Clinical trial results:
Do ACE inhibitors reduce postural instability in older people?: Towards a novel approach to falls prevention.

Summary

EudraCT number	2013-001677-24
Trial protocol	GB
Global end of trial date	30 September 2015

Results information

Result version number	v1 (current)
This version publication date	17 November 2016
First version publication date	17 November 2016

Trial information

Trial identification

Sponsor protocol code	2012GR06

Additional study identifiers

ISRCTN number	ISRCTN58995463
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Dundee and NHS Tayside
Sponsor organisation address	Residency Block, Level 3, Ninewells Hospital, George Pirie, Dundee, United Kingdom, DD1 9SY
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2015
Global end of trial reached?	Yes
Global end of trial date	30 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to examine the effect of perindopril compared with placebo on the change in standing balance (postural stability) over a 15 week period in older people with falls.
Evidence from our group and others suggests that ACE inhibitors (ACEi) have a number of effects that might lead to a reduction in falls risk. These include beneficial effects on muscle function, nerve function, central postural integration and orthostatic hypotension (OH). However ACEi are often stopped in people with falls due to worries about increasing falls through worsening OH. We therefore aimed to study the effect of ACEi on postural stability as an intermediate phenotype for falls risk. Postural stability was measured using a force plate.

Protection of trial subjects:

Potential participants were given the Participant Information sheet at least 24 hours prior to written informed consent being taken. The trial was explained to them and they were given opportunities to ask questions prior to consent. They were allowed withdraw from the study at any time.
At every visit participants were asked about potential adverse events and any adverse events were documented. This information was provided to the DMC for safety assessment.
Blood tests and blood pressure was measured at baseline, week 2, 5 and 15 to monitor renal function and blood pressure both of which can be affected by the trial medication. Protocol specified rules of uptitration or down titration of medication and when medication was to be discontinued. Clinical acumen was also employed to ensure participant safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	64
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

From September 2013, 80 participants were recruited from Tayside and Fife. Last participant last visit was 30 September 2015.
Participants aged > 65 years with ≥1 self-reported falls in the previous 12 months fulfilling inclusion and exclusion criteria were recruited. Sources were from primary care, secondary care and volunteers from community.

Pre-assignment

Screening details:

4289 potential participants were invited to participate . 3793 declined or did not reply, 408 were found ineligible on telephonic pre-screening and 88 attended a screening visit. 80 participants were randomised to receive perindopril or placebo. All usual medication was continued.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Perindopril

Arm description:

Participants were randomised to receive Perindopril or placebo in a 1:1 ratio. Starting dose of 2 mg Perindopril was uptitrated to 4 mg after 2 weeks if tolerated.

Arm type	Experimental
Investigational medicinal product name	Perindopril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Initial dose on randomisation was 2 mg which was uptitrated at 2 weeks to 4 mg if tolerated (Blood pressure and renal function).
If 2 mg was tolerated but not 4 mg, participant was kept on 2 mg for the duration of the study.

Arm title	Placebo

Arm description:

Participants were randomised to receive Perindopril or placebo in a 1:1 ratio. The placebo group also received a mock uptitration at 2 weeks.

Arm type	Placebo
Investigational medicinal product name	Perindopril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Initial dose on randomisation was 2 mg which was uptitrated at 2 weeks to 4 mg if tolerated (Blood pressure and renal function).
If 2 mg was tolerated but not 4 mg, participant was kept on 2 mg for the duration of the study.

Number of subjects in period 1	Perindopril	Placebo
Started	40	40
Completed	39	38
Not completed	1	2
Adverse event, non-fatal	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Perindopril
Reporting group description:	
Participants were randomised to receive Perindopril or placebo in a 1:1 ratio. Starting dose of 2 mg Perindopril was uptitrated to 4 mg after 2 weeks if tolerated.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomised to receive Perindopril or placebo in a 1:1 ratio. The placebo group also received a mock uptitration at 2 weeks.	

Reporting group values	Perindopril	Placebo	Total
Number of subjects	40	40	80
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	31	33	64
85 years and over	9	7	16
Age continuous			
Recruited participants aged 65 years or over			
Units: years			
arithmetic mean	78.1	78	
standard deviation	± 7.3	± 7.6	-
Gender categorical Units: Subjects			
Female	30	30	60
Male	10	10	20
SIMD decile			
Scottish index of multiple deprivation			
Units: Subjects			
1-5	10	10	20
6-10	30	30	60
Home circumstances Units: Subjects			
Home alone	20	17	37
Home with family/friends	17	16	33
Sheltered housing	3	7	10
Walking aid Units: Subjects			
None	20	19	39
Walking stick	16	14	30

Other	4	7	11
Hypertension			
Past medical history			
Units: Subjects			
Yes	16	16	32
No	24	24	48
Ischaemic heart disease			
Past medical history			
Units: Subjects			
Yes	5	3	8
No	35	37	72
Stroke/TIA			
Past medical history			
Units: Subjects			
Yes	3	3	6
No	37	37	74
Peripheral vascular disease			
Past medical history			
Units: Subjects			
Yes	0	1	1
No	40	39	79
Diabetes			
Past medical history			
Units: Subjects			
Yes	2	2	4
No	38	38	76
COPD			
Past medical history			
Units: Subjects			
Yes	4	5	9
No	36	35	71
Anaemia			
Past medical history			
Units: Subjects			
Yes	3	2	5
No	37	38	75
Peripheral neuropathy			
Past medical history			
Units: Subjects			
Yes	2	7	9
No	38	33	71
Vertigo			
Past medical history			
Units: Subjects			
Yes	3	4	7
No	37	36	73
Tinnitus			
Past medical history			
Units: Subjects			
Yes	6	9	15
No	34	31	65

Registered blind			
Past medical history			
Units: Subjects			
Yes	1	0	1
No	39	40	79
Concomitant betablockers Units: Subjects			
Yes	11	8	19
No	29	32	61
Concomitant thiazides Units: Subjects			
Yes	6	4	10
No	34	36	70
Concomitant calcium channel blockers Units: Subjects			
yes	5	10	15
No	35	30	65
Concomitant sedatives and antipsychotics Units: Subjects			
yes	2	2	4
No	38	38	76
Concomitant opiate based analgesia Units: Subjects			
Yes	10	5	15
No	30	35	65
Height Units: metres			
arithmetic mean	1.58	1.59	
standard deviation	± 0.1	± 0.08	-
Weight Units: Kg			
arithmetic mean	72.5	71.9	
standard deviation	± 14	± 14.3	-
Height adjusted muscle mass Units: Kg/m			
arithmetic mean	13.9	13.7	
standard deviation	± 2.9	± 3	-
Height adjusted fat mass Units: Kg/m			
arithmetic mean	18.9	18.2	
standard deviation	± 4.9	± 5.8	-

End points

End points reporting groups

Reporting group title	Perindopril
Reporting group description:	
Participants were randomised to receive Perindopril or placebo in a 1:1 ratio. Starting dose of 2 mg Perindopril was uptitrated to 4 mg after 2 weeks if tolerated.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomised to receive Perindopril or placebo in a 1:1 ratio. The placebo group also received a mock uptitration at 2 weeks.	

Primary: Between group change in Anterioposterior sway (eyes closed) from baseline to 15 weeks

End point title	Between group change in Anterioposterior sway (eyes closed) from baseline to 15 weeks
End point description:	
Primary outcome was Difference in static Anteroposterior (AP) sway at 15 weeks between the two groups, adjusted for baseline values. Postural stability was measured using the Advanced Medical Technology Inc. force plate (measuring ground reaction force velocity and pressure distribution). For the static postural stability, participants stood on the force plate with feet slightly apart, eyes open and closed each for 40 seconds and this was repeated 3 times. The sway range was calculated.	
End point type	Primary
End point timeframe:	
Assessed at baseline and at 15 weeks	

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Millimeter				
arithmetic mean (standard deviation)				
Baseline	63 (± 33)	64 (± 35)		
15 weeks	59 (± 31)	57 (± 31)		

Statistical analyses

Statistical analysis title	Between group difference in AP sway
Statistical analysis description:	
Analyses were performed comparing change in outcomes at 15 weeks using ANOVA, adjusted for baseline values of the variable under test. A multivariate model including treatment and any significant co-variables from baseline data gave similar results.	
Comparison groups	Perindopril v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	12

Primary: Between group difference in Anterioposterior sway (eyes open) from baseline to 15 weeks

End point title	Between group difference in Anterioposterior sway (eyes open) from baseline to 15 weeks

End point description:

Difference in static Anteroposterior (AP) sway at 15 weeks between the two groups, adjusted for baseline values.

Postural stability was measured using the Advanced Medical Technology Inc. force plate (measuring ground reaction force velocity and pressure distribution). For the static postural stability, participants stood on the force plate with feet slightly apart, eyes open and closed each for 40 seconds and this was repeated 3 times.

End point type	Primary

End point timeframe:

Outcome was measured at baseline and at 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: millimeters				
arithmetic mean (standard deviation)				
Baseline	53 (± 27)	53 (± 30)		
15 weeks	45 (± 19)	45 (± 28)		

Statistical analyses

Statistical analysis title	Between group difference in AP sway
Comparison groups	Perindopril v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	7

Secondary: Between group difference in mediolateral sway (eyes closed) from baseline to 15 weeks

End point title	Between group difference in mediolateral sway (eyes closed) from baseline to 15 weeks

End point description:

Postural stability was measured using the Advanced Medical Technology Inc. force plate (measuring ground reaction force velocity and pressure distribution). For the static postural stability, participants stood on the force plate with feet slightly apart, eyes open and closed each for 40 seconds and this was repeated 3 times. Sway range in the mediolateral direction was calculated

End point type	Secondary

End point timeframe:

Outcomes were measured at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: millimeter(s)				
arithmetic mean (standard deviation)				
Baseline	37 (± 40)	44 (± 55)		
15 weeks	34 (± 27)	41 (± 50)		

Statistical analyses

Statistical analysis title	Change in mediolateral sway

Statistical analysis description:

Analyses were performed comparing change in outcomes using ANOVA, adjusted for baseline values of the variable under test. The multivariate model including treatment and any significant co-variables gave similar results. Other types of analyses yielded similar results.

Comparison groups	Perindopril v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	5

Secondary: Between group difference in mediolateral sway (eyes open) from baseline to 15 weeks

End point title	Between group difference in mediolateral sway (eyes open) from baseline to 15 weeks

End point description:

End point type	Secondary

End point timeframe:

Outcome was measured at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: millimeter(s)				
arithmetic mean (standard deviation)				
Baseline	37 (± 34)	40 (± 29)		
15 weeks	27 (± 19)	32 (± 27)		

Statistical analyses

Statistical analysis title	Between group difference in mediolateral sway
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	5

Secondary: Between group difference in sway velocity (eyes closed) from baseline to 15 weeks

End point title	Between group difference in sway velocity (eyes closed) from baseline to 15 weeks

End point description:

End point type	Secondary

End point timeframe:

Outcome measured at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: mm/s				
arithmetic mean (standard deviation)				
Baseline	83 (± 19)	86 (± 22)		
15 weeks	81 (± 16)	85 (± 28)		

Statistical analyses

Statistical analysis title	Between group differrence in sway velocity
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	3

Secondary: Between group difference in sway velocity (eyes open) from baseline to 15 weeks

End point title	Between group difference in sway velocity (eyes open) from baseline to 15 weeks

End point description:

End point type	Secondary

End point timeframe:

Outcome measured at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: mm/s				
arithmetic mean (standard deviation)				
Baseline	79 (± 15)	81 (± 16)		
15 weeks	78 (± 14)	77 (± 20)		

Statistical analyses

Statistical analysis title	between group difference in sway velocity
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	6

Secondary: between group difference in total sway area (eyes closed) baseline to 15 weeks

End point title	between group difference in total sway area (eyes closed) baseline to 15 weeks

End point description:

End point type	Secondary

End point timeframe:

Outcome measured at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: square millimeter				
arithmetic mean (standard deviation)				
Baseline	2389 (± 6100)	2071 (± 3753)		
15 weeks	1666 (± 3095)	1647 (± 2184)		

Statistical analyses

Statistical analysis title	Between group difference in total sway area
Statistical analysis description: Adjusted for baseline total sway area	
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-150
Confidence interval	
level	95 %
sides	2-sided
lower limit	-757
upper limit	457

Secondary: Between group difference in total sway area (eyes open) from baseline to 15 weeks

End point title	Between group difference in total sway area (eyes open) from baseline to 15 weeks
End point description:	
End point type	Secondary
End point timeframe: Outcome measured at baseline and 15 weeks	

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: square millimeter				
arithmetic mean (standard deviation)				
Baseline	1311 (± 1558)	1287 (± 1285)		
15 weeks	893 (± 1179)	1064 (± 1536)		

Statistical analyses

Statistical analysis title	Between group difference in total sway area
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.43
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-179
Confidence interval	
level	95 %
sides	2-sided
lower limit	-634
upper limit	275

Notes:

[1] - Adjusted for baseline variable

Secondary: Between group difference in anterioposterior reach

End point title	Between group difference in anterioposterior reach

End point description:

End point type	Secondary

End point timeframe:

Outcome measured at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: millimeter				
arithmetic mean (standard deviation)				
Baseline	48 (± 23)	47 (± 21)		
15 weeks	48 (± 30)	45 (± 28)		

Statistical analyses

Statistical analysis title	Between group difference in forward reach
Statistical analysis description: Adjusted for baseline variable	
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	16

Secondary: Between group difference in mediolateral left reach from baseline to 15 weeks

End point title	Between group difference in mediolateral left reach from baseline to 15 weeks
End point description:	
End point type	Secondary
End point timeframe: outcome measured at baseline and 15 weeks	

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: millimeter(s)				
arithmetic mean (standard deviation)				
Baseline	53 (± 44)	49 (± 40)		
15 weeks	45 (± 27)	36 (± 24)		

Statistical analyses

Statistical analysis title	Between group difference in left reach
Statistical analysis description: Adjusted for baseline variable	
Comparison groups	Perindopril v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	20

Secondary: Between group difference in mediolateral right reach from baseline to 15 weeks

End point title	Between group difference in mediolateral right reach from baseline to 15 weeks

End point description:

End point type	Secondary

End point timeframe:

Outcome measure at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: millimeter(s)				
arithmetic mean (standard deviation)				
Baseline	49 (± 35)	48 (± 42)		
15 weeks	46 (± 44)	42 (± 25)		

Statistical analyses

Statistical analysis title	Between group difference in right reach

Statistical analysis description:

Adjusted for baseline variable

Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	18

Secondary: Falls at baseline

End point title	Falls at baseline

End point description:

End point type	Secondary

End point timeframe:

Reported at baseline - number of falls in 12 months prior to recruitment

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: subjects				
1-2 falls	14	19		
3-5 falls	19	11		
6-10 falls	2	8		
>10 falls	5	2		
Median falls (IQR)	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Falls during the study

End point title	Falls during the study

End point description:

End point type	Secondary

End point timeframe:

Number of falls reported in study period

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: subjects				
No falls	17	13		
1-2 falls	10	18		
3-5 falls	5	6		
6-10 falls	1	1		
>10 falls	6	2		

Statistical analyses

Statistical analysis title	Between group difference in falls during the study

Statistical analysis description:

Number of falls data was skewed so a number of sensitivity analyses were done using different modelling techniques.

Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.24
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	4.5

Notes:

[2] - A number of sensitivity analyses using different modelling techniques were conducted to investigate the difference in falls between the two groups: Mixed model analysis mean difference 1.7 (-1.1 to 4.5, p=0.24); quasi-poisson regression mean difference -0.6 (-1.6 to 0.3, p=0.19); ordinal regression 0.4 (95% CI -0.9 to 1.6; p=0.58). Mixed model analyses are presented in the tables

Secondary: Between group difference in voluntary muscle strength (QMVC)

End point title	Between group difference in voluntary muscle strength (QMVC)

End point description:

Isometric quadriceps maximum voluntary contraction strength (QMVC) was measured 3 times in a sitting position with the knee joint at 90 degrees using a Biopac tension dynamometer and output was recorded using a data acquisition system. QMVC was taken as the highest mean force that could be sustained over 1 second.

End point type	Secondary

End point timeframe:

Outcome measure at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: kilogram(s)				
arithmetic mean (standard deviation)				
Baseline	18.6 (± 9)	19.2 (± 7.5)		
15 weeks	16.8 (± 6.7)	18.5 (± 7.4)		

Statistical analyses

Statistical analysis title	Between group difference in QMVC
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.11
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	0.3

Notes:

[3] - Adjusted for baseline variable

Secondary: Between group difference in Magnetic twitch of quadriceps (TwQ)

End point title	Between group difference in Magnetic twitch of quadriceps (TwQ)

End point description:

This was used to test non volitional muscle strength and fatigability in participants who had no contraindications to magnetic nerve stimulation. Greatest Twitch tension generated in the Quadriceps (TwQ) using magnetic femoral nerve stimulation with the Magstim 2002 device was recorded. Endurance was tested by repeated QMVC, until force fell to < 70% of baseline maximum QMVC and the number of 'kicks' were recorded. Magnetic stimulation was repeated to estimate fatigue immediately and 10 minutes later. Fatigability was further tested by measuring TwQ following a 6 minute walking test (6MW), a valid, reliable test of submaximal endurance capacity in older people.

End point type	Secondary

End point timeframe:

Outcome measured at baseline and 15 weeks

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: kilogram(s)				
arithmetic mean (standard deviation)				
Baseline rest	2.7 (± 1.1)	2.8 (± 1.6)		
15 weeks rest	2.9 (± 1.3)	2.6 (± 1.2)		
Baseline follwing kicks	3.1 (± 1.5)	3.6 (± 2)		
15 weeks following kicks	3.5 (± 2.5)	2.9 (± 1.6)		
Baseline following 6MW	2.9 (± 1.2)	2.8 (± 1.5)		
15 weeks following 6MW	3 (± 1.3)	2.8 (± 1.3)		

Statistical analyses

Statistical analysis title	Between group difference in TwQ at rest
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.04
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[4] - Adjusting for baseline variable

Statistical analysis title	Between group difference in TwQ following kicks
Statistical analysis description: Adjusted for baseline variable	
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.8

Statistical analysis title	Between group difference in TwQ following 6MW
Statistical analysis description: Adjusted for baseline variable	
Comparison groups	Perindopril v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.7

Secondary: Between group difference in 6minute walking distance	
End point title	Between group difference in 6minute walking distance
End point description:	
End point type	Secondary
End point timeframe: Outcome measured at baseline and 15 weeks	

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: meters				
arithmetic mean (standard deviation)				
Baseline	336 (± 94)	330 (± 113)		
15 weeks	338 (± 104)	351 (± 111)		

Statistical analyses

Statistical analysis title	Between group difference in 6MW distance
Statistical analysis description: Adjusted for baseline variable	
Comparison groups	Perindopril v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.41
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29
upper limit	12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the study

Adverse event reporting additional description:

At each visit participants were asked about any adverse events and these were recorded in the Adverse event log

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Perindopril

Reporting group description:

Active arm receiving perindopril - adverse events occurring during the study

Reporting group title	Placebo

Reporting group description:

Placebo arm - adverse events occurring during the study

Serious adverse events	Perindopril	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall	Additional description: Fall associated with dizziness admitted to hospital		
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture ankle	Additional description: Had stroke - and fell fracturing ankle		
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ear and labyrinth disorders			
Menieres disease	Additional description: Dizziness and fall admitted to hospital		
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess	Additional description: Breast abscess		
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Perindopril	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 40 (90.00%)	38 / 40 (95.00%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	23 / 40 (57.50%)	27 / 40 (67.50%)	
occurrences (all)	156	95	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 40 (5.00%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			

subjects affected / exposed	4 / 40 (10.00%)	2 / 40 (5.00%)	
occurrences (all)	4	2	
Nasopharyngitis			
subjects affected / exposed	3 / 40 (7.50%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Rhinitis			
subjects affected / exposed	6 / 40 (15.00%)	7 / 40 (17.50%)	
occurrences (all)	6	7	
Musculoskeletal and connective tissue disorders			
Ligament injury	Additional description: Ligament sprain		
subjects affected / exposed	4 / 40 (10.00%)	0 / 40 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2013	Change to the protocol to add an extra inclusion criteria, namely to add that participants must have been assessed at a Medicine for the Elderly (MFE) clinic within the past 18 months. This is to ensure that all participants have received standard treatment currently recommended for their falls risk. This will ensure that they are not recruited under the misperception that participating in this study is a substitute for standard care.
26 March 2014	Amendment included several points: 1.A brief participant information sheet (BPIS) created 2.New Patient Information Sheet to replace the original Patient Information Sheet with a table of visits and tests added for ease of reference. 3. Heading on the poster, and PIS's altered to 'Falls Research Study'. 4.To send only the new brief PIS to potential participants initially. When these potential participants have contacted the study team to discuss the study further they will be sent a full Patient Information Sheet in advance of their screening visit to give them further details on the trial. 5. To distribute posters and brief PISs to community settings . 6. Additional information in Participant Information Sheet regarding contact details for participants if they become unwell during the study and advice on what to do if feeling unwell on study medications. 7. Following a redesign in services, people who fall were referred from different sources to a Falls Coordinator We therefore extended recruitment through this Falls service. 8. Use of 24 hour BP monitor in participants with high screening BP in case there was a white coat effect 9. Measure postural BP at home visits as per DMC suggestion 10. Extend recruitment to NHS Fife in addition to NHS Tayside
26 November 2014	Protocol: We have added that we wish to use the national SHARE registry as a potential source of recruitment - this database has Tayside and Fife volunteers who have given prior consent to be approached for clinical research projects which could be a useful source of recruitment. To the PIS: We added the new number for NHS 24 and put the NHS Tayside logo on the PIS. We have had a recent Data Monitoring Committee and they specifically requested that we give consideration to spelling out clearly in the PIS that if a participant experiences diarrhoea or vomiting they are to stop study meds immediately. Addition of new invitation letter to patients who have been seen on the wards as part of the Medicine for the Elderly (MFE) services.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Please note that issues with AE resolution reporting were identified by an MHRA inspection in July 2016, data were reanalyzed after correction of errors - hence date of final analysis is 26/10/16 and report posting is beyond a year from end of trial

Notes: