Central Blood Pressure

Randomized Trial of Guiding Hypertension Management Using Central Aortic Blood Pressure Compared With Best-Practice Care

Principal Findings of the BP GUIDE Study

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Abstract—Arm cuff blood pressure (BP) may overestimate cardiovascular risk. Central aortic BP predicts mortality and could be a better method for patient management. We sought to determine the usefulness of central BP to guide hypertension management. This was a prospective, open-label, blinded–end point study in 286 patients with hypertension randomized to treatment decisions guided by best-practice usual care (n=142; using office, home, and 24-hour ambulatory BP) or, in addition, by central BP intervention (n=144; using SphygmoCor). Therapy was reviewed every 3 months for 12 months, and recommendations were provided to each patient and his/her doctor on antihypertensive medication titration. Outcome measures were as follows: medication quantity (daily defined dose), quality of life, and left ventricular mass (3-dimensional echocardiography). There was 92% compliance with recommendations on medication titration, and quality of life improved in both groups (post hoc \( P<0.05 \)). For usual care, there was no change in daily defined dose (all \( P>0.10 \)), but with intervention there was a significant stepwise decrease in daily defined dose from baseline to 3 months (\( P=0.008 \)) and each subsequent visit (all \( P<0.001 \)). Intervention was associated with cessation of medication in 23 (16%) patients versus 3 (2%) in usual care (\( P<0.001 \)). Despite this, there were no differences between groups in left ventricular mass index, 24-hour ambulatory BP, home systolic BP, or aortic stiffness (all \( P>0.05 \)). We conclude that guidance of hypertension management with central BP results in a significantly different therapeutic pathway than conventional cuff BP, with less use of medication to achieve BP control and no adverse effects on left ventricular mass, aortic stiffness, or quality of life.

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Key Words: aorta ■ clinical trial ■ heart ventricles ■ hemodynamics

Intensive blood pressure (BP) lowering is advocated in some patients,1–3 but this may have no benefit or possible harm,4–10 which draws into question the wide perception that lower BP is always better, and supports the need for exploring other effective ways of guiding hypertension management. Several lines of evidence suggest that central (aortic) BP could be useful for this purpose: first, major differences in central systolic BP (SBP) can occur between individuals with the same or similar brachial SBP;11,12 second, end-organ damage is more closely related to central rather than brachial BP;13 third, central BP indices have higher power than brachial BP in predicting cardiovascular events and all-cause mortality14,15; fourth, in-office central BP predicts future mortality with similar prognostic capacity as the reference standard of 24-hour ambulatory BP16; fifth, changes in end-organ disease have a stronger relationship with central BP compared with brachial BP;17,18; and finally, common antihypertensive drugs may lower central BP more than brachial BP.19,20 Thus, when decisions on medication titration are based only on brachial BP, there may be a risk of overtreatment, whereas reducing therapy may be possible with knowledge of central BP. This study aimed to determine the value of central BP to guide management of patients with hypertension. We hypothesized that central BP–guided intervention would result in less use of antihypertensive medication.
and improved quality of life but no significant change in left ventricular (LV) mass.

**Methods**

**Study Design**

The detailed rationale and design of this multicenter, 12-month, prospective, randomized trial have been published. The study began in January 2008, there were 286 patients allocated to intervention, and the last patient assessment was conducted in July 2012. There were no major changes in methods after trial commencement.

**Participants**

Patients with uncomplicated hypertension were recruited via community advertisement and primary care clinics in 3 Australian centers (Brisbane, Queensland; Hobart, Tasmania; and Canberra, Australian Capital Territory). Inclusion criteria were as follows: 18 to 75 years of age; nonpregnant; receiving antihypertensive therapy for uncomplicated essential hypertension and taking ≥1 but not >3 antihypertensive drugs (to rule out complicated or resistant hypertension). Exclusion criteria were as follows: severely abnormal LV mass index (>59 g/m² in women and >64 g/m² in men); clinical history of coronary artery disease or renal disease; serum creatinine >1.6 mg/dL; secondary causes of hypertension; uncontrolled hypertension (office brachial BP >180/100 mm Hg); aortic valve stenosis; or upper limb obstructive atherosclerosis.

**Protocol**

Patients were randomized to have hypertension management decisions made on the basis of the highest standard (usual care) or with the addition of central BP measures to guide decisions (intervention). For usual care patients, management decisions were based on a variety of tests as would be the case with best practice care (eg, office BP, 7-day home BP, 24-hour ambulatory BP, 2-dimensional LV mass index, symptoms, and other clinical considerations as per absolute cardiovascular risk), with out-of-office BP measures taking precedence over in-office brachial BP. The addition of central BP to guide care with intervention patients was made with the aim of determining whether central BP may be of value above and beyond best practice care. To achieve this, intervention patients had medications titrated to normalize seated central SBP. Given that BP levels are dependent on both age and sex, we considered that the central SBP target range should be based on age- and sex-specific normative central SBP values, and these were derived from the largest population study published at the time of planning the study design. In the absence of other data to guide cutoff values, we defined the normative range as within +1 SD from the mean normative values (Table S1 in the online-only Data Supplement).

All patients were assessed at 3-month intervals for 12 months. After each visit, a letter with titration recommendations was sent to each patient and his/her doctor, with adherence to recommendations being checked at each subsequent visit. An overview of the time points at which measures were acquired is shown in Figure 1. Titration recommendations were made according to 5 expected clinical scenarios in the central BP group (Table S2), and usual care titration recommendations were made on agreement by hypertension/cardiology specialists (M.S. and T.M.). To eliminate bias, the choice of drug titration was left to the discretion of the patient’s attending doctor. In the event of ceasing medication, an additional visit was booked for patients to be re-evaluated within 4 weeks, and medication was reinstated if average 7-day home or 24-hour ambulatory BP control was not within accepted standards (<135/85 or <130/80 mm Hg, respectively).

A substudy was performed to test the level of agreement between observers with respect to titration recommendations. Comparison was made between recommendations provided for 100 randomly selected patient visits (n=50 per allocation group) and the recommendations provided by a cardiologist (W.A.) blinded to the recommendations made.

**Randomization, Outcomes, and Masking**

Each patient was randomly assigned, using a standard computer protocol, to intervention in a 1:1 ratio using sealed opaque envelopes (sequentially...
numbered) at each site. Enrollment and intervention assignment were conducted by the study co-ordinators at each site. Primary outcomes were as follows: medication quantity determined by daily defined dose (DDD) calculated as per World Health Organization standard (the DDD is a system for exact quantification of drug amount and standardization to enable comparison across drug classes, eg, 1×DDD=150 mg irbe-sartan or 5 mg amloidipine);27 quality of life by the Bumpitt hyperten-sion-specific questionnaire24 and the multipurpose short form-36 health survey;25 and LV mass by real-time 3-dimensional echocardiography as previously described.26 Investigators and participants were blinded to all the above outcome variables (which were calculated at the end of the study), and assessment of LV mass was undertaken on side-by-side images by a technician blinded to allocation. Sample size (142 participants per group) was determined on the basis of LV mass noninferiority between 2 independent groups (t=0.05 and β=0.10) and were derived with data from our previous work27 as previously described.21

**BP and Aortic Stiffness**

Office brachial BP (Omron HEM 907; Omron Healthcare, Kyoto, Japan) and central aortic BP (SphygmoCor 8.0; AtCor Medical, Sydney, NSW, Australia) were recorded in duplicate after 10 minutes of seated rest. Seven-day home BP was recorded using a valid device owned by the patient or with an A&D UA 767 machine provided (A&D Mercury, Thebarton, SA, Australia).29 Participants were asked to take duplicate BP readings 3× per day (1, morning 6 am–10 am; 2, midday; 3, evening 6 pm–10 pm) after 5 minutes of seated rest, with the first reading discarded and the second reading recorded. Twenty-four-hour ambulatory BP was recorded using a TM 2430 device (A&D Mercury, Thebarton, SA, Australia).30 Aortic stiffness was measured by tonometry (SphygmoCor 8.0; AtCor Medical, Sydney, NSW, Australia) as per expert consensus.25

**Statistical Analysis**

Data were analyzed by intention-to-treat analysis on all patients who received the allocated intervention, with P<0.017 denoting significance (Bonferroni correction because of 3 primary end points). Means and SDs are presented, except where indicated. All regression models were adjusted for age, sex, and body mass index because these variables could have affected the primary outcomes (none of the findings were changed whether adjusted or unadjusted). For continuous variables of LV mass index, 24-hour ambulatory BP, heart rate, and quality of life, analysis was undertaken using linear regression, with the dependent variable calculated as change over time. Distribution of the short form-36 subscales was leptokurtic as a result of the high frequency of zero values. Therefore, change scores were categorized as decrease, no change, and increase and then analyzed using log-multinomial regression, with no change as the reference category. DDD medication data recorded at all visits were analyzed using mixed regression models to account for repeated measures on individuals over time, with outcome variables log-transformed to correct heteroskedasticity where necessary. The back-transformed means and confidence intervals are presented. Recommendations on medication use at each visit were categorized as maintain, increase, decrease, or cease. The cease category contained sparse data and could not be estimated in the models; therefore, analysis was conducted with this category omitted and then combined with the category decrease. A log-multinomial regression model was used to assess the group differences for each of these 3 categories, with clustering on individuals to account for repeated measures over time. χ² test was used to determine the relationship between categorical variables. Intraclass correlations were used to assess the between-observer comparisons of recommendations. All models were assessed using either SPSS 20 (IBM, Armonk, NY) or Stata 12.1 (StataCorp, College Station, TX).

**Results**

**Patient Characteristics and Flow**

Table 1 presents the characteristics of study patients (99% were white). There were no significant between-group differences in the number of patients taking antihypertensive medications within each drug class (all P>0.27). A small percentage of patients in each group was taking β-blockers, with atenolol used by 9 patients in the intervention group and 10 patients in usual care (see Figure 2 for patient flow).

**Medication Quantity**

Table 2 shows the total DDD for antihypertensive medications; at baseline, there were no significant differences between groups (P=0.27). For usual care patients, there was no significant change over time for total antihypertensive DDD (all P>0.10). However, for intervention patients, there was a significant stepwise decrease in DDD from baseline to 3 months and each subsequent visit thereafter. Compared with baseline, by the end of the study, antihypertensive medication was reduced by 15.4% in the intervention group, whereas there was a 2.6% reduction with usual care (change from baseline data is depicted in Figure 3). Intervention was associated with cessation of medication in significantly more patients compared with usual care (n=23 [16% of group] versus n=3 [2% of group]; P<0.001).

Table S3 details the DDD changes in antihypertensive medication class. At baseline, there were no significant differences between groups in the DDD of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers. Despite no difference in the number of people taking different antihypertensive drug classes (Table 1), the baseline DDD of diuretics was lower, and β-blockers were higher, in the intervention group. For diuretics, this between-group difference remained at all time points. During the study period, there was a significant decrease in DDD for each of the antihypertensive medication classes in the intervention group, but there were no significant changes...
in the usual care group. Figure 4 shows the between-group percentage of titration recommendations. From baseline and at each subsequent visit until 9 months, significantly more people in the intervention group received the recommendation to reduce medication.

Table 2. Between-Group Total Daily Defined Dose of Antihypertensive Medications for 12 Months

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Usual Care (n=142)</th>
<th>Central BP (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.29 (2.06–2.51)</td>
<td>2.47 (2.25–2.69)</td>
</tr>
<tr>
<td>3 mo</td>
<td>2.30 (2.08–2.52)</td>
<td>2.33 (2.11–2.55)</td>
</tr>
<tr>
<td>6 mo</td>
<td>2.24 (2.02–2.47)</td>
<td>2.14 (1.91–2.36)</td>
</tr>
<tr>
<td>9 mo</td>
<td>2.23 (2.00–2.45)</td>
<td>2.09 (1.86–2.31)</td>
</tr>
<tr>
<td>12 mo</td>
<td>2.22 (2.00–2.45)</td>
<td>2.02 (1.80–2.25)</td>
</tr>
</tbody>
</table>

Overall difference (group×time interaction) P<0.001. Data adjusted for age, sex, and body mass index. BP indicates blood pressure; and CI, confidence interval.

Quality of Life
There were no significant differences between groups in quality of life measures at baseline. On post hoc analysis, each group had an improvement in health status index as determined by the Bulitpitt questionnaire from baseline to 12 months (usual care, 0.75±0.12–0.77±0.12, P=0.042; intervention, 0.73±0.15–0.75±0.14, P=0.017); however, between-group differences were not significant (P=0.79). The short form-36 survey data showed no statistically significant patterns among any of the 8 quality of life subscales (all P>0.10).

LV Mass
There were no significant differences between groups in LV mass index at baseline. There was a small, but nonsignificant reduction in LV mass index for patients in the intervention group (Δ=–0.23, 31.8–31.5 g/m²), whereas there was a small, but nonsignificant increase in the usual care group (Δ=+0.28, 30.8–31.0 g/m²), with the overall difference being of borderline significance (P=0.079) in favor of intervention.
There were no significant differences between groups in any BP variable at baseline. Table 3 shows the between-group BP differences from baseline to 12 months. There were no significant changes in any of these variables, including 24-hour ambulatory BP, office brachial BP, or central BP. Figure 5 depicts the between-group changes in 7-day home BP; there were no differences in SBP. Diastolic BP was higher in the intervention group at 6 and 12 months but was still below the threshold of raised home diastolic BP. There was no significant difference between groups in heart rate at baseline \((P=0.72)\) nor was there a significant between-group difference for the change in heart rate from baseline to 12 months (Table 3). When analysis was confined to comparing those participants who ceased or reduced antihypertensive medication with those who maintained or increased medication in the intervention group, there was no significant difference in heart rate whether analyzed as the change from baseline to 12 months \((P=0.77)\) or at 12 months alone \((P=0.97)\).

### Aortic Stiffness

There were no significant differences between groups in aortic pulse wave velocity at baseline. From baseline to 12 months, there was no significant change in aortic pulse wave velocity between groups (intervention, from 9.34±1.92 to 9.35±1.99 m/s; usual care, from 9.47±2.30 to 9.43±2.14 m/s; \(P=0.80)\).

### Adherence to Recommendations

In total, >1400 recommendations were provided, and there was strong adherence (92%). The most common reason for nonadherence (54% prevalence) was based on a different clinical decision made by the patient’s doctor for a variety of reasons, including a change in the clinical presentation or home/life circumstances cited by the patient. For the substudy to test the level of agreement between observers on titration recommendations, the same recommendations were made between observers in 84% of cases (intraclass coefficient, 0.86; 95% confidence interval, 0.79–0.93; \(P<0.001\) and Cohen \(k=0.67\); \(P<0.001)\), indicating good agreement.

### Adverse Events

Although the study was not powered to test harm-related hypotheses, there were 19 patients in whom a separate adverse event was reported, with a higher proportion of events in usual care participants \(n=14\) [9.9% of group] versus \(n=5\) [3.5% of group]; \(P<0.001;\) Table S4).

### Discussion

The principal findings of this study were that central BP guidance of hypertension management resulted in a highly significant reduction in the quantity of antihypertensive medication across all drug classes, but despite this, good BP control was still achievable, quality of life was improved, and there were no adverse effects on LV structure or aortic stiffness. Indeed, trending against our hypotheses that there would be no difference between groups in LV mass, the change in this variable was of borderline significance, with favor toward improvement in the central BP group. Together, these data establish proof of concept that measurement of central BP could be clinically advantageous in treatment of lower- to medium-risk patients with hypertension.
The first clue that central BP could be useful in providing extra information on the responses to antihypertensive medication was provided in an invasive study of 14 patients in which brachial and central aortic BP responses to glyceryl trinitrate were recorded.31 Central SBP fell in all patients, but the responses were highly variable (range, 6–44 mm Hg; average, 22 mm Hg). Brachial SBP also fell, but to a lesser degree, and in 3 people, there was no appreciable change. Thus, the effect of vasoactive medication on LV afterload was not consistently discernible using conventional brachial BP. A similar type of variability in terms of brachial-to-central SBP differences was observed in patients in this current study. Many other studies have reported differential responses to antihypertensive agents, which are highly variable among individuals and occur across all drug classes.39 Atenolol is the only agent with definitive evidence of adverse (relatively raised) central BP effects, but <7% of patients in our study were taking this drug. Our data demonstrate that paying attention to central BP can result in therapeutic decisions that are substantially different from best-practice usual care where only brachial BP is considered.

However, because the normative range of both brachial and central SBP increases with age, it may be suggested that less treatment will be required with increasing age, and, therefore, similar results could have been obtained (in terms of reducing antihypertensive medications) if treatment was guided by an age-specific brachial SBP target. However, if the reduction in medications seen in the intervention group was simply a result of less stringent targets at higher age brackets, the mean LV mass index in this group would have been expected to rise, when it showed a tendency to fall (unlike in the usual care group). This is in keeping with the notion that the use of central BP to assist in decision making helps to achieve more appropriate antihypertensive medication for individuals with hypertension, particularly in those in whom central SBP and brachial SBP levels are markedly discrepant in terms of their relationships to their respective target levels. Indeed, it is now well established that major differences exist in central SBP among people with similar brachial SBP, irrespective of age, sex, hypertensive status, or cardiovascular risk.11,12,22

To our knowledge, this is the first randomized trial specifically designed to test the efficacy of using central BP monitoring to guide therapy in patients with hypertension. This conclusion is based on our own recently completed review of data pertaining to central BP in the management of hypertension and also from a systematic review and meta-analysis of all longitudinal studies reporting the relationship between central BP and outcomes (published in 2010).15 An open-label, blinded-end point study design was adopted with the intention of providing results that were applicable to real-world medical care of patients with hypertension. This goal was resistance by patients or attending doctors with respect to adhering to medication titration recommendations.34 The high rate of compliance with the protocol, including barriers, including lack of confidence with in-office BP recordings, perceived patient reluctance, and comorbidity considerations.14 The high rate of compliance with the protocol,
together with improvements in hypertension-specific quality of life scores and lack of adverse clinical outcomes, suggests that the model of care using central BP used in this study may be valid for direct clinical application. However, the long-term clinical significance of the different therapeutic course guided by central BP will need to be tested in other studies beyond 1 year of intervention. The health consequences of the slight rise in nighttime SBP (albeit nonsignificant), as well as the increase in home diastolic BP (albeit maintaining levels well below accepted standards for home BP control), will need to be ascertained.

Limitations

Study participants comprised relatively healthy, older, white, lower- to moderate-risk patients with uncomplicated hypertension, and the results should not be generalized to populations beyond this presentation. It may be argued that the 12-month follow-up period was too short for significant changes in LV mass to be detected, and, therefore, the lack of between-group significance was not unexpected. This assertion is weakened by the observed trend for improvement in LV mass index, despite major reductions in antihypertensive therapy using central BP-guided care. Furthermore, cardiac remodeling is a highly labile process that is acutely sensitive to alterations in loading conditions, with major changes in LV size being detectable within weeks to months of intervention. The largest withdrawal of medications in the intervention group occurred at baseline (37.7%) and 3 months (40%; Figure 4), which should have left sufficient time for LV remodeling effects to be identified. Furthermore, we used 3-dimensional echocardiography to assess cardiac structure, which has greater accuracy and reproducibility than conventional echocardiography. Finally, although participants and investigators were blinded to the DDD, the drug name and dose were not concealed because of the open-label design, and this is a potential limitation.

Perspectives

This study found that noninvasive central BP information helped in the management of patients with hypertension. Significantly less antihypertensive medication was used to maintain appropriate BP control, and quality of life was improved to the same degree as best-practice usual care. Despite significant withdrawal of medication, there was a trend toward lower LV mass than those treated according to usual care, which was unexpected and merits further investigation because this could be a clue toward helping to understand why intensive BP lowering may increase risk in some patients. The maintenance of good out-of-office BP control using less antihypertensive medication suggests that central BP monitoring may be especially valuable in patient populations where there may be a risk of promoting harmful outcomes by pursuing low BP targets, such as in the elderly where fall risk may be increased. Overall, the findings provide extra impetus to undertake large, hard-end point trials on the efficacy of central BP assessment in hypertension management.

Appendix

The BP GUIDE investigators were as follows: Tim Albion, Janette Bain, Warrick Bishop, Leigh Blizzard, Seanna Gall, Di Marston, Thomas Marwick, Petr Otahal, Phillip Roberts-Thomson, James Sharman (Tasmania); Carly Jenkins, Deborah Gilroy, Tony Stanton, Michael Stowasser, Leah Wright (Queensland); Kate Abhayaratna, Walter Abhayaratna, Janine Vickers, Wichat Srikusalanukul (Canberra).

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Disclosures

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References