**Effect of Perindopril or Leucine on physical performance in older people with sarcopenia: the LACE randomised controlled trial**

**Supplementary information**

**Supplementary Table 1: Body mass index and sex-specific screening cut offs for bioimpedance derived appendicular muscle mass:**

|  |  |
| --- | --- |
|  | Muscle mass cutoffs |
|  | Men | Women |
| Body mass index <18.5 kg/m2 | <=6.02 kg/m2 | <=5.25 kg/m2 |
| 18.5 – 24.9 | <=7.14 | <=5.70 |
| 25.0 – 29.9 | <=8.00 | <=6.19 |
| >=30 kg/m2 | <=8.77 | <=6.72 |

**Supplementary Table 2: Exclusion criteria**

|  |
| --- |
| a) *Contraindications or existing indications to therapies or placebo* |
| -Known clinical diagnosis of chronic heart failure (by European Society of Cardiology criteria) |
| -Confirmed LV systolic dysfunction on any imaging modality |
| -Known aortic stenosis (peak gradient >30mmHg) |
| -Systolic BP<90 mmHg (supine) |
| -Dizziness on standing associated with a postural drop of >20/10mmHg (asymptomatic orthostatic hypotension will not be a contraindication) |
| -Serum Creatinine >170 umol/L or eGFR<30ml/min by MDRD4 calculation |
| -K>5.0 mmol/L; Na<130 mmol/L |
| -Using ACEi, Angiotensin receptor blocker, aldosterone blocker or leucine already |
| -Previous adverse reaction to ACEi or leucine |
| -Current use of oral NSAIDs (aspirin is permitted, as are topical NSAIDs) |
| -Current use of potassium supplements, aliskiren, spironolactone or other potassium-sparing diuretics |
| -Hereditary or idiopathic angioedema |
| -Lactose intolerance |
|  |
| b) *Contraindications to consent or undertaking study outcomes* |
| -Implantable cardioverter defibrillator or pacemaker with atrial sensing lead (pacemakers with ventricular sensing lead only are allowed) |
| -Peripheral oedema present above knee level |
| -Unable to mobilise without human assistance (walking aids allowed) |
| -Unable to give written informed consent |
| -Currently enrolled in another intervention research study, or less than 30 days since completing another intervention research study. Concomitant enrolment in observational studies is permitted. |
|  |
| c) *Overlap with other myopathic conditions or important confounders* |
| -Currently enrolled in a time-limited exercise-based rehabilitation programme |
| -Any progressive neurological or malignant condition with life expectancy <6 months  |
| -Severe COPD (GOLD stage IV) |
| -Known myositis or other established myopathy |
| -Self-reported weight loss of >10% in last 6 months (to exclude significant cachexia) |
| -Known uncontrolled thyrotoxicosis |
| -7.5mg/day or greater prednisolone use (or equivalent) |

**Supplementary Table 3: List of all secondary outcomes**

|  |  |  |
| --- | --- | --- |
| Outcome | Measurement details | Measurement timepoints |
| Maximum grip strength | Jamar dynamometer; best of three [1] | 0, 6 and 12 months |
| Maximum Quadriceps strength | Lafayette dynamometer; best of three [2] | 0, 6 and 12 months |
| Six-minute walk distance | 25m course with standardised encouragement [3] | 0, 6 and 12 months |
| Four metre walk speed | Done as part of Short Physical Performance Battery [4] | 0, 6 and 12 months |
| Five times sit to stand test | Done as part of Short Physical Performance Battery [5] | 0, 6 and 12 months |
| Instrumental Activities of Daily Living | Nottingham extended ADL questionnaire [6] | 0, 6 and 12 months |
| Health-related quality of life | EuroQoL EQ5D-3L questionnaire [7] | 0, 6 and 12 months |
| Appendicular muscle mass / height squared | Dual energy X-ray absorptiometry (DXA) | 0 and 12 months |
| Neck of femur bone mineral density | Dual energy X-ray absorptiometry (DXA) | 0 and 12 months |
| Insulin resistance | Homeostatic measure of Insulin Resistance (HOMA-IR) [8] | 0, 3 and 12 months |

**Supplementary Table 4. Adverse events by System Order Class**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 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 |

**Supplementary Table 5: Trials included in meta-analysis**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Country | N | Mean age | % women | Inclusion criteria | Intervention | Comparator | Primary outcome | Secondary outcomes | Duration of treatment |
| **ACEi/ARB trials** |
| Leonetti 1991 [9] | Italy | 36 | 66 | 72 | Older people with hypertension | Captopril 25-50mg twice daily | Placebo | Bicycle endurance exercise time | None | 2 months |
| Gerdts 2006 [10] | Norway | 51 | 68 | 49 | 55-80 years with hypertension and LVH on ECG | Losartan 50-100mg once daily + HCTZ if required | Atenolol 50-100mg once daily + HCTZ if required | VO2max | Maximum load (W) | 1 year |
| Sumukadas 2007 [11] | Scotland | 130 | 79 | 71 | 65 and over with impairment of ADLs | Perindopril 2-4mg once daily | Placebo | 6MWD | TUAG10-rep STS | 20 weeks |
| Bunout 2009 [12] | Chile | 120 | 75 | 76 | 70 and over with stage I hypertension | Enalapril 10-20mg once daily + HCTZ if required | Nifedipine slow-release 20mg once daily | 12MWD | Handgrip strengthQuadriceps strengthSPPBTUAG | 9 months |
| Cesari 2010 [13] | USA | 294 | 66 | 42 | 55 and over with elevated cardiovascular risk | Fosinopril 20-40mg once daily | Placebo | Rescaled SPPB | Handgrip strength | 6 months |
| Sumukadas 2013 [14] | Scotland | 170 | 76 | 42 | 65 and over with SPPB ≤ 10 | Perindopril 2-4mg once daily + mixed modality exercise training | Placebo + mixed modality exercise training | 6MWD | SPPBQuadriceps strengthHandgrip strength | 20 weeks |
| Sumukadas 2018 [15] | Scotland | 80 | 78 | 75 | 65 and over with >1 self-reported fall in last 12 months | Perindopril 2-4mg once daily | Placebo  | Postural sway | 6MWDQuadriceps strength | 15 weeks |
| Heisterberg 2018 [16] | Denmark | 71 | 72 | 0 | Healthy, untrained males without hypertension or other disease | Losartan 50-100mg once daily + resistance training | Placebo + resistance training | Quadriceps mass | Isometric Quadriceps strengthIsokinetic quadriceps strength | 16 weeks |
| **Leucine trials** |
| Verhoeven 2009 [17] | Netherlands | 30 | 71 | 0 | Healthy older men | Leucine 2.5g three times a day | Placebo | Leg press strength | Fat free massLeg extension strengthInsulin resistance | 12 weeks |
| Leenders 2011 [18] | Netherlands | 60 | 71 | 0 | Older men with type 2 diabetes mellitus | Leucine 2.5g three times a day | Placebo | Leg press strength | Fat free massLeg extension strengthInsulin resistance | 6 months |
| Ispoglou 2016 [19] | England | 25 | 72 | 56 | Healthy non-smokers aged 65-75 | Essential amino acid mix with 0.08g/kg/day leucine | Essential amino acid mix with 0.04 g/kg/day leucine | Lean body mass | 6MWDChair stand testArm curl testHandgrip strength | 12 weeks |
| Martinez-Arnau 2020 [20] | Spain | 50 | 79 | 67 | Nursing home residents aged 65 and over | Leucine 3g twice a day | Placebo | Handgrip strength | Walking timeWhole body muscle massCalf and arm circumferencePeak flow | 13 weeks |

SPPB: Short Physical Performance Battery. TUAG: Timed Up And Go test. 6MWD: Six minute walk distances. 12MWD: Twelve minute walk distance. VO2max: Maximal oxygen uptake. STS: Sit to stand test.

**Supplementary Figure 1: Flowchart for perindopril uptitration**



**Supplementary Figure 2:** **Change in lying blood pressure and postural blood pressure drop for perindopril vs placebo analysis**

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**Supplementary Figure 3. Meta-analysis Forest plots**

1. **Effect of ACEi/ARB on Short Physical Performance Battery**



1. **Effect of ACEi/ARB on six-minute walk distance (in metres)**



1. **Effect of ACEi/ARB on handgrip strength (in kg)**



1. **Effect of ACEi/ARB on quadriceps strength (in kg)**



1. **Effect of Leucine on six-minute walk distance (in metres)**



1. **Effect of Leucine on walk speed (in m/s)**



1. **Effect of Leucine on handgrip strength (in kg)**



1. **Effect of Leucine on quadriceps strength (in kg)**



1. **Effect of Leucine on lean body mass (z scores)**



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