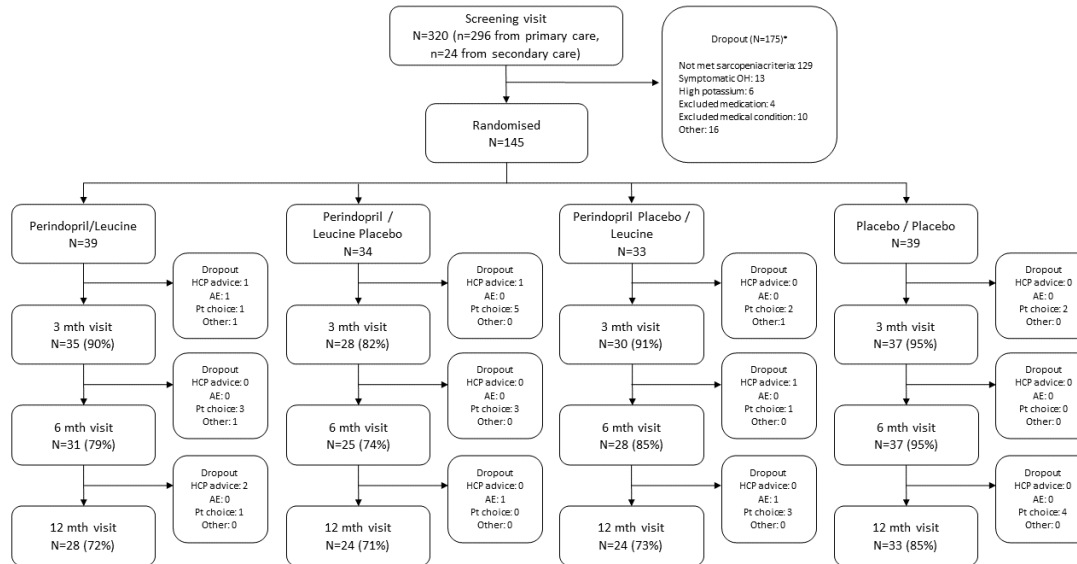


# Leucine and ACEi to treat sarcopenia (LACE)

Trial Registration: ISRCTN90094835

CONSORT flow diagram



**Table 1. Baseline characteristics**

	Perindopril and leucine (N=39)	Perindopril and leucine placebo (N=34)	Perindopril placebo and leucine (N=33)	Double placebo (N=39)	Perindopril (n=73)	No perindopril (n=72)	Leucine (n=72)	No leucine (n=73)	
Mean age (years) (SD)	78.1 (5.5)	79.5 (6.6)	78.6 (6.5)	79.0 (5.7)	78.7 (6.0)	78.8 (6.1)	78.3 (5.9)	79.3 (6.1)	
Female sex (%)	22 (56)	17 (50)	16 (48)	23 (59)	39 (53)	39 (54)	38 (53)	40 (55)	
Mean Charlson comorbidity score (SD)	0.8 (1.0)	0.6 (1.1)	0.6 (0.9)	0.7 (0.9)	0.7 (1.1)	0.7 (0.9)	0.7 (1.0)	0.7 (1.0)	
Mean SARC-F score (SD)	4.2 (1.3)	3.9 (1.4)	4.1 (1.3)	4.6 (1.7)	4.1 (1.3)	4.4 (1.5)	4.1 (1.3)	4.3 (1.6)	
<i>Comorbid disease:</i>									
Hypertension (%)	12 (31)	11 (32)	13 (39)	7 (18)	23 (32)	20 (28)	25 (35)	18 (25)	
Ischaemic heart disease (%)	4 (10)	5 (15)	1 (3)	4 (10)	9 (12)	5 (7)	5 (7)	9 (12)	
Osteoarthritis (%)	21 (54)	18 (53)	15 (45)	23 (59)	39 (53)	38 (53)	36 (50)	41 (56)	
Rheumatoid arthritis (%)	1 (3)	2 (6)	5 (15)	2 (5)	3 (4)	7 (10)	6 (8)	4 (5)	
Cataracts (%)	20 (51)	14 (41)	13 (39)	15 (38)	34 (47)	28 (39)	33 (46)	29 (40)	
Retinopathy (%)	2 (5)	1 (3)	1 (3)	1 (3)	3 (4)	2 (3)	3 (4)	2 (3)	
Registered blind (%)	1 (3)	1 (3)	0 (0)	0 (0)	2 (3)	0 (0)	1 (1)	1 (1)	
Anaemia (%)	10 (26)	5 (15)	4 (12)	4 (11)	15 (21)	8 (11)	14 (19)	9 (12)	
Peripheral neuropathy (%)	4 (10)	3 (9)	3 (9)	2 (5)	7 (10)	5 (7)	7 (10)	5 (7)	
Fragility fracture (%)	11 (28)	12 (35)	6 (18)	12 (31)	23 (32)	18 (25)	17 (24)	24 (33)	
Median number of medications [IQR]	4 [2,6]	5 [4,7]	5 [2.5,7]	5 [3,7]	5 [3,7]	5 [3,7]	5 [2,7]	5 [3,7]	
Mean weight (kg) (SD)	Men	80.4 (12.9)	81.6 (10.1)	80.3 (9.8)	81.5 (21.1)	81.0 (11.4)	80.9 (16.0)	80.4 (11.3)	81.6 (16.1)
	Women	66.4 (12.3)	63.4 (14.2)	66.1 (7.9)	64.1 (11.3)	65.1 (13.1)	64.9 (10.0)	66.3 (10.5)	63.8 (12.5)
Mean Body mass index (kg/m <sup>2</sup> ) (SD)					26.7 (3.7)	27.0 (4.3)	27.1 (3.3)	26.5 (4.5)	
Mean estimated GFR (ml/min/1.73m <sup>2</sup> ) (SD)	80 (21)	81 (21)	80 (18)	82 (22)	80 (20)	81 (21)	80 (19)	82 (21)	
Mean serum albumin (g/L) (SD)	40 (4)	40 (4)	41 (4)	40 (4)	40 (4)	40 (4)	40 (4)	40 (4)	
Mean systolic blood pressure (mmHg) (SD)	146 (20)	144 (20)	143 (18)	144 (16)	145 (20)	144 (17)	145 (19)	144 (18)	
Mean diastolic blood pressure (mmHg) (SD)	80 (10)	77 (10)	77 (10)	77 (11)	79 (10)	77 (10)	79 (10)	77 (10)	
Mean SPPB (SD)	7.3 (2.1)	6.8 (2.5)	6.7 (2.2)	7.1 (2.6)	7.1 (2.3)	6.9 (2.4)	7.0 (2.1)	7.0 (2.5)	
Mean appendicular muscle mass by DXA (kg/m <sup>2</sup> ) (SD)	Men	7.34 (0.84)	7.19 (0.67)	7.07 (2.02)	7.34 (1.06)	7.26 (0.75)	7.21 (1.53)	7.26 (0.87)	7.21 (1.61)
	Women	5.69 (0.58)	5.88 (0.81)	5.82 (0.56)	5.60 (0.72)	5.77 (0.68)	5.75 (0.57)	5.72 (0.76)	5.69 (0.66)
Mean maximal handgrip strength (kg) (SD)	Men	21.8 (6.7)	24.1 (5.8)	22.8 (6.4)	23.6 (4.9)	23.0 (6.3)	22.3 (6.4)	23.9 (5.3)	23.2 (5.6)
	Women	14.1 (3.6)	14.6 (4.4)	13.2 (4.3)	13.1 (3.5)	14.3 (3.9)	13.7 (3.9)	13.7 (3.9)	13.1 (3.8)

Mean maximal quadriceps strength (kg) (SD)	Men	15.0 (8.0)	15.4 (5.6)	18.8 (8.8)	15.6 (5.6)	15.2 (6.9)	16.8 (8.5)	15.5 (5.5)	17.2 (7.4)
	Women	9.7 (4.9)	11.5 (5.4)	9.6 (3.7)	11.4 (5.3)	10.5 (5.1)	9.7 (4.4)	11.5 (5.2)	10.6 (4.7)
Mean six-minute walk distance (m) (SD)		307 (104)	288 (115)	315 (120)	311 (105)	298 (109)	313 (111)	310 (111)	301 (110)
Mean 4 metre walk speed (m/s) (SD)		0.73 (0.21)	0.73 (0.22)	0.75 (0.25)	0.77 (0.26)	0.73 (0.21)	0.76 (0.25)	0.74 (0.23)	0.75 (0.24)
Median chair rise time (s) [IQR]		21.2 [17.0, 26.8]	23.7 [18.1, 27.6]	21.9 [17.5, 27.7]	20.9 [15.4, 28.7]	22.0 [18.0, 27.4]	21.9 [16.9, 27.9]	21.6 [17.5, 26.9]	22.9 [16.3, 27.9]
Mean EQ5D-3L (SD)		0.77 (0.11)	0.78 (0.11)	0.78 (0.11)	0.77 (0.09)	0.77 (0.11)	0.77 (0.10)	0.77 (0.11)	0.78 (0.10)
Mean EQ5D thermometer (SD)		71 (19)	67 (14)	76 (14)	73 (12)	69 (17)	74 (13)	73 (17)	70 (13)
Mean Nottingham EADL (SD)		56.0 (7.9)	54.6 (10.2)	54.5 (11.9)	54.2 (10.5)	55.3 (9.0)	54.3 (11.1)	55.3 (9.9)	54.4 (10.3)
Mean T-score at hip (SD)		-1.2 (1.5)	-1.4 (1.3)	-1.2 (1.3)	-1.5 (0.9)	-1.3 (1.4)	-1.4 (1.1)	-1.2 (1.4)	-1.4 (1.1)
Mean total protein intake per day (g/kg body weight) (SD)		1.11 (0.60)	1.37 (1.36)	1.01 (0.33)	1.12 (0.33)	1.23 (1.01)	1.07 (0.33)	1.05 (0.50)	1.24 (0.96)

SPPB: Short Physical Performance Battery. EQ5D: EuroQol 5 dimension quality of life score. DXA: Dual energy X-ray Absorptiometry

**Table 2. Primary outcome for perindopril vs perindopril placebo analysis**

	Perindopril	No perindopril	Unadjusted treatment effect (95% CI)	p	Adjusted treatment effect (95% CI)	p
Baseline SPPB (N, SD)	7.1 (73, 2.3)	6.9 (72, 2.4)	0.0 (-0.7, 0.8)	0.91	-0.1 (-1.2, 1.0)	0.89
6 month SPPB (N, SD)	7.3 (56, 2.5)	7.0 (65, 2.7)				
12 month SPPB (N, SD)	7.2 (52, 2.9)	7.6 (57, 2.6)				
<i>Sensitivity analyses (12 months only)</i>						
12 month SPPB (N, SD)	7.2 (52, 2.9)	7.6 (57, 2.6)	-0.6 (-1.4, 0.2)	0.12	0.5 (-2.6, 3.6)	0.73
12 month SPPB, worst-case* (N, SD)	5.1 (73, 4.1)	6.0 (72, 3.9)	-1.0 (-2.2, 0.2)	0.10	0.2 (-2.4, 2.8)	0.87

SPPB: Short Physical Performance Battery

\*Imputing SPPB=0 for all missing data

Adjusted analyses adjusted for age, sex, SPPB, Charlson Comorbidity Score and baseline handgrip strength

**Table 3. Primary outcome for leucine vs leucine placebo analysis**

	Leucine	No leucine	Unadjusted treatment effect (95% CI)	p	Adjusted treatment effect (95% CI)	p
Baseline SPPB (N, SD)	7.0 (72, 2.1)	7.0 (73, 2.5)	0.1 (-0.7, 0.8)	0.83	0.1 (-1.0, 1.1)	0.90
6 month SPPB (N, SD)	7.2 (59, 2.6)	7.1 (62, 2.6)				
12 month SPPB (N, SD)	7.3 (52, 2.7)	7.5 (57, 2.8)				
Sensitivity analysis (12 months only)						
12 month SPPB (N, SD)	7.3 (52, 2.7)	7.5 (57, 2.8)	0.0 (-0.8, 0.8)	0.98	-0.5 (-3.1, 2.0)	0.66
12 month SPPB, worst-case* (N, SD)	5.3 (72, 4.0)	5.8 (73, 4.0)	-0.6 (-1.8, 0.6)	0.34	0.6 (-1.9, 3.1)	0.60

SPPB: Short Physical Performance Battery

\*Imputing SPPB=0 for all missing data

Adjusted analyses adjusted for age, sex, SPPB, Charlson Comorbidity Score and baseline handgrip strength

**Table 4. Secondary outcomes analysis**

Outcome	Perindopril vs no perindopril		Leucine vs no leucine	
	Adjusted treatment effect (95% CI)	p	Adjusted treatment effect (95% CI)	p
Muscle mass	-0.4 (-1.1, 0.3)	0.27	-0.25 (-0.95, 0.44)	0.47
Grip strength	0.2 (-0.9, 1.2)	0.74	-0.3 (-1.2, 0.7)	0.55
Quadriceps strength (kg)	0.6 (-3.0, 4.1)	0.75	-1.0 (-4.4, 2.4)	0.55
Six min walk (m)	-32 (-75, 12)	0.15	17 (-25, 59)	0.43
Gait speed (m/s)	0.01 (-0.18, 0.19)	0.96	0.01 (-0.18, 0.19)	0.96
Chair stand time (s)	-1.7 (-8.7, 5.3)	0.64	-3.1 (-9.5, 3.3)	0.34
NEADL	-1.6 (-7.4, 4.2)	0.58	-2.0 (-7.4, 3.5)	0.48
EQ5D main	-0.04 (-0.10, 0.02)	0.23	-0.06 (-0.11, -0.01)	0.03
EQ5D thermometer	-12 (-21, -3)	0.01	-3 (-12, 6)	0.53
Hip T score	0.03 (-0.74, 0.81)	0.93	0.17 (-0.59, 0.93)	0.66
Median HOMA IR	-1.8 (-5.1, 1.4)	0.26	-1.3 (-4.5, 1.9)	0.42

NEADL: Nottingham extended activities of daily living. EQ5D: EuroQoL 5D score.

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

Analyses adjusted for age, sex, SPPB, Charlson Comorbidity Score and baseline handgrip strength

**Table 5. Number of participants with adverse events by System Order Class (SOC)**

	Perindopril and leucine	Perindopril and leucine placebo	Perindopril placebo and leucine	Double placebo
Number with at least one adverse event (%)	38 (97)	31 (91)	29 (88)	33 (85)
Number of adverse events:	117	101	70	95
Blood and lymphatic system disorders	0	2	2	0
Cardiac disorders	5	1	2	5
Eye disorders	2	1	2	3
Gastrointestinal disorders	20	17	12	14
General disorders and administration site conditions	3	6	2	4
Hepatobiliary disorders	0	0	1	0
Infections and infestations	20	20	14	24
Injury, poisoning and procedural complications	13	9	6	6
Investigations	2	0	1	1
Metabolism and nutrition disorders	7	1	1	2
Musculoskeletal and connective tissue disorders	12	9	8	11
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	5	1	3
Nervous system disorders	15	11	9	8
Psychiatric disorders	1	5	1	0
Renal and urinary disorders	2	3	0	1

Reproductive system and breast disorders	0	2	0	0
Respiratory, thoracic and mediastinal disorders	6	4	3	6
Skin and subcutaneous tissue disorders	5	4	1	7
Vascular disorders	4	1	4	0



**Table 6. Key adverse outcomes of interest**

	Perindopril (n=73)	No perindopril (n=72)	Leucine (n=72)	No Leucine (n=73)
Deaths (all) (%)	1 (1)	0 (0)	0 (0)	1 (1)
Fragility fractures (distal radius, vertebra or neck of femur) (%)	3 (4)	1 (1)	1 (1)	3 (1)
Number with at least one fall (%)	30 (41)	37 (51)	34 (47)	30 (41)
Number of falls	121	132	121	132
Falls rate (per year) (95% CI)	2.0 (1.1, 3.0)	2.8 (0.6, 5.1)	1.9 (0.9, 2.9)	2.9 (0.8, 5.0)