

## **Blood pressure lowering in patients with central hypertension: a randomized clinical trial**

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## Methods

**Inclusion criteria.** Included: being aged 18 – 70 years on stable antihypertensive therapy (at least one month); taking at least one, but no more than three, antihypertensive drugs to lower blood pressure (BP) (to rule out complicated or resistant hypertension which may require special clinical attention beyond the study protocol); seated cuff BP <140/90 mmHg (controlled cuff BP); seated central systolic BP (SBP) greater than or equal to 0.5SD above age- and gender-specific normal values (raised central BP; see below).

**Exclusion criteria.** Included: seated cuff BP  $\geq$ 140/90 mmHg (uncontrolled cuff BP); seated cuff BP <140/90 mmHg but central SBP less than 0.5SD above age- and gender-specific normal values as per eTable 1 (controlled central BP). For example, a 55 year old male with central SBP of 119 mmHg or less); women who are pregnant, breastfeeding or of child bearing age with intending pregnancy; concomitant therapy with both an angiotensin converting enzyme inhibitor and an angiotensin receptor blocker (due to risk of hyperkalaemia); therapy with digoxin or lithium or nondepolarizing skeletal muscle relaxants; a clinical history of CVD which may affect estimation of central BP or complicate therapeutic decisions. This included; established coronary artery disease, coronary artery bypass graft surgery, aortic valve stenosis (gradient >20 mmHg), systolic heart failure or ejection fraction <50% or other serious cardiovascular event within 6 months of enrolment; chronic use of sex hormone therapy or non-steroidal anti-inflammatory drugs; using any aldosterone inhibitor (eplerenone, spironolactone) within 30 days of enrolment; contraindication to spironolactone including anuria, acute renal insufficiency, significant impairment of renal excretory function (creatinine clearance  $\leq$ 50 mL/min [Cockcroft-Gault formula]) or hyperkalemia (plasma potassium >5.0 mmol/l at initiation) or; using potassium supplements or potassium-sparing diuretics (e.g. amiloride or triamterene).

**Screening for BP eligibility.** Central BP and cuff BP were recorded with SphygmoCor XCEL (AtCor Medical, Sydney, NSW). Radial applanation tonometry was also used to estimate central BP<sup>1-3</sup> (SphygmoCor 8.1, AtCor Medical, Sydney, NSW). For eligibility assessment only, the radial pressure waveform was calibrated using two methods; 1) with average cuff SBP and diastolic BP (DBP) from the XCEL measurements; and 2) from the average mean arterial pressure (calculated by cuff DBP + 0.4\* cuff pulse pressure) and DBP from the XCEL measurements. All measures were taken with a correct sized cuff, feet flat on floor, back supported and without talking (as per recommendations).<sup>4</sup> After five minutes rest, measures were acquired in duplicate using SphygmoCor 8.1, immediately after the BP recordings with SphygmoCor XCEL. A second and a third set of duplicate measures (one minute apart) were taken after 10 and after 15 minutes rest, and the average of any two consecutive measurements from either SphygmoCor XCEL or SphygmoCor 8.1 were used to assess eligibility using the calibration methods mentioned above.

**Criteria for raised central BP.** Values denoting raised central BP were derived from the largest normative central BP dataset published at the time the trial was designed and recruitment had commenced.<sup>5</sup> At trial initiation, criteria for raised central BP was defined as central SBP  $\geq$ 1.0 SD above age- and sex-specific normal values. However, based on this threshold, only 12 from the first 120 people screened were eligible. To enable trial completion but still ensuring that participants had raised central SBP relative to cuff SBP, the central SBP threshold was reduced to  $\geq$ 0.5 SD above age- and sex-specific normal values. For example, a 55 year-old man with central SBP of  $\geq$ 120 mmHg was eligible if cuff BP <140/90 mmHg (see Table S1). Despite this relaxation in criteria, failure to have raised central BP was the main reason for exclusion of participants at screening. This significantly

extended the recruitment phase and resulted in insufficient resourcing to deal with interim, secondary data. Furthermore, since the study was commenced, age- and sex-specific central BP reference values have been reported in a large meta-analysis of cohorts.<sup>6</sup> The central SBP thresholds from this larger study were not the same as the thresholds used to determine criteria for inclusion in this study. Had central SBP thresholds been based on the meta-analysis data, this could have influenced the characteristics of people ultimately recruited.

**Monitoring of potassium levels.** In all study participants, plasma potassium was measured at baseline, 12 and 24 months. For those randomized to intervention, potassium was also measured 7 days after commencing study medication as well as 1, 3, 6, 12 and 18 months. In the event of hypokalaemia (plasma potassium <3.5 mmol/l), participants were advised to increase potassium levels through diet. A repeat blood sample was taken within two weeks, and if hypokalaemia persisted, the participant's doctor was notified for appropriate follow up. Participants were withdrawn if they developed serious hyperkalaemia, defined as a single plasma potassium concentration >5.5 mmol/l. Participants with potassium levels between 5.0 and 5.5 mmol/l (confirmed by urgent repeat sampling) had spironolactone dose halved to 12.5 mg and repeat blood samples were taken one week later. If potassium resolved to <5.0 mmol/l then they continued and had a repeat sample at the next scheduled visit. If potassium maintained  $\geq 5.0$  mmol/l despite being on half dose, then the patient was withdrawn. Serious adverse events included participant withdrawal due to side effects associated with the medication (e.g., gynaecomastia).

**Monitoring of BP control.** Participants were enrolled on the basis of controlled clinic cuff BP. However, in some instances increased 24-hour ambulatory BP (masked hypertension) may be detected, which could indicate poor BP control that may confer additional cardiovascular risk related to BP. To ensure appropriate management of all participants BP control was confirmed using 7-day home BP recordings as well as 24-hour ambulatory BP. In cases where both 7-day home BP and 24-hour ambulatory BP were raised (>135/85 mmHg) despite acceptable clinic BP (<140/90 mmHg), a letter was sent to the participant's general practitioner recommending to uptitrate antihypertensive medication without altering spironolactone dose among intervention participants.

With regard to timing of BP measures, clinic, 7-day home and 24-ABPM were measured at baseline, 6, 12, 18 and 24 months in all participants. Additional measures of clinic cuff and central BP were recorded in all participants at months 1 and 3 to see if any major falls in clinic cuff BP had occurred (defined as cuff SBP <110 mmHg with concomitant symptoms related to hypotension such as dizziness, syncope, blurred vision, nausea). Participants experiencing such a fall at 1 or 3 months had a letter sent to their general practitioner recommending to downtitrate antihypertensive medications other than spironolactone.

**Monitoring of estimated glomerular filtration rate (eGFR).** For patients randomized to receive spironolactone, eGFR was monitored at each visit (baseline, week 1 and at 1, 3, 6, 18 and 24 months). Participants were withdrawn if eGFR dropped below 30 mL/min/1.73m<sup>2</sup>. For usual care participants, eGFR was measured at baseline, 12 and 24 months.

**Concomitant medications.** Medications were checked at each visit for all study participants. If intervention participants were prescribed with medications known to interact with spironolactone by their general practitioner during the course of the study, they were asked to return for an additional blood sample within a week after the initiation of treatment. The blood results were reviewed by the study's doctor and any decisions regarding changes in the

medications or withdrawal from the study were made in collaboration with the patient's general practitioner according to protocol.

**Cardiac magnetic resonance (CMR) imaging operator reliability.** One trained expert performed all CMR image analysis measures for the study. Performance of this operator was compared with another independent expert between both CMR scanners used in the study. Analysis was conducted on images from 30 randomly selected participants in which the two operators performed LV mass measurements blinded to each other's readings. The mean difference  $\pm$  standard deviation and intra-class correlation coefficient (Two-Way Mixed Model with 95% confidence intervals) for LV mass between operators using the different devices were  $0.0 \pm 20$  g and 0.90 (95%CI 0.79 – 0.95), respectively.

**Table S1.** Age- and gender-specific central SBP cut off values for inclusion into trial (from Sharman et al<sup>7</sup>)

Age (years)		<20	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70 – 79
Target central SBP (mmHg)	Male	≥107	≥109	≥114	≥118	≥120	≥122	≥122
	Female	≥103	≥106	≥111	≥115	≥121	≥123	≥124

Data from the largest normative central BP dataset published to date (n=4002).<sup>5</sup>

**Table S2.** Regression analyses for the associations between the change from baseline to 24-months in left ventricular mass index and the change in cuff and central systolic blood pressure (SBP)

Variable	Group	Adjusted estimates $\beta$ (95% CI)
Seated clinic cuff SBP (mmHg)	Control	0.05 (-0.06 – 0.15)
	Intervention	0.14 (0.04 – 0.25)
Seated clinic C1 central SBP (mmHg)	Control	0.05 (-0.07 – 0.17)
	Intervention	0.14 (0.02 – 0.26)
24-hour cuff SBP (mmHg)	Control	0.10 (-0.06 – 0.26)
	Intervention	0.17 (0.02 – 0.31)
24-hour C1 central SBP (mmHg)	Control	0.09 (-0.09 – 0.27)
	Intervention	0.16 (0.01 – 0.32)
24-hour C2 central SBP (mmHg)	Control	0.08 (-0.08 – 0.23)
	Intervention	0.19 (0.05 – 0.33)
Daytime cuff SBP (mmHg)	Control	0.09 (-0.07 – 0.25)
	Intervention	0.16 (0.02 – 0.30)
Daytime C1 central SBP (mmHg)	Control	0.08 (-0.10 – 0.25)
	Intervention	0.17 (0.02 – 0.31)
Daytime C2 central SBP (mmHg)	Control	0.03 (-0.11 – 0.18)
	Intervention	0.19 (0.05 – 0.33)
Nighttime cuff SBP (mmHg)	Control	0.07 (-0.04 – 0.18)
	Intervention	0.10 (-0.04 – 0.24)
Nighttime C1 central SBP (mmHg)	Control	0.07 (-0.05 – 0.19)
	Intervention	0.09 (-0.06 – 0.23)
Nighttime C2 central SBP (mmHg)	Control	0.07 (-0.02 – 0.17)
	Intervention	0.10 (-0.00 – 0.21)
7-day home cuff SBP (mmHg)	Control	0.25 (0.06 – 0.45)
	Intervention	0.07 (-0.09 – 0.23)
7-day home C1 central SBP (mmHg)	Control	0.24 (0.02 – 0.45)
	Intervention	0.07 (-0.11 – 0.25)
7-day home C2 central SBP (mmHg)	Control	0.20 (0.03 – 0.37)
	Intervention	0.11 (-0.04 – 0.25)

Data analysis corrected for baseline age, sex, diabetes and change in antihypertensive medications. C1, calibration with cuff SBP and diastolic blood pressure (DBP); C2, calibration with mean arterial pressure and DBP using the Mobil-O-Graph device. The  $\beta$

estimate refers to the change from baseline to 24-months in left ventricular mass index ( $\text{g}/\text{m}^2$ ) for each 1 mmHg change from baseline to 24-months in each of the listed SBP measures.

**Table S3.** Regression analyses for the associations between the change from baseline to 24-months in aortic stiffness and the change in cuff and central systolic blood pressure (SBP)

Variable	Group	Adjusted estimates	
		$\beta$ (95% CI)	R <sup>2</sup>
Seated clinic cuff SBP (mmHg)	Control	0.05 (0.03 – 0.06)	0.185
	Intervention	0.03 (0.01 – 0.05)	0.082
Seated clinic C1 central SBP (mmHg)	Control	0.05 (0.03 – 0.07)	0.164
	Intervention	0.04 (0.02 – 0.06)	0.105
24-hour cuff SBP (mmHg)	Control	0.04 (0.01 – 0.07)	0.040
	Intervention	0.03 (0.01 – 0.05)	0.076
24-hour C1 central SBP (mmHg)	Control	0.04 (0.01 – 0.07)	0.035
	Intervention	0.02 (0.00 – 0.05)	0.058
24-hour C2 central SBP (mmHg)	Control	0.03 (-0.00 – 0.05)	0.012
	Intervention	0.02 (-0.00 – 0.04)	0.040
Daytime cuff SBP (mmHg)	Control	0.04 (0.01 – 0.07)	0.045
	Intervention	0.02 (0.00 – 0.04)	0.056
Daytime C1 central SBP (mmHg)	Control	0.04 (0.01 – 0.07)	0.040
	Intervention	0.02 (-0.00 – 0.04)	0.048
Daytime C2 central SBP (mmHg)	Control	0.02 (-0.01 – 0.05)	0.004
	Intervention	0.02 (-0.00 – 0.04)	0.048
Nighttime cuff SBP (mmHg)	Control	0.02 (0.00 – 0.05)	0.024



	Intervention	0.03 (0.01 – 0.05)	0.083
Nighttime C1 central SBP (mmHg)	Control	0.03 (0.00 – 0.05)	0.024
	Intervention	0.02 (0.00 – 0.04)	0.058
Nighttime C2 central SBP (mmHg)	Control	0.02 (0.00 – 0.04)	0.035
	Intervention	0.01 (-0.00 – 0.03)	0.038
7-day home cuff SBP (mmHg)	Control	0.04 (0.01 – 0.08)	0.026
	Intervention	0.02 (-0.01 – 0.04)	0.012
7-day home C1 central SBP (mmHg)	Control	0.05 (0.01 – 0.09)	0.024
	Intervention	0.02 (-0.01 – 0.04)	0.010
7-day home C2 central SBP (mmHg)	Control	0.04 (0.01 – 0.07)	0.027
	Intervention	0.02 (-0.00 – 0.04)	0.024

Data analysis corrected for baseline age, sex, diabetes and change in antihypertensive medications. C1, calibration with cuff SBP and diastolic blood pressure (DBP); C2, calibration with mean arterial pressure and DBP using the Mobil-O-Graph device. The  $\beta$  estimate refers to the change in aortic stiffness (m/s) for each 1 mmHg change in SBP.

**Table S4.** Correlation coefficients for the associations between left ventricular (LV) mass index, cuff and central systolic blood pressure (SBP) variables at baseline

	<b>LV mass index</b>	<b>Seated clinic cuff SBP</b>	<b>24-hour cuff SBP</b>	<b>Daytime cuff SBP</b>	<b>Nighttime cuff SBP</b>	<b>7-day home cuff SBP</b>
LV mass index		0.10	0.36	0.35	0.30	0.21
Seated clinic C1 central SBP	0.04	0.96				
24-hour C1 central SBP	0.34		0.95			
24-hour C2 central SBP	0.41		0.88			
Daytime C1 central SBP	0.33			0.95		
Daytime C2 central SBP	0.39			0.89		
Nighttime C1 central SBP	0.29				0.96	
Nighttime C2 central SBP	0.36				0.83	
7-day home C1 central SBP	0.21					0.95
7-day home C2 central SBP	0.26					0.83

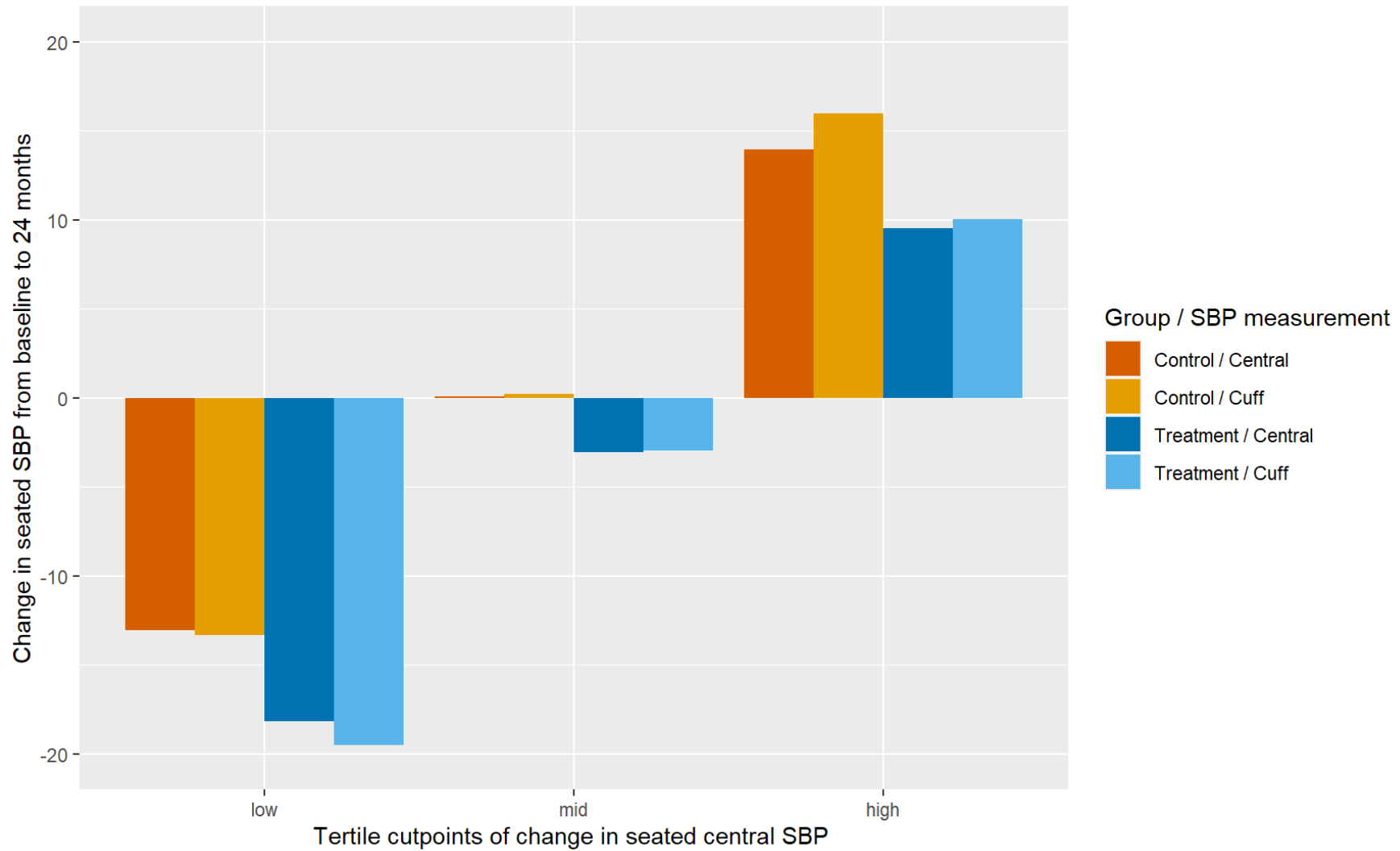
C1, calibration with cuff SBP and diastolic blood pressure; C2, calibration with mean arterial pressure and diastolic blood pressure using the Mobil-O-Graph device.

**Table S5.** Adverse events (AE) and serious adverse events (SAE) reported by study participants

Adverse events	Control (n)		Intervention (n)	
	AE	SAE	AE	SAE
Cardiovascular				
Expected	1	-	1	-
Unexpected	5	3	-	6
Dizziness/hypotension				
Expected	2	-	35	-
Unexpected	-	-	-	-
Gastrointestinal				
Expected	-	-	6	-
Unexpected	6	4	8	5
Musculoskeletal				
Expected	-	-	12	-
Unexpected	9	5	12	12
Neoplasm				
Expected	-	-	-	-
Unexpected	-	8	-	2
Neurological				
Expected	-	-	3	-
Unexpected	2	3	6	5
Renal				
Expected	-	-	2	-
Unexpected	1	1	9	-
Other				
Expected	1	-	29	-
Unexpected	15	15	34	5
Total adverse events				
Expected	4	-	88	-
Unexpected	38	39	69	35

AE and SAE data were recorded by asking participants at each study visit. Expectedness was based on whether an AE or SAE may be anticipated to occur based on current knowledge related to the study medication. ‘Other’ refers to all other reported AEs not otherwise related to the listed categories e.g. genitourinary infection, lethargy, dermatitis.

**Figure S1.** Bar plot for the between-group changes in cuff systolic BP and central systolic BP across tertiles of change in seated central systolic BP. Data are the uncorrected changes from baseline to 24-months. Changes are similar for cuff and central systolic BP across tertiles.



## References

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