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The effect of perindopril on postural instability in older people with a history of falls—a randomised controlled trial

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Abstract

Angiotensin converting enzyme inhibitors may improve exercise capacity and muscle function in older people but are often thought to increase falls risk. We investigated the effect of perindopril on postural stability in older people with a history of falls.

Design: double-blind, parallel group, placebo-controlled randomised trial.

Methods: we recruited people aged >65 years with at least one fall in the previous year. Participants received 4 mg perindopril or placebo daily for 15 weeks. The primary outcome was the between-group difference in force-plate measured antero-posterior (AP) sway at 15 weeks. Secondary outcomes included other measures of postural sway, limits of stability during maximal forward, right and left leaning, blood pressure, muscle strength, 6-min walk distance and falls. The primary outcome was assessed using two-way ANOVA, adjusted for baseline factors.

Results: we randomised 80 participants. Mean age was 78.0 (SD 7.4) years; 60 (75%) were female. About 77/80 (96%) completed the trial. At 15 weeks there were no significant between-group differences in AP sway with eyes open (mean difference 0 mm, 95% CI –8 to 7 mm, $P = 0.91$) or eyes closed (mean difference 2 mm, 95% CI –7 to 12 mm, $P = 0.59$); no differences in other measures of postural stability, muscle strength or function. About 16/40 (42%) of patients in each group had orthostatic hypotension at follow-up. The median number (IQR) of falls was 1 (0,4) in the perindopril versus 1 (0,2) in the placebo group ($P = 0.24$).

Conclusions: perindopril did not improve postural sway in older people at risk of falls.

Clinical Trials Registration: ISRCTN58995463

Keywords: Falls, clinical trial, angiotensin converting enzyme inhibitor, postural sway, older people

Introduction

One in three community-dwelling individuals over 65 fall at least once per year with resultant injury, disability, loss of confidence, dependence on others and poor quality of life. Postural instability, a major risk for falls, increases with age [1]. Exercise is the single most effective intervention for falls prevention, and both lower limb strength and balance training and tai chi programmes can reduce falls risk—primarily through a reduction in postural instability [2, 3].

Although antihypertensive medication are commonly thought to cause falls, angiotensin converting enzyme inhibitors (ACEi) might in fact have a number of effects that could lead to a reduction in falls risk. ACEi can improve 6-min walking distance in older people to a similar extent as 6 months of an exercise programme that reduced falls and is associated with a slower decline in muscle strength and walking speed with ageing [4, 5].

Other effects include beneficial effects on nerve function [6, 7], central postural control [8] and orthostatic hypotension (OH) related to baroreceptor sensitivity [9]. Population based

studies in older people have variously reported an increased [10–12], unchanged [13, 14] or a reduced [15] risk of falls, especially injurious ones, with cardiovascular medications like ACEi.

Randomised controlled trials are required to resolve this uncertainty; we therefore tested the effect of the long-acting ACEi perindopril on postural instability as an intermediate phenotype that reflects falls risk in older people.

Methods

We performed a parallel group, double-blind randomised placebo-controlled trial. The study followed the principles of the Declaration of Helsinki was approved by the Scotland—A Research Ethics committee (13/SS/0086) and the Medicines and Healthcare Regulatory Authority (EuDRACt number 2013-001677-24). The trial was registered with www.isrctn.com (ISRCTN58995463). The work was supported by funding from the Scottish Chief Scientist Office (grant number CZH/4/856). The funders had no role in the design, execution, analysis and interpretation of data, or writing of the study report.

We recruited community-dwelling participants from the Tayside area of Scotland, aged ≥ 65 years with at least one self-reported fall in the previous 12 months. To ensure that all participants had had the opportunity to engage with currently provided strategies for falls management, we recruited only people who had sought medical attention for a fall within the last 18 months. Exclusion criteria were: already taking ACEi or Angiotensin Receptor Blocker (ARB); contraindication to ACEi (previous intolerance; significant aortic outflow obstruction with peak gradient >30 mmHg; serum potassium >5.0 mmol/l; eGFR < 30 ml/min/1.73 m² by MDRD4 equation [16]; serum creatinine >170 umol/l); stopped ACEi or ARB following specialist falls assessment in the previous 6 months; a clinical diagnosis of heart failure; asymptomatic left ventricular systolic dysfunction; Systolic blood pressure (BP) >160 mmHg or <100 mmHg at screening or on 24 h BP monitor within the last year; wheelchair bound; inability to stand or walk without assistance; Parkinson's disease; taking non-steroidal anti-inflammatory drugs (aspirin was permitted); participation in a previous clinical trial of investigational medicinal products within 30 days; lactose intolerance; cognitive impairment precluding informed consent.

We identified participants from a variety of sources: (i) Letters of invitation through the East node of the Scottish Primary Care Research Network (SPCRN); (ii) Local Day Hospitals, outpatient clinics, falls services, and elderly services; (iii) Advertising in community settings; (iv) Volunteer databases including the Scottish Health Research Register. We prescreened potential participants for eligibility via telephone (see Supplementary data, Appendix 1, available at *Age and Ageing* online).

We randomised participants using a web-based randomisation system run independently from the trial team by Tayside Clinical Trials Unit (TCTU) to ensure allocation concealment. Eligible participants received either Perindopril

or placebo identically over-encapsulated, for 15 weeks in a 1:1 ratio. We employed a minimisation algorithm using three factors: baseline systolic BP ($>$ or <140 mmHg), thiazide diuretic use and source of recruitment (Primary care and volunteers; secondary care falls services; and other secondary care). After 2 weeks, perindopril was up-titrated from 2 mg to 4 mg with mock up-titration of placebo. All usual medication was continued.

Outcomes

We measured outcomes at baseline and 15 weeks during a hospital-based study visit. The primary outcome was the between-group difference in static Anteroposterior (AP) sway from baseline to 15 weeks, adjusted for baseline values.

Postural stability

Postural stability was measured using a force-plate (AMTI model BP400600, Advanced Mechanical Technologies Inc. Watertown, MA, USA). For static postural stability, participants stood on the force-plate with feet slightly apart for 40 s. The largest value from three runs was used for analyses. Each set of runs was performed with eyes open, then with eyes closed. A scatter plot of the AP and Medio-Lateral (ML) displacement of centre of pressure (COP) was used to calculate AP and ML sway, total sway area (TSA) [17] and average sway velocity (SV). For dynamic postural stability, the maximum COP displacement during three 5 second trials of maximal forward, right and left leaning was measured with eyes open to measure limits of stability (LOS) [18].

Physical function measures

We measured quadriceps strength, non-volitional muscle strength using magnetic femoral nerve stimulation and 6-min walk (6 MW) distance were recorded (see Supplementary data, Appendix 1, available at *Age and Ageing* online).

Falls

Participants prospectively recorded falls using the validated monthly fall diaries method [19]. Diaries were administered at the baseline visit and returned at the 15 week visit. Participants were instructed on what was considered a fall and asked to complete the diary daily. They were reminded about the diaries at each visit/telephone call.

Other measures

We recorded baseline information on age, sex, height, weight, body mass index (BMI), bioimpedance measures of muscle and fat mass (BIA 101, Akern, Pontasseive, Italy), concomitant medications, co-morbidities, smoking, alcohol consumption, type of accommodation, Scottish Index of Multiple Deprivation (SIMD) and walking aid use.

Blood pressure was measured at baseline and 15 weeks using a standard digital monitor (Omron 705IT; Milton

Keynes, UK) in the supine position and then immediately on standing, repeated at 2 and 3 min, to identify OH. OH was defined as a reduction of BP systolic >20 mmHg or diastolic >10 mmHg within 3 min of standing as per the consensus statement from a group of leading scientific societies [20].

Statistical analysis

Sample size calculation

We anticipated a reduction in mean AP sway of 5.6 mm (SD 7.1) from a baseline of 24.5 mm between perindopril and placebo group as seen with Tai Chi [17], a recommended intervention for falls prevention. To detect this change with 90% power at $\alpha = 0.05$, we required 34 participants per group. Allowing for a dropout of 15%, we aimed to recruit 80 participants (40 per group).

We recorded data using the OpenClinica database system (OpenClinica, Waltham, MA 02451, USA), which was locked prior to final analysis. Analyses were conducted by a statistician in Tayside CTU using the SAS statistical package (SAS Institute Inc., North Carolina, USA, version 9.3). For all outcomes save falls, analyses were performed comparing difference in outcomes at 15 weeks using ANOVA, adjusted for baseline values of the variable under test. The fully adjusted analysis entered all independently significant baseline covariates into a multivariate model; only those covariates retained in a backwards elimination analysis were included in the final adjusted model. Between-group changes in outcomes were analysed on an intention to treat basis. A sensitivity analysis using multiple imputation to account for missing data was also performed, using the combined results from 100 rounds of imputation. To take into account the highly skewed distribution of number of falls we tested a series of models including ANOVA, other distributions (quasi-poisson) and ordinal data categorising participants as having 0, 1–2, 3–5, 6–10 and >10 falls.

Results

In total 4,289 potential participants were invited to participate in the study. About 3,793 (88%) declined or did not reply, 408 (9.5%) were found to be ineligible at pre-screening (most frequent reasons were already taking ACEi, taking NSAIDs, not had a fall in previous 18 months or not sought medical attention for falls). Of the case, 88 attended a screening visit, and 80 participants progressed to randomisation between September 2013 and September 2015. About 77/80 (96%) completed the study. The CONSORT participant flow diagram is given in Figure 1. The two groups were well matched at baseline (Table 1). Study medication was stopped in 7 participants taking perindopril (4 for cough, 1 increased potassium, 1 participant felt was causing muscle weakness, 1 commenced on ACEi for hypertension) and 2 taking placebo (1 for dizziness, 1 participant choice). Two participants in the perindopril group remained on the 2 mg dose due to complaints of dizziness (both had OH at screening but only 1 at follow-up).

Primary outcome

There was no significant difference in change in AP sway between groups with eyes open (mean difference 0 mm, 95% CI -8 to 7 mm, $P = 0.91$) or eyes closed (mean difference 2 mm, 95% CI -7 to 12 mm, $P = 0.59$). Details of the primary outcome analyses are given in Table 2. After adjusting for all significant univariate factors (baseline AP sway, height and walking aids) difference in AP sway with eyes closed was 6 mm (95% CI -2 to 13 mm) and with eyes open was 0 mm (95% CI -7 to 7 mm).

The number of dropouts was low ($n = 3$). There was no significant between-group difference in change in AP sway when multiple imputation was used to account for missing data; AP sway mean difference was 3 mm (95% CI -6 to 12 mm; $P = 0.5$) with eyes closed 0 mm (95% CI -8 to 7 mm; $P = 0.92$) with eyes open.

Secondary outcomes

Postural stability

There were no significant differences between groups in change in ML sway, SV or TSA or in Dynamic stability measures of LOS whilst reaching forward, left or right (see Supplementary data, Appendix 2, available at *Age and Ageing* online).

Physical function measures

There were no significant differences between groups in change in voluntary or involuntary muscle strength. Difference in 6 MW distance between groups was -9 m (95% CI -29 to 12; $P = 0.41$) (Table 2).

Blood pressure

A treatment effect was seen in both systolic (-11 mmHg 95% CI -18 to -4 ; $P = 0.003$) and diastolic (-5 mmHg 95% CI -9 to -1 ; $P = 0.02$) BP at 15 weeks. There was no difference between groups in postural drop in BP (-1 mmHg 95% CI -6 to 4, $P = 0.78$) or the number of people fulfilling the criteria of OH (16 in both groups; $P = 0.90$) (Table 2).

No participant died in the study period. Hospital admission occurred in 1 participants in the perindopril group (2 admissions for breast abscess and subcutaneous abscess) and 3 in the placebo group (1 for stroke and ankle fracture; 1 dizziness and fall; 1 biliary sepsis). Adverse events were common (perindopril $n = 84$ versus placebo $n = 82$). Most adverse events (70%) were of mild severity (see Supplementary data, Appendix 3, available at *Age and Ageing* online).

The number of falls was greater in the perindopril group (156 versus 95), but the data were heavily skewed by a small number of participants who fell frequently. More frequent falls in the perindopril group during the trial period reflected a higher rate of falls in this group prior to trial enrolment (592 versus 536). More participants in the perindopril group had no falls during the trial (17 versus 13).

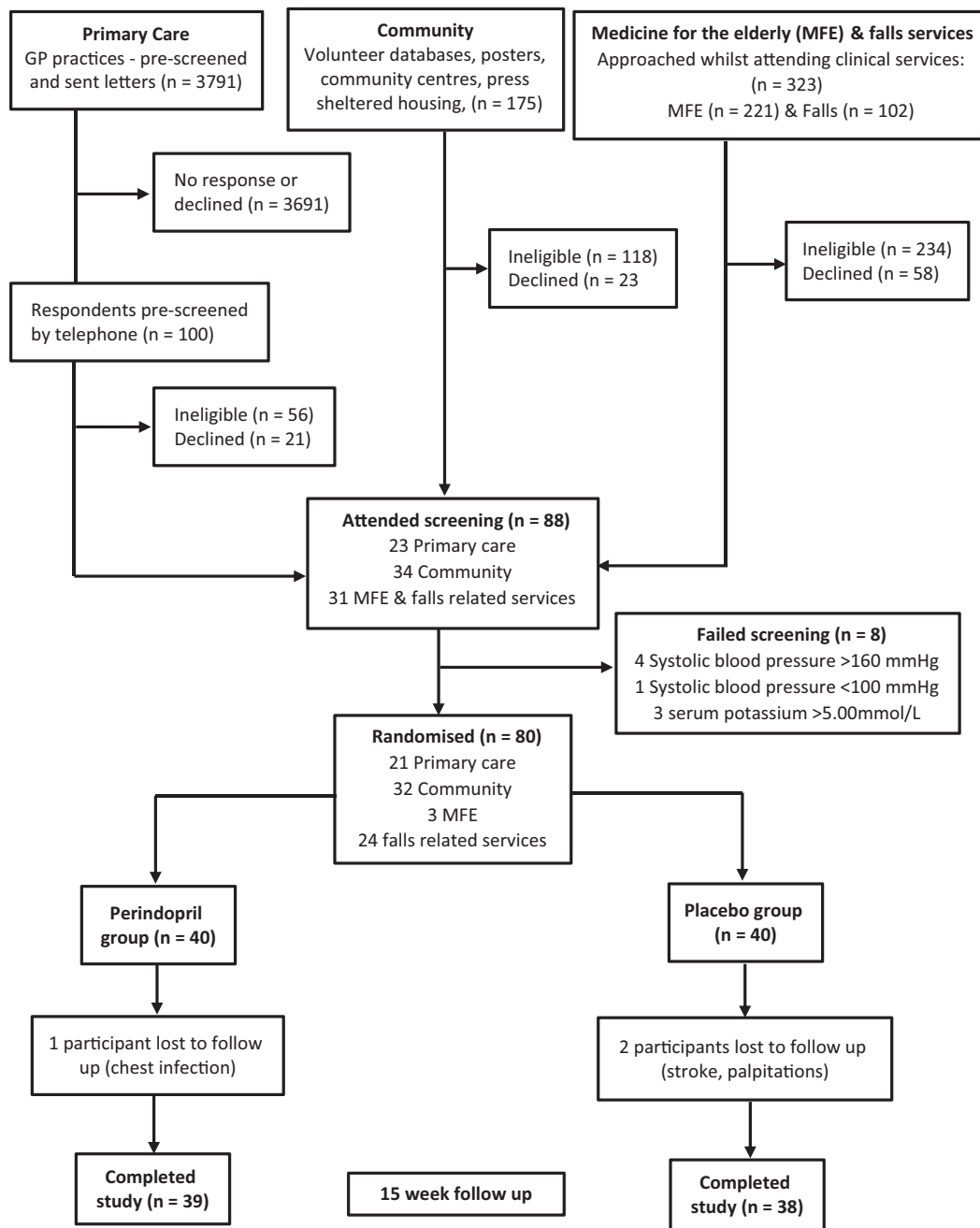


Figure 1. CONSORT Flow chart for trial participation.

The median number (IQR) of falls was 1 (0,4) in the perindopril group versus 1 (0,2) in the placebo group. The difference between groups was not statistically significant (difference in mean number of falls per person by ordinal regression 0.4 [95% CI -9 to 1.6]; $P = 0.58$) (see Supplementary data, Appendix 4, available at *Age and Ageing* online).

Discussion

We found no statistically significant effect of 15 weeks of perindopril on postural stability in older people with falls, albeit with wide confidence intervals. This suggests that

perindopril may not be an effective treatment to improve postural stability in those who had received all currently available standard therapy for falls. An important caveat is that the minimal clinically important difference in stability measures for falls risk reduction is not known and there is variability in the techniques used to measure postural stability [21]; our results cannot exclude a possibly clinically important effect.

More positively, perindopril did not appear to worsen OH. ACEi are often discontinued in people with falls due to the widespread belief that antihypertensive medication exacerbates OH and increases falls. The evidence linking long-acting ACEi with OH is weak however. People with

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Table 1. Baseline characteristics

	Perindopril (<i>n</i> = 40)	Placebo (<i>n</i> = 40)
Mean age (years) (SD)	78.1 (7.3)	78.0 (7.6)
Male sex (%)	10 (25)	10 (25)
Mean BMI (kg/m ²) (SD)	29.0 (4.3)	28.5 (5.2)
Height-adjusted muscle mass kg/m (SD)	13.9 (2.9)	13.7 (3.0)
Height-adjusted fat mass kg/m (SD)	18.9 (4.9)	18.2 (5.8)
Mean eGFR	73.4 (21.5)	76.7 (21.7)
Mean SBP mmHg (SD)	147 (13)	143 (14)
Mean DBP mmHg (SD)	82 (11)	76 (11)
OH present	11 (28)	13 (33)
Walking aid		
None (%)	20 (50)	19 (47)
Walking stick (%)	16 (40)	14 (35)
Other (%)	4 (10)	7 (18)
Co-morbidities		
Hypertension (%)	16 (40)	16 (40)
Cardiovascular disease (%)	8 (20)	6 (15)
Peripheral neuropathy (%)	2 (5)	7 (18)
Vertigo (%)	3 (7)	4 (10)
Registered blind (%)	1 (2)	0
Concomitant medications		
Total number of medications median (IQR)	7 (4,9)	6 (4,8)
Number cardiovascular medications median (IQR)	1 (0,2)	1 (0,2)
Any Cardiovascular medication (%)	26 (65)	24 (60)
Sedatives and antipsychotics (%)	2 (5)	2 (5)
Opioid based analgesia (%)	10 (25)	5 (13)

eGFR, estimated Glomerular Filtration Rate; SBP/DBP, systolic/diastolic blood pressure.

Table 2. Outcome measures

		Perindopril	Placebo	Treatment effect ^a (95% CI)	<i>P</i>		
Primary outcome							
AP sway range (mm) (<i>eyes closed</i>)	Baseline	<i>N</i> = 36	63 (33)	<i>N</i> = 39	64 (35)	2 (-7 to 12)	0.59
	Follow-up	<i>N</i> = 34	59 (31)	<i>N</i> = 37	57 (31)		
AP sway range (mm) (<i>eyes open</i>)	Baseline	<i>N</i> = 40	53 (27)	<i>N</i> = 40	53 (30)	0 (-8 to 7)	0.91
	Follow-up	<i>N</i> = 39	45 (19)	<i>N</i> = 38	45 (28)		
Secondary outcomes							
Maximal voluntary quadriceps contraction (kg)	Baseline	<i>N</i> = 39	18.6 (9.0)	<i>N</i> = 39	19.2 (7.5)	-1.4 (-3.0 to 0.3)	0.11
	Follow-up	<i>N</i> = 36	16.8 (6.7)	<i>N</i> = 35	18.5 (7.4)		
Quadriceps twitch tension at rest (kg)	Baseline	<i>N</i> = 31	2.7 (1.1)	<i>N</i> = 33	2.8 (1.6)	0.2 (0.0 to 0.4)	0.08
	Follow-up	<i>N</i> = 29	2.9 (1.3)	<i>N</i> = 30	2.6 (1.2)		
6-min walk distance (m)	Baseline	<i>N</i> = 40	336 (94)	<i>N</i> = 40	330 (113)	-9 (-29 to 12)	0.41
	Follow-up	<i>N</i> = 38	338 (104)	<i>N</i> = 38	351 (111)		
Postural change in systolic BP ^b (mmHg)	Baseline	<i>N</i> = 40	-11 (12)	<i>N</i> = 40	-15 (16)	-1 (-6 to 4)	0.79
	Follow-up	<i>N</i> = 38	-18 (11)	<i>N</i> = 38	-18 (14)		
Postural change in diastolic BP ^a (mmHg)	Baseline	<i>N</i> = 40	-3 (9)	<i>N</i> = 40	-4 (6)	-1 (-4 to 2)	0.48
	Follow-up	<i>N</i> = 38	-4 (9)	<i>N</i> = 38	-4 (7)		

Figures in brackets are SD unless otherwise noted.

^aAdjusted for baseline values of variable under test.

^bNegative values denote a fall in blood pressure on standing.

controlled hypertension have a lower prevalence of OH than those with uncontrolled hypertension and OH is associated with a 2.5 times higher risk of falls in those with uncontrolled compared to those with controlled hypertension [22]. Population based studies in older people have variously reported an increased [10–12], unchanged [13, 14] or a reduced [15] risk of falls, especially injurious ones, with cardiovascular medications like ACEi. The results from the

current trial suggest that ACEi may not increase falls risk in older people who fall. This finding should be interpreted with caution as our study was not powered to detect falls as an outcome, but was included as a safety measure and confidence intervals are wide. Moreover there was an imbalance in the number of falls between groups at baseline. Trial results in this area are scanty; a recent medication withdrawal trial [23] showed no benefit from withdrawal of

medications, including antihypertensives, on falls rates, but withdrawal of antihypertensive medication in older people with mild cognitive impairment and OH improved OH in another recent trial [24].

Our previous trial of perindopril in older people showed an improvement in 6MWD after 20 weeks of treatment which we did not find in this study [5]; however participants in our previous trial were more functionally impaired, and were selected because of functional impairment rather than for their falls risk. It is therefore possible that in our previous trial, endurance rather than the fast-twitch muscle function that balance relies on was compromised, and that it was endurance muscle function rather than fast-twitch function that responded to ACEi.

Our trial had several strengths. The groups were well balanced at baseline. We ensured that all participants had had the opportunity to receive currently available interventions for falls—any influence of treatment was therefore additional. The dropout rate was low (4%) which may suggest that the study population, was fitter than some people routinely seen in geriatric medical practice. Some weaknesses also deserve comment. Only 2% of those invited to participate ($n = 4,289$) were recruited to the study. This response rate is similar to a previous study in which we recruited functionally impaired older people to a clinical trial of ACEi and exercise [25] but much lower than that seen in other trials using pharmacological approaches to improve physical function (randomisation rates typically 5–10% of those approached) [5]. This demonstrates the difficulty in recruiting older people to trials of pharmaceutical interventions, but also suggests specific issues around recruitment to studies examining falls interventions. We did not perform formal tests of cognitive function. The study was of 15 weeks duration and may be too short to reach definite conclusions, although our previous trial demonstrated that differences in walk speed had started to appear by 10 weeks. A larger number of participants in the perindopril group discontinued medication (7 versus 2)—mostly due to cough ($n = 4$), a common side effect of ACEi.

What do our results mean for clinical practice? The results do not support a strategy of using ACEi to reduce falls in older people with a history of falls, but they equally suggest that ACEi may not have a deleterious effect on key risks for falls, including OH. There may therefore be little to gain by stopping ACEi in those who fall, particularly if other indications for ACEi (e.g. heart failure, previous stroke or other vascular event) are present. Further work, including pooling of falls data from multiple trials of ACEi in older people, would help to further clarify the effect of ACEi on falls risk in this patient population.

Key points

- We conducted a trial of ACE inhibitors (ACEi) as a pharmacological approach to improving postural sway.

- We found no improvement in postural sway to support a role for ACEi in improving postural balance.
 - We found no worsening of falls rates or OH to support stopping ACEi in people with falls.
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Supplementary data

Supplementary data are available at *Age and Ageing* online. The full trial protocol and statistical analysis plan are available on request from the authors.

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Conflicts of interest

Dr Witham, Dr Sumukadas and Professor Struthers are investigators on a multicentre RCT examining the effects of perindopril on sarcopenia (funded by NIHR/MRC Efficacy and Mechanisms Evaluation funding stream).

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