RECENT STUDIES IN HYPERTENSION

Cuff or central blood pressure as a treatment target for hypertension management?

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"Central hypertension" is a condition that has come to light with the advent of non-invasive central BP technology and describes an individual with controlled cuff SBP (e.g. <140 mmHg) but relatively high central SBP (e.g. ≥130 mmHg). In observational studies, this BP phenotype is associated with greater BP-related cardiovascular risk despite having cuff BP below the hypertension threshold.[1] It is not known if controlling central hypertension with optimised antihypertensive therapy will have benefits beyond the control of cuff measured hypertension, and we set out to determine this in our recently published trial.[2]

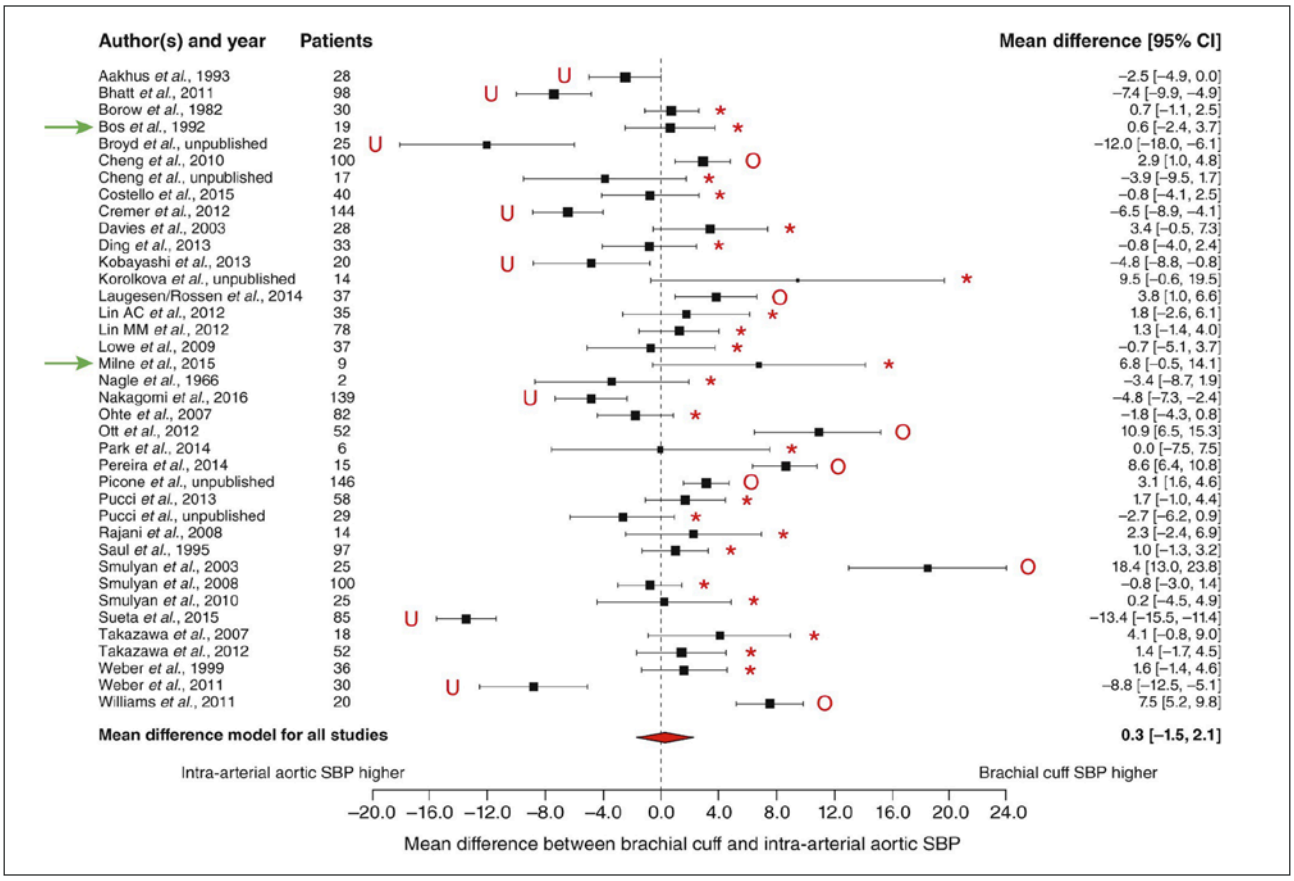
301 people with cuff BP controlled by antihypertensive treatment, but with central hypertension, were randomised to 24-months intervention with spironolactone 25 mg/d or usual care. The primary outcome was the change in left ventricular mass index (LVMi) measured by cardiac magnetic resonance imaging. At the time of trial design there wasn't an accepted central hypertension threshold, and we defined this as central SBP ≥1.0 standard deviation above age- and sex-specific normal values, ascertained from the largest central BP dataset available.[3] We hypothesised that spironolactone would reduce LVMi and have greater central BP lowering effects than for cuff BP. Further, we expected that reduction in LVMi would be associated with central (not cuff) BP and that central BP lowering would be associated with reduced aortic stiffness. These ambitious expectations were based on published rationale, and if proven would provide the first clinical trial evidence justifying central BP as a treatment target.

As predicted, intervention reduced LVMi, but cuff and central BPs were lowered to the same magnitude (no differential effects), and the relationships between the change in BPs with the change in LVMi were virtually identical for cuff and central BPs. This was irrespective of the BP measurement setting (either office BP, 7-day home BP or 24-hour ambulatory BP) or calibration mode of the central BP device (using Type 1 cuff SBP/DBP or Type 2[4] cuff mean arterial pressure/DBP). Aortic stiffness did not change despite significant BP reduction, which was surprising but not inconsistent with other drug trials among different patient cohorts.[5, 6]

A cautionary note to investigators seeking to study people with central hypertension – the phenotype is hard to find. The prevalence is now known to approximate 1.4%[7] to 3.7%.[1] During screening for recruitment in our trial, most of the people with cuff SBP treated and controlled to <140 mmHg also had controlled central SBP. Thus, most were ineligible, and this forced a change in central hypertension criteria early in the trial. A contributory factor to this issue, only discovered post facto,[8] was that the central BP device used for screening overestimated the true level of SBP amplification (difference between cuff SBP and central SBP) at low values, meaning that potentially eligible people may have been incorrectly screened out of participation. This highlights the issue of device-specific differences in BP measurement accuracy and the imperative for clinical triallists to fully understand central BP device performance against invasive central BP at the trial design phase.

Along the above lines, new knowledge from individual participant data meta-analysis[9] published after we started the trial, show that standard automated cuff BP devices may already

Figure 1. Forest plot of the difference between standard cuff SBP and invasive central SBP from an individual participant data meta-analysis of 1838 participants. Two studies used manual devices (green arrows); the remainder were automated BP devices. There was no significant difference overall between cuff and invasive SBP (P = 0.77). *Denotes the cuff devices where SBP was not significantly different from invasive central SBP; "U" and "O" denote the cuff devices where invasive SBP were underestimated or overestimated, respectively. CI, confidence interval. Adapted from Picone et al.9 Copyright © 2017 by The American College of Cardiology Foundation, with permission from The American College of Cardiology Foundation.



provide a good estimate of central SBP. **Figure 1** is a forest plot comparing cuff SBP with invasive central SBP across 38 studies and BP devices. Sixty one percent of the cuff devices provided SBP values that were not significantly different from invasive central SBP; in other words, they were effectively 'central BP devices.' There was wide variability in the remaining devices, either over- or under-estimating invasive central SBP. Unless these types of comparisons are made there is no way of knowing which cuff device measures what invasive BP value, and this has implications for the accuracy of central BP devices.

The default calibration of cuff SBP/DBP used by most central BP devices (Type 1), including those used in our trial, results in systematic underestimation of central SBP and pulse pressure.[4] This calibration also leads to near perfect correlation between cuff SBP and derived central SBP (r≈0.95), as also witnessed in our trial. The alternative Type 2 device calibration method can be applied, however, this made no difference to our trial findings. We were aware of, or suspected, several of the above BP measurement issues before designing the trial, but several emerged in the time taken to complete the trial. Altogether, the panoply of measurement nuances leaves little opportunity for demonstrating clinical superiority of central BP in clinical trials such as the one we did using a surrogate endpoint of LVMi, or other large ones with hard cardiovascular outcomes still yet to be undertaken.

In the years since starting the trial, the US Hypertension Guidelines have lowered the cuff hypertension threshold from 140/90 mmHg to 130/80 mmHg. If we applied this criterion to our trial, all participants would have qualified for up-titration of antihypertensive therapy. Importantly, our finding that LVMi improved with intervention despite people having controlled cuff hypertension according to the 140/90 mmHg threshold, supports the clinical value of achieving lower cuff BP targets, as is also advocated by the International Society of Hypertension.

Ultimately our trial failed in the attempt to target central BP and control central hypertension for cardiovascular risk benefits in isolation from standard cuff BP. Of course with every study there are limitations and caveats on appropriate interpretation of the results which we extensively discuss in the paper.[2] Until there is data to the contrary, the trial findings support the general opinion[10] for standard cuff BP rather than central BP remaining as the recommended method for hypertension management.

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