; 48). Dose information was not available for one participant in the continued ACE inhibitor group.

We compared baseline characteristics of these four groups with ANOVA for normally distributed variables, non-parametric Kruskal-Wallis tests for skewed variables, and χ² analyses for dichotomous variables. To assess differences in 3-year change in muscle strength and walking speed across the groups, we used the mixed model analysis of covariance (SAS proc mixed version 6.12). For these analyses we used a random intercept and a random slope in a growth curve model. The advantage of our approach is that it used all available data and adjusted results on the basis of correlations between outcomes and predictor variables. We were thus able to make unbiased estimates in the presence of missing data.

We obtained adjusted means of the outcome variables for the different time points and treatments. Analyses were adjusted for age, race, body-mass index, baseline systolic blood pressure, and prevalence of diabetes, ischaemic heart disease, and stroke.

To determine whether change in muscle strength and walking speed across the four groups could be accounted for by a difference in the number of cardiovascular events, we did further mixed model analyses of covariance in which frequency of myocardial infarction, stroke, and CHF were added.

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

Results
The women in this study had a mean age of 78·9 years (SD 8·0). A tenth of patients were continuous users of...
ACE inhibitors, a fifth used ACE inhibitors intermittently, almost half were continuous/intermittent users of other antihypertensive drugs, and almost a quarter had never used antihypertensive drugs. Continuous users of ACE inhibitors had significantly higher baseline comorbidity than those who had never used antihypertensive drugs (table 1), and had lower baseline systolic and diastolic blood pressure than those who had intermittently used ACE inhibitors (table 1). No significant differences were recorded across the four groups for baseline knee extensor muscle strength and walking speed (table 1).

Ten (16%) of 61 continuous users of ACE inhibitors died, and four (7%) were lost to follow-up, compared with 24 (18%) and 11 (8%) of 133 intermittent users, 51 (17%) and 25 (8%) of 301 continuous/intermittent users of other antihypertensive drugs, and 36 (25%) and 14 (10%) of 146 never users, respectively. The proportion of women who died and were lost to follow-up did not differ between groups (p=0·238 and p=0·910, respectively).

Over the 3 years of the study, overall mean knee extensor muscle strength fell from 12·9 to 10·2 kg, and overall mean walking speed declined from 61·0 to 47·4 cm/s.

Mean 3-year decline in muscle strength in continuous users of ACE inhibitors was significantly lower than that of either continuous/intermittent users of other antihypertensive drugs or never-users of antihypertensive drugs, and did not differ from that of intermittent users of ACE inhibitors (table 2; figure 1). For both walking speed and muscle strength, unadjusted and adjusted analyses yielded very similar results. Therefore, only adjusted analyses are presented.

In subgroup analysis, the 194 (30%) patients who had ever used ACE inhibitors had a significantly lower 3-year decline in knee extensor muscle strength (–2·2 kg vs –3·6 kg; p=0·048) and walking speed (–10·0 cm/s vs –16·4 cm/s; p=0·019) than the 447 (70%) who had never used ACE inhibitors over the 3 years.

Among continuous users of ACE inhibitors, knee extensor muscle strength over the 3 years was weakened by 1·2 kg (SE 1·6) in the low-dose/change-dose group and strengthened by 1·1 kg (SE 3·1) in the high-dose group (p=0·439). Similarly, walking speed slowed by 4·9 cm/s (7·0) in the low-dose/change-dose group and improved by 6·0 cm/s (14·1) in the high dose group (p=0·335).

Decline in walking speed, but not in muscle strength, was predicted by the number of new cardiovascular events (stroke β=−1·5; p<0·001; myocardial infarction −3·8, p=0·045; CHF −4·5, p=0·034). No significant difference in the number of cardiovascular events between continuous users of ACE inhibitors users and the other three groups (stroke 16·4% vs 15·3%, p=0·829; myocardial infarction 11·4% vs 9·8%, p=0·803; CHF 4·9% vs 6·4%, p=0·654). After adjustment for the number of cardiovascular events during follow-up, the results were unchanged, and continuous users of ACE inhibitors showed a significantly lower 3-year decline in muscle strength and walking speed than continuous/intermittent users of other antihypertensive drugs and with never-users of antihypertensive drugs.

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### Table 1: Baseline characteristics of the study population according to antihypertensive drug use

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Continuous users of ACE inhibitors (n=61)</th>
<th>Intermittent users of ACE inhibitors (n=133)</th>
<th>Continuous/intermittent users of other drugs (n=301)</th>
<th>Never drug users (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean [SD], years)</td>
<td>78·3 (8·2)</td>
<td>77·2 (8·3)</td>
<td>78·8 (7·7)</td>
<td>80·3 (7·9)</td>
</tr>
<tr>
<td>Black race</td>
<td>19 (31%)</td>
<td>59 (44%)</td>
<td>96 (32%)</td>
<td>35 (24%)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>&lt;8</td>
<td>28 (46%)</td>
<td>65 (49%)</td>
<td>130 (43%)</td>
</tr>
<tr>
<td></td>
<td>9–11</td>
<td>13 (21%)</td>
<td>30 (23%)</td>
<td>66 (22%)</td>
</tr>
<tr>
<td></td>
<td>&gt;12</td>
<td>20 (33%)</td>
<td>38 (29%)</td>
<td>104 (35%)</td>
</tr>
<tr>
<td>Income $US</td>
<td>&lt;6000</td>
<td>10 (17%)</td>
<td>31 (23%)</td>
<td>59 (20%)</td>
</tr>
<tr>
<td></td>
<td>6000–9999</td>
<td>25 (41%)</td>
<td>46 (35%)</td>
<td>94 (31%)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 000</td>
<td>26 (43%)</td>
<td>56 (42%)</td>
<td>148 (49%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>20 (33%)</td>
<td>45 (34%)</td>
<td>101 (34%)</td>
<td>69 (47%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (12%)</td>
<td>11 (8%)</td>
<td>25 (18%)†</td>
<td>4 (3%)†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (21%)</td>
<td>42 (32%)</td>
<td>39 (13%)</td>
<td>15 (10%)†</td>
</tr>
<tr>
<td>Systolic blood pressure (mean [SD], mm Hg)</td>
<td>143·9 (28·6)</td>
<td>154·7 (23·3)§</td>
<td>144·8 (22·5)</td>
<td>150·0 (17·4)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean [SD], mm Hg)</td>
<td>66·8 (13·0)</td>
<td>71·8 (15·6)‡</td>
<td>67·6 (15·2)‡</td>
<td>70·7 (14·4)‡</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>&lt;18·5</td>
<td>1 (2%)</td>
<td>6 (5%)</td>
<td>9 (3%)</td>
</tr>
<tr>
<td></td>
<td>18·5–24·9</td>
<td>21 (35%)</td>
<td>28 (21%)</td>
<td>95 (32%)</td>
</tr>
<tr>
<td></td>
<td>≥25</td>
<td>39 (64%)</td>
<td>99 (74%)</td>
<td>200 (66%)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Inactive</td>
<td>6 (10%)</td>
<td>16 (12%)</td>
<td>43 (14%)</td>
</tr>
<tr>
<td></td>
<td>Slightly active</td>
<td>33 (53%)</td>
<td>69 (52%)</td>
<td>161 (54%)</td>
</tr>
<tr>
<td></td>
<td>Moderately active</td>
<td>22 (37%)</td>
<td>47 (36%)</td>
<td>97 (32%)</td>
</tr>
<tr>
<td></td>
<td>Hormone replacement therapy</td>
<td>4 (7%)</td>
<td>12 (9%)</td>
<td>29 (10%)</td>
</tr>
<tr>
<td></td>
<td>Knee extensor muscle strength (mean [SD], kg)</td>
<td>13·8 (5·5)</td>
<td>12·8 (5·1)‡</td>
<td>13·2 (5·1)§</td>
</tr>
<tr>
<td></td>
<td>Walking speed (mean [SD], cm/sec)</td>
<td>64·3 (30·3)</td>
<td>59·7 (30·5)‡</td>
<td>60·2 (30·3)</td>
</tr>
</tbody>
</table>

### Table 2: Mean 3-year decline in knee extensor muscle strength and walking speed

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Continuous users of ACE inhibitors (n=61)</th>
<th>Intermittent users of ACE inhibitors (n=133)</th>
<th>Continuous/intermittent users of other drugs (n=301)</th>
<th>Never drug users (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strength (mean [SE], kg)</td>
<td>−1·0 (1·1)</td>
<td>−3·0 (0·7)</td>
<td>−3·7 (0·5)</td>
<td>−3·9 (0·7)</td>
</tr>
<tr>
<td>Walking speed (mean [SE], cm/sec)</td>
<td>−1·7 (4·1)</td>
<td>−13·6 (2·7)</td>
<td>−15·7 (1·8)</td>
<td>−17·9 (2·7)†</td>
</tr>
</tbody>
</table>
ACE inhibitors produce a shift of the myosin heavy chains and are associated with increased glucose and amino acid uptake, leading to higher metabolic efficiency and a positive trophic effect. Second, ACE inhibitors could lower the proinflammatory response that is triggered by angiotensin. In older people, high concentrations of cytokines are strong independent predictors of incident disability, probably through accelerated muscle catabolism that leads to muscle wasting. Angiotensin II increases production of interleukin-6 and tumour necrosis factor-α in smooth vascular cells, through activation of nuclear factor κB, a transcription factor system generally involved in inflammatory and immune responses. ACE inhibitors could inhibit this process and, subsequently reduce the concentration of cytokines. Moreover, the increase in concentration of bradykinin caused by ACE inhibition stimulates production of nitric oxide, a molecule that can suppress inflammatory activation.

Third, ACE inhibitors could favourably affect nutritional status through inhibition of interleukin-6. In fact, this cytokine reduces appetite and causes undernutrition, a frequent disorder in older adults, which can lead to progressive frailty and reduced physical function. ACE inhibitors could thus also have a beneficial effect on undernutrition through regulation of intestinal absorption.

Several genetic studies suggest that the renin-angiotensin system affects function of skeletal muscle. Healthy people who had reduced expression of ACE because of a genetic polymorphism showed greater muscle anabolic response and improved muscular efficiency after physical training.

Finally, the beneficial effect of treatment with ACE inhibitors on physical function could be affected by potential antianginal actions of these drugs. However, in our sample, presence of angina was not a significant predictor of decline in muscle strength and walking speed, and therefore, this mechanism is unlikely to account for our results.

Low activity of ACE leads to improved muscle response in women who are postmenopausal and who are on hormone replacement treatment. Although this hypothesis could have important clinical implications, we were unable to study the interaction between hormone replacement treatment and ACE inhibitors because of the low use of replacement therapy (8%) in our participants. In our study, patients who had used ACE inhibitors continuously had a baseline muscle strength and walking speed that was slightly higher than those of other participants. These better baseline values might be the result of exposure to ACE inhibitors before the study started. The difference in baseline means could have been greater, but was probably lessened by criteria used to recruit participants who were frail and disabled, which restricted variation in baseline level of function, leading to underestimation of baseline differences across groups.

Our findings are limited by the fact that they apply only to disabled, hypertensive elderly women (the population studied in WHAS). However, results of other clinical studies have shown that ACE inhibitors have similar positive effects in men and women with congestive heart failure.
failure. Further, preliminary cross-sectional results⁵ from a sample of healthy elderly men and women showed a significant positive association between use of ACE inhibitors and skeletal muscle mass. Although the data on which our analyses are based are from an observational study, the WHAS data were obtained prospectively, and the WHAS study population was a representative sample of older women. Our results suggest that the positive association between use of ACE inhibitors and muscle strength and walking speed are independent of occurrence of cardiovascular events, suggesting that this drug could have a direct effect on muscle. Additionally, although based on small numbers, our analyses suggest that use of ACE inhibitors has a dose-response relation with physical function. However, such a relation needs to be investigated in randomised controlled clinical trials.

Our results suggest that ACE inhibitor treatment could decrease long-term decline in physical function in elderly women who do not have CHF. If these findings can be confirmed in randomised controlled trials, ACE inhibitors could not only be used as first-line treatment of older adults with hypertension, but could also be used to slow physical decline in elderly people.

Contributors
All authors contributed to the writing of the paper and to interpretation of data. G Onder, B W J H Penninx, and M Pahor designed the study. G Onder, B W J H Penninx, and R Balkrishnan analysed the results. L P Fried, P H M Chavez, J D Williamson, and J M Guralnik were responsible for the overall design of the WHAS study. Conflict of interest statement
None declared.

References
2 Ferrucci L, Guralnik JM, Pahor M, Corti MC, Havlik RJ. Hospital diagnoses, Medicare charges and nursing home admissions in the year when older persons become severely disabled. JAMA 1997; 278: 728–34.