Identifying and treating high blood pressure in men under 55 years with grade 1 hypertension: the TREAT CASP study and RCT

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Scientific summary

The TREAT CASP study and RCT

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Scientific summary

Background

High blood pressure is a major risk factor for cardiovascular-related morbidity and mortality. A substantial body of evidence demonstrates the benefit of blood pressure lowering in reducing risk and premature morbidity and mortality. Blood pressure is routinely measured over the brachial artery. However, the pressure pulse is amplified to a variable degree from the aortic root to the brachial artery, particularly systolic blood pressure. Thus, brachial systolic blood pressure is usually higher than central aortic systolic pressure (also known as CASP) and the two may differ markedly, especially in younger people in whom amplification is higher and more variable than in older people. Consequently, younger patients with similar brachial systolic blood pressure levels may show considerable differences in central aortic systolic pressure. This may have clinical consequences for young people with mildly elevated brachial blood pressure in whom central aortic systolic pressure may or may not be elevated. In extreme cases, elevated brachial blood pressure with a normal central aortic systolic pressure has been termed 'spurious systolic hypertension of youth'. Whether this is benign or associated with elevated risk remains controversial.

Central aortic systolic pressure can be derived non-invasively by mathematical computation using an *n*-point moving average acting as a simple low-pass filter. In this, arterial pressure waveforms sampled over the wrist using a sensitive pressure sensor and calibrated to a contemporaneous measurement of brachial blood pressure are processed using the moving average. Prior studies have shown that this method estimates central aortic systolic pressure accurately when compared with direct invasive measurement of aortic pressures.

There is considerable uncertainty about whether or not to offer blood pressure-lowering therapy to younger patients (i.e. those patients aged < 55 years) with grade 1 hypertension (i.e. a brachial blood pressure of 140–159/90–99 mmHg), especially those without overt cardiovascular disease or hypertension-mediated organ damage. This study aimed to test whether or not measurement of central aortic systolic pressure could be used to stratify younger patients for treatment based on the hypothesis that patients with grade 1 hypertension and high central aortic systolic pressure (≥ 125 mmHg) would have early evidence of hypertension-mediated cardiac structural remodelling (i.e. a greater left ventricular mass index) versus those patients with low central aortic systolic pressure (< 125 mmHg). The cut-off point for central aortic systolic pressure (≥ 125 mmHg) was derived from data in a meta-analysis of all clinical studies published up to 2014 reporting brachial systolic blood pressure and central aortic systolic pressure. If the hypothesis was proven, that is, that people with grade 1 hypertension and high central aortic systolic pressure show early evidence of cardiac structural change, a randomised controlled trial comparing blood pressure-lowering treatment versus no treatment (usual care) would be warranted. The randomised controlled trial would test the second hypothesis that treatment to lower blood pressure will regress early cardiac structural change in patients with grade 1 hypertension and high central aortic systolic pressure.

Confirmation of an association between high central aortic systolic pressure and increased left ventricular mass index at baseline, prior to commencing a randomised controlled trial, was included as a study stop–go criterion. Left ventricular mass index was selected as the primary outcome measure because this is a well-validated pressure-sensitive outcome that has been extensively characterised as a potent predictor of increased cardiovascular risk and mortality. The study included only men because of the complexity of conducting a drug treatment study in women of childbearing age. To determine whether or not there was progression of left ventricular mass index with time in patients with grade 1 hypertension and low central aortic systolic pressure, a parallel observational study was undertaken in this group.

Objectives

The TREAT CASP study aimed to test the hypothesis that non-invasive central aortic systolic pressure measurement identifies young men with grade 1 hypertension with early cardiovascular structural change, who are likely to benefit from antihypertensive treatment. Two study objectives were specified:

1. to compare left ventricular mass index in younger men with grade 1 hypertension and no other cardiovascular disease, stratified by central aortic systolic pressure status (high vs. low central aortic systolic pressure) from a screening study in the general population
2. to investigate whether or not blood pressure-lowering treatment reduces left ventricular mass index in a randomised controlled trial of blood pressure-lowering treatment versus no treatment (usual care) in younger men with high central aortic systolic pressure.

First phase of the study: relationship between central aortic systolic pressure and left ventricular mass index

The first objective of the study was to determine whether or not central aortic systolic pressure was related to left ventricular mass index, as assessed by cardiac magnetic resonance imaging, and, specifically, whether or not high central aortic systolic pressure was associated with a greater left ventricular mass index than low central aortic systolic pressure. This formed the stop–go checkpoint for progression to the randomised controlled trial. The first phase of the study also allowed evaluation of whether or not central aortic systolic pressure was more strongly related to left ventricular mass index than conventional clinic blood pressure or ambulatory blood pressure, which would suggest that central aortic systolic pressure measurement may be a better means of stratifying younger patients with grade 1 hypertension for treatment.

Second phase of the study: randomised controlled trial to determine whether or not reducing central aortic systolic pressure in patients with high central aortic systolic pressure leads to a reduction of left ventricular mass index versus no treatment

Primary outcome of the randomised controlled trial

The primary outcome of the TREAT CASP randomised controlled trial was the change in left ventricular mass index, as measured by cardiac magnetic resonance imaging, evaluated between baseline and study closeout (i.e. 12 months following treatment initiation), comparing blood pressure-lowering treatment with usual care (no treatment) in participants with high central aortic systolic pressure. Left ventricular mass index is expressed as left ventricular mass (g) indexed to body surface area and expressed as g/m^2.

Methods

This was a two-stage study in untreated younger (i.e. aged < 55 years) men with grade 1 hypertension and no other cardiovascular disease or evidence of hypertension-mediated organ damage.

Stage 1: screening study

A cross-sectional screening study was undertaken in men with grade 1 hypertension recruited from the community and stratified by central aortic systolic pressure (high vs. low central aortic systolic pressure).

Inclusion criteria

Inclusion criteria were men who:

- were aged 18 to < 55 years
- had a clinical diagnosis of grade 1 hypertension based on a seated clinic blood pressure of 140–159/90–99 mmHg, and/or 24-hour ambulatory blood pressure monitoring
- were receiving no antihypertensive therapy (for at least the previous 3 months)
- were without evidence of hypertension-mediated organ damage, established cardiovascular disease, diabetes mellitus or chronic kidney disease on routine clinical screening
- for the randomised controlled trial, had a central aortic systolic pressure of ≥ 125 mmHg
- were able to provide written informed consent.

Exclusion criteria

Exclusion criteria included:

- women of any age
- men –
    - with grade 1 hypertension with hypertension-mediated organ damage, established cardiovascular disease, diabetes mellitus or chronic kidney disease
    - with white coat hypertension (i.e. normal blood pressure on 24-hour ambulatory blood pressure monitoring daytime mean blood pressure of < 135/85 mmHg)
    - with secondary hypertension
    - in whom it is not possible to measure brachial blood pressure
    - with atrial fibrillation or other significant pulse rhythm irregularity precluding accurate measurement of brachial blood pressure and central aortic systolic pressure
    - with previous hypersensitivity to antihypertensive drugs planned for use in the randomised controlled trial
    - unwilling to undergo, or with a contraindication to, magnetic resonance imaging scanning
    - with any clinical condition the investigator considers unsuitable for trial participation
    - unwilling or unable to provide written informed consent.

Recruited participants underwent a detailed cardiovascular investigation including measurement of blood pressure, height, weight, waist and hip circumference, and body fat, electrocardiography, and blood and urine tests. Recruited participants undertook questionnaires regarding lifestyle, medical history, socioeconomic status, exercise, smoking, ethnicity, diet and a cardiovascular risk calculation (QRISK®; ClinRisk, Leeds, UK). Brachial systolic blood pressure was measured using a validated oscillometric device (OMRON 705CP-II; Omron Corporation, Kyoto, Japan). Central aortic systolic pressure was measured by applanation tonometry over the radial artery using the BPro® device (Healthstats International Pte Ltd, Singapore). The BPro device incorporates a high-fidelity tonometer (with a sampling frequency of 60 Hz), which was used to collect 10-second samplings of radial waveforms. Sampled waveforms were ensemble-averaged, calibrated to brachial systolic and diastolic blood pressure (measured within 60 seconds) and central aortic systolic pressure was derived by applying an *n*-point moving average.

Stage 2: randomised controlled trial and observational study

To confirm that any increase in left ventricular mass index was due to hypertension, and that treatment would be beneficial at regressing left ventricular mass index, a randomised controlled trial was undertaken in patients with high central aortic systolic pressure. Patients with high central aortic systolic pressure were randomly assigned (internet-based simple 1 : 1 randomisation; sealed envelope™; Sealed Envelope Ltd, London, UK; www.sealedenvelope.com; accessed 1 February 2017) to blood pressure-lowering treatment versus no treatment (usual care) and followed up for 12 months. Treatment comprised standard blood

pressure-lowering medication recommended by national guidelines (50 mg of losartan daily up-titrated to 100 mg with the addition of 5 mg of amlodipine daily if necessary) and was titrated to reduce central aortic systolic pressure by at least 5 mmHg, a reduction previously shown to reduce risk for cardiovascular events and stroke in older, higher-risk patients. A prospective, open, blinded, end-point study design was used because of the need to titrate open-label treatment in the intervention arm.

The primary outcome was the change in left ventricular mass index (baseline to study closeout), comparing treatment versus no treatment. Left ventricular mass index at baseline and study closeout was measured using a five-element phased-array coil setup on a 1.5-tesla magnetic resonance imager (MAGNETOM® Avanto; Siemens Healthineers AG, Erlangen, Germany). In addition to the primary outcome, a number of secondary outcomes were prespecified, including:

- changes in cardiac magnetic resonance imaging left ventricular functional parameters (systolic and diastolic function) with treatment
- changes to additional markers of hypertension-mediated organ damage, including retinal vasculature urine albumin excretion, pulse wave velocity and cardio-ankle vascular index.

Measurement of ambulatory blood pressure and its relationship to left ventricular mass index was also prespecified as a secondary outcome.

Patients with grade 1 hypertension and low central aortic systolic pressure at baseline (i.e. a central aortic systolic pressure of < 125 mmHg) were entered into a 12-month observational follow-up study to determine the natural progression of left ventricular mass index, testing the hypothesis that low central aortic systolic pressure was benign and did not require treatment because:

- the elevated brachial systolic blood pressure in these patients was spurious as a result of physiological amplification
- these patients would have a lower left ventricular mass index at baseline versus a high central aortic systolic pressure
- there would be no progression of left ventricular mass index on cardiac magnetic resonance imaging after 12 months.

Results

Stage 1: screening study

A total of 726 participants were recruited into the stage 1 screening study, of whom 302 had grade 1 hypertension. From these 302 participants, 162 participated in the stage 2 randomised controlled trial and observational studies: 105 participants with high central aortic systolic pressure, who entered the randomised controlled trial (51 randomised to treatment and 54 to no treatment), and 57 with low central aortic systolic pressure, who participated in the observational study.

Stop–go checkpoint confirmation

Left ventricular mass index at end-systole in participants with high central aortic systolic pressure, who went on to participate in the randomised controlled trial, was significantly greater than in participants with low central aortic systolic pressure [high central aortic systolic pressure left ventricular mass index 67.9 $\pm$ 8.8 g/m^2 (n = 101); low central aortic systolic pressure left ventricular mass index 64.0 $\pm$ 8.5g/m^2 (n = 54); difference 4.0 g/m^2, 95% confidence interval 1.1 to 6.9 g/m^2; $p < 0.01$]. This confirmed the first hypothesis of the study, that is, that participants with grade 1 hypertension and high central aortic systolic pressure would have higher left ventricular mass index than those participants with low central aortic systolic pressure.

Correlation of central aortic systolic pressure versus other blood pressure indexes with left ventricular mass index

In univariate analysis, the regression coefficients and slopes were similar for the regression of left ventricular mass index for clinic systolic blood pressure, ambulatory systolic blood pressure and central aortic systolic pressure.

Pressure amplification differed between men with grade 1 hypertension and high or low central aortic systolic pressure [brachial systolic blood pressure minus central aortic systolic pressure (low vs. high central aortic systolic pressure) difference 1.7 mmHg, 95% confidence interval 0.4 to 3.1 mmHg; $p = 0.01$]. However, the proportion of participants with low central aortic systolic pressure and high-pressure amplification (i.e. systolic blood pressure in the upper range for grade 1 hypertension (i.e. 150–159 mmHg), but low central aortic systolic pressure, was very small, comprising only 1% of the total recruited.

Stage 2: randomised controlled trial and observational study

In the randomised controlled trial, both seated clinic blood pressure and ambulatory blood pressure were significantly reduced in men receiving treatment compared with men receiving no treatment after 12 months:

- Treatment –
  - clinic blood pressure change (baseline to study closeout): –20.0 mmHg (95% confidence interval –23.3 to –16.6 mmHg)/–13.0 mmHg (95% confidence interval –15.0 to –11.1 mmHg)
  - central aortic systolic pressure change (baseline to study closeout): –21.1 mmHg (95% confidence interval –24.4 to –17.9 mmHg)
  - ambulatory blood pressure monitoring 24-hour blood pressure change (baseline to study closeout): –10.3 mmHg (95% confidence interval –12.8 to –7.9 mmHg)/–6.9 mmHg (95% confidence interval –8.6 to –5.2 mmHg).
- No treatment –
  - clinic blood pressure change (baseline to study closeout): –9.6 mmHg (95% confidence interval –12.9 to –6.3 mmHg)/–5.8 mmHg (95% confidence interval –7.9 to –3.7 mmHg)
  - central aortic systolic pressure change (baseline to study closeout): –10.2 mmHg (95% confidence interval –13.3 to –7.1 mmHg)
  - ambulatory blood pressure monitoring 24-hour blood pressure change (baseline to study closeout): –0.1 mmHg (95% confidence interval –2.3 to 2.2 mmHg)/–0.3 mmHg (95% confidence interval –1.7 to 1.1 mmHg).

Treatment was well tolerated, and there was no difference in reported serious adverse events. Although adverse events were more frequently reported for men randomised to treatment than for men randomised to no treatment (i.e. 22 vs. 14), only five adverse events were attributed to treatment and none led to discontinuation. Quality of life, assessed using the Short Form questionnaire-36 items, did not differ between men receiving treatment and men receiving no treatment.

Primary outcome

Blood pressure-lowering treatment was associated with a greater change (baseline to study closeout) in left ventricular mass index evaluated at end-systole versus no treatment [treatment: left ventricular mass index change (baseline to study closeout) –3.3 g/m^2, 95% confidence interval –4.5 to –2.2 g/m^2; no treatment: left ventricular mass index change (baseline to study closeout) –0.9 g/m^2, 95% confidence interval –1.7 to –0.2 g/m^2; difference: –2.4 g/m^2, 95% confidence interval –3.8 to –1.0 g/m^2; $p < 0.01$]. The effect size was medium to large. This difference was maintained after adjustment for baseline factors.

Left ventricular mass index changes in the low central aortic systolic pressure observational cohort

No significant change (baseline to study closeout) in left ventricular mass index (evaluated at end-systole) was seen for participants in the low central aortic systolic pressure cohort after 12 months' follow-up [observational: left ventricular mass index change (baseline to study closeout) –0.5 g/m^2, 95% confidence interval –1.2 to 0.2 g/m^2; $p = 0.18$]. There was also no change in blood pressure (baseline to study closeout) during the observational study [observational: clinic blood pressure change (baseline to study closeout) –1.7 mmHg (95% confidence interval –4.3 to 1.0 mmHg)/0.1 mmHg (95% confidence interval –1.8 to 1.9 mmHg); central aortic systolic pressure change (baseline to study closeout) –1.0 mmHg (95% confidence interval –3.3 to 1.3 mmHg); 24-hour ambulatory blood pressure change (baseline to study closeout) –1.6 mmHg (95% confidence interval –3.6 to 0.5 mmHg)/–0.3 mmHg (95% confidence interval –1.7 to 1.1 mmHg); all p = not significant].

Secondary outcomes

Comparison of the change in un-indexed left ventricular mass (treatment vs.no treatment) showed a similar pattern of change to that for the primary outcome (i.e. left ventricular mass index). Moreover, the effect of treatment in men with high central aortic systolic pressure was to reduce left ventricular mass index and left ventricular mass to values approaching those seen in men with low central aortic systolic pressure at study closeout.

In the randomised controlled trial, blood pressure-lowering treatment was associated with a greater change (from baseline to study closeout) in electrocardiography voltage criteria for left ventricular mass [treatment vs. no treatment: Cornell voltage change (from baseline to study closeout) –0.2 mV (95% confidence interval –0.2 to –0.1 mV) vs. 0.1 mV (95% confidence interval 0.0 to 0.2 mV); difference –0.3 mV (95% confidence interval –0.4 to –0.2 mV); $p < 0.01$; treatment vs. no treatment: augmented vector left voltage change (from baseline to study closeout) –51.5 µV (95% confidence interval –104.6 to 1.6 µV) vs. 68.7 µV (95% confidence interval 5.0 to 132.4 µV); difference –120.2 µV (95% confidence interval –202.6 to –37.8 µV); $p < 0.01$].

In patients with high central aortic systolic pressure with a detectable urinary albumin-to-creatinine ratio, treatment elicited a reduction (baseline to study closeout) compared with no treatment [treatment vs. no treatment: detectable urinary albumin-to-creatinine ratio change (from baseline to study closeout) –0.5 (95% confidence interval –1.1 to 0.1) vs. 0.1 (95% confidence interval –0.2 to 0.4); difference –0.6 (95% confidence interval –1.2 to 0.0); $p = 0.04$]. No patient had a urinary albumin-to-creatinine ratio outside the normal clinical range.

Conclusions

The TREAT CASP study has shown that, although central aortic systolic pressure was generally lower than brachial systolic blood pressure, the central aortic systolic pressure value tended to track with brachial systolic blood pressure (as defined by clinic blood pressure and/or ambulatory blood pressure monitoring) in patients with grade 1 hypertension. Very few patients (i.e. 1%) had a low central aortic systolic pressure value (< 125 mmHg) at a brachial systolic blood pressure level typical of those patients with high central aortic systolic pressure (i.e. a brachial systolic blood pressure of 150–159 mmHg). High central aortic systolic pressure was associated with both early evidence of hypertension-mediated organ damage (i.e. an increased left ventricular mass index) and reduced pressure amplification relative to patients with low central aortic systolic pressure. However, the correlation of central aortic systolic pressure with left ventricular mass index was no greater than that seen with clinic brachial systolic blood pressure or ambulatory blood pressure. Thus, the measurement of central aortic systolic pressure was not found to be a superior means of stratifying younger people with grade 1 hypertension for antihypertensive therapy, when compared with conventional blood pressure measurement. Nevertheless, the increased left ventricular mass index in patients with high central aortic systolic pressure was likely to be as a result of higher blood pressure because left ventricular mass index was reduced after blood pressure lowering with treatment for 12 months. The treatment-induced regression in left ventricular mass index on cardiac magnetic resonance imaging was also evident on a standard

12-lead electrocardiogram. In addition, there was evidence of treatment-induced regression of the urinary albumin-to-creatinine ratio. Increased left ventricular mass index and urinary albumin-to-creatinine ratio are potent biomarkers of future cardiovascular risk and the TREAT CASP study demonstrates that these adverse changes are reversible with blood pressure-lowering treatment in younger people with grade 1 hypertension.

Trial registration

The trial is registered as ISRCTN09502665.

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