Different associations between beta-blockers and other antihypertensive medication combinations with brachial blood pressure and aortic waveform parameters

John D. Sluyter[a,#], Alun D. Hughes[b], Andrew Lowe[c], Kim H. Parker[d], Carlos A. Camargo Jr[e], Bernhard Hametner[f], Siegfried Wassertheurer[f], Robert K.R. Scragg[a]

[a] School of Population Health, University of Auckland, Auckland, New Zealand

[b] Institute of Cardiovascular Sciences, University College London, London, UK

[c] Institute for Biomedical Technologies, Auckland University of Technology, Auckland, New Zealand

[d] Department of Bioengineering, Imperial College London, London, UK

[e] Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA

[f] Health & Environment Department, AIT Austrian Institute of Technology, Vienna, Austria

[#]Corresponding author at: School of Population Health, University of Auckland, Private Bag 92019, Auckland, New Zealand.

Abstract

Background

Comparing the relationships of antihypertensive medications with brachial blood pressure (BP) and aortic waveform parameters may help clinicians to predict the effect on the latter in brachial BP-based antihypertensive therapy. We aimed to make such comparisons with new waveform measures and a wider range of antihypertensive regimens than examined previously.

Methods

Cross-sectional analysis of 2933 adults (61% male; aged 50–84 years): 1637 on antihypertensive treatment and 1296 untreated hypertensives. Sixteen medicine regimens of up to 4 combinations of drugs from 6 antihypertensive classes were analysed. Aortic systolic BP, augmentation index (AIx), excess pressure integral (EPI), backward pressure amplitude (Pb), reflection index (RI) and pulse wave velocity (PWV) were calculated from aortic pressure waveforms derived from suprasystolic brachial measurement.

Results

Forest plots of single-drug class comparisons across regimens with the same number of drugs (for between 1- and 3-drug regimens) revealed that AIx, Pb, RI and/or $\log_e$(EPI) were higher (maximum difference = 5.6%, 2.2 mm Hg, 0.0192 and 0.13 $\log_e$(mm Hg · s), respectively) with the use of a beta-blocker compared with vasodilators and diuretics, despite no brachial systolic and diastolic BP differences. These differences were reduced (by 34–57%) or eliminated after adjustment for heart rate, and similar effects occurred when controlling for systolic ejection period or diastolic duration.

Conclusions

Beta-blocker effects on brachial BP may overestimate effects on aortic waveform parameters. Compared to other antihypertensives, beta-blockers have weaker associations with wave reflection measures and EPI; this is predominantly due to influences on heart rate.

Keywords: Arterial stiffness; Beta-blocker; Central blood pressure; Pulse waveform; Vasodilating antihypertensive agents; Wave reflection

Introduction

Antihypertensive medications are widely utilised and prevent incident cardiovascular (CV) events. While brachial blood pressure (BP) is routinely used as a target in such therapy, new technological advances have made it possible to make practical, non-invasive measurements that provide estimates of aortic pressure waveforms [1]. Aortic waveform parameters, which include aortic systolic BP (SBP), augmentation index (AIx) and pulse wave velocity (PWV), have been shown to predict CV events independently of brachial BP [2, 3]. Thus, given their relationships with CV risk and their easy measurement in clinical practice, they may be useful targets in antihypertensive therapy. In support of this, large trials have found that antihypertensives have clinical benefits beyond those expected from decreases in brachial BP [4, 5].

However, there are some issues associated with antihypertensive therapy based on aortic waveform parameters that appear to warrant further research. One issue is the relative efficacies of various antihypertensive polytherapies on these parameters. A few studies have compared the effectiveness on these waveform measures of two drugs used in combination [6, 7, 8, 9, 10] but we are not aware of any published study that has compared combinations of three or more antihypertensives. Further, these studies measured a limited range of parameters and drug combinations. In addition, some believe that heart rate and the diastolic filling period may account for differences between antihypertensive classes [11, 12] and that ejection duration may also play a role [13], although the sizes of these contributions are largely unknown.

A second issue is the degree to which changes in brachial BP following antihypertensive therapy reflect changes in aortic waveform parameters. In other words, how well does brachial BP measurement capture effects of antihypertensives on these parameters? Knowledge of this would help clinicians to predict the effect on the latter when brachial BP is used as a target in such therapy. One body of evidence that informs such predictions is a meta-analysis of clinical trials, which showed that, relative to their effects on brachial BP, antihypertensives had differential effects on central BP and AIx [14]. Other clinical trials have shown that different antihypertensives had similar effects on brachial BP yet differential effects on other waveform parameters [10, 15]. However, as this prior research measured a limited scope of parameters and drug combinations, study of a wider range of waveform parameters and antihypertensive regimens appears worthwhile.

The objectives of this paper were to: 1) compare associations that various antihypertensives (no treatment, monotherapies and polytherapies) have with BP variables (waveform

parameters) and, 2) examine the contributions of heart rate, systolic ejection period (SEP) and diastolic duration to therapy-related differences in these associations. Particular attention was given to beta-blockers (βBs) as previous studies have found them to be less effective than other antihypertensives in reducing some of these parameters [7, 16, 17, 18]. To build on existing research, in our analyses, we included a wider range of aortic waveform measures and antihypertensive regimens than used in previous studies.

Material and methods

Participants

The present study is a baseline (cross-sectional) analysis of the ViDA (Vitamin D Assessment) study, a randomised controlled trial of the health effects of vitamin D supplementation. Inclusion criteria were men and women aged 50–84 years and resident in Auckland at recruitment. Exclusion criteria included: 1) diagnosis of a terminal illness and/or in hospice care, 2) intending to leave New Zealand during the follow-up period, 3) taking vitamin D supplements (including cod liver oil) of > 600 IU per day, 4) history of renal stones, hypercalcaemia, or medical conditions that can cause hypercalcaemia and 5) baseline serum calcium > 2.50 mmol/L. All baseline data were collected during 2011–2012. Ethics approval was provided by the Ministry of Health Multi-region Ethics Committee. Written, informed consent was obtained from each participant. Full details have been published elsewhere [19].

Anthropometry, demographics and past medical history

All measurements were carried out by trained staff using a standardised protocol. Without shoes and in light clothing, height was measured with a stadiometer (± 0.1 cm) and weight with digital scales (± 0.1 kg). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Demographic and past medical history data were collected via questionnaires administered by trained interviewers. Ethnicity was defined by self-identification. Because patients may be more likely to be administered specific antihypertensives if they have diabetes or heart failure [20], and this could introduce indication bias in our analyses, we recorded these conditions at baseline. Participants were identified as having diabetes if they indicated that they had been told by a doctor that they have diabetes and were currently receiving insulin, medicines,

tablets or pills as treatment. Participants were identified as having a history of heart failure if they had been told by a doctor that they have heart failure.

Medications

Records of all medicine prescriptions dispensed for participants before and after their interview dates were collected from the Ministry of Health. Such data included the medicine name, dose, daily dose, frequency and days of supply. To determine that measured waveform parameters could be influenced by prescribed medicines, these medicines must have been taken just prior to the interview. Therefore, medication use was defined as the prescription of a medication with days of supply that encompassed the interview date. Medicines were categorised into nitrates and six major antihypertensive classes: alpha blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), βBs, calcium channel blockers (CCBs) and diuretics. βBs were divided into vasodilating and non-vasodilating βBs, while diuretics were separated into thiazide(-like), loop and potassium-sparing diuretics, as these therapeutic sub-classes may have differential relationships with BP variables [21, 22].

BP variables

After 15 minutes rest while sitting, BP (± 1 mm Hg) was measured three times with an Omron T9P oscillometric device (Omron Healthcare, Kyoto, Japan) placed above the cubital fossa of the left arm and the mean of the two closest measurements were used for analyses. Suprasystolic oscillometry was carried out using a BP + device (Uscom, Sydney, Australia) (formerly called a *R6.5 cardiovascular monitor*; Pulsecor, Auckland, New Zealand), with an appropriately sized cuff positioned on the left upper arm. The BP + device has been shown to: 1) yield central systolic blood pressures that are highly correlated with those assessed by catheter measurement at the ascending aorta or aortic arch [23] and, 2) measure central systolic BP with good intratest and intertest reliability [24]. To improve the quality of the waveforms used in analyses, we decided *a priori* to exclude readings with a signal-to-noise ratio of < 6 dB.

Augmentation index (AIx), an index of arterial stiffness and wave reflection [25], was calculated from the aortic pressure waveform using custom-written Matlab software (Mathworks, Natick, MA). A meta-analysis has shown AIx to be a predictor of CV events [2].

Aortic pressure was separated into reservoir and wave components using custom-written Matlab software (Mathworks, Natick, MA). Reservoir pressure was calculated from pressure measurements, as described elsewhere [26]. Excess pressure was calculated as measured pressure minus reservoir pressure [27]. The integral of the excess pressure waveforms (area under these waveforms) over the cardiac cycle was used to calculate excess pressure integral (EPI). EPI measures pressure associated with excess ventricular work and has been shown to predict CV events independently of brachial SBP [26].

Wave separation analysis was used to separate the aortic pressure waveform into forward and backward components [28]. The amplitude of backward pressure (Pb) was then calculated. Pb determined from this technique has previously been shown to be similar to values obtained using aortic flow waveforms measured by Doppler ultrasound [29]. Moreover, Pb has been shown to predict mortality [30] and CV events [31] independently of brachial BP. Reflection index (RI) was defined as Pb divided by the sum of Pb and the amplitude of the forward pressure [15, 31].

PWV was calculated from the aortic pressure waveform using validated algorithms and derived PWV values have been shown to predict CV events independently of brachial BP [32, 33]. PWV is a known predictor of CV events, as demonstrated in a meta-analysis [3].

The periods of time from the incisura to the start and end of the aortic waveform were taken as the SEP and diastolic duration, respectively [10].

Statistical analysis

Data were analysed using SAS version 9.3 (SAS Institute, Cary, NC). Statistical significance was set at $P < 0.05$. Because of the positively skewed distribution of EPI, this was converted to $\log_e$ for analyses. Among untreated participants, hypertensives were defined as those with a brachial SBP of $\geq$ 140 mm Hg and/or a brachial diastolic BP (DBP) of $\geq$ 90 mm Hg. Characteristics of participants across therapies (none and treatment regimens) were compared using ANOVA (for continuous variables) and χ^2 tests (for categorical variables).

Associations between medicines and BP variables were examined by multivariate linear regression, with potential confounders, age, sex and ethnicity, included as covariates. Further adjustment for BMI, height, diabetes mellitus, heart failure and nitrate use had minimal influence on the regression coefficients of the antihypertensive regimen variables, and results for these less parsimonious statistical models are not reported. For comparisons between untreated and treated people, the former was restricted to those who were hypertensive and was coded as the reference group. This is because at the onset of antihypertensive therapy,

treated participants are assumed to have been hypertensive as this is an implicit requirement of such therapy. Accordingly, untreated normotensives were excluded from all analyses. Including this exclusion group would introduce unwanted reverse causation (higher brachial BP encouraging clinicians to prescribe antihypertensives) as these participants would have brachial BP that is too low to warrant treatment. Heart rate, SEP and diastolic duration were separately added to these models to explore their effects on the relationships.

Differences in BP variables across antihypertensive regimens among treated participants only were examined for statistical significance with the F test. This was done separately for 1- and all-drug regimens. In each case, the reference group was the regimen with the highest sample size.

Using Review Manager version 5.2 (Nordic Cochrane Centre, Copenhagen) [34], forest plots were constructed to illustrate the associations between differences in antihypertensive regimens and BP variables. These show the effect sizes and associated 95% confidence intervals for each pairwise regimen comparison. Overall estimates of the pooled relation were calculated using inverse-variance weighting and with the use of random-effects models (to account for differences in drugs and daily doses across comparisons in each forest plot). Bivariate correlations between BP variables, pulse rate, SEP and diastolic duration were summarised with Pearson correlation coefficients (r).

Results

Table 1 shows participant characteristics and details of their antihypertensive therapy. Sixteen different medicine regimens were analysed: six 1- (n = 840), six 2- (n = 494), three 3- (n = 240) and one 4- (n = 63) drug combinations of antihypertensives grouped into their classes. Across these regimens, age, sex (both $P < 0.0001$) and ethnicity ($P = 0.0029$) varied. Supplementary Table S1 shows the daily doses of the antihypertensives used in these regimens. There was a broad range of drugs and daily doses. While the composition of the regimens was heterogeneous, some antihypertensives made up a significant proportion of their respective class: bendrofluazide and hydrochlorothiazide (diuretics), cilazapril (ACE inhibitors), metoprolol (βBs) and felodipine (CCBs).

Waveform parameters differences between untreated and treated people

Differences in waveform parameters between untreated and treated participants are shown in Table 2. For all regimens, brachial SBP and DBP were lower with antihypertensive use compared to untreated. The difference between treated and untreated ranged from ~ 9 to

18 mm Hg for brachial SBP and from ~ 3 to 9 mm Hg for brachial DBP. Across all regimens, brachial SBP did not vary (P = 0.17) but AIx, $\log_e$(EPI), Pb and RI (all P ≤ 0.0001) did. Similarly, across the 1-drug regimens, there was no difference in brachial SBP (P = 0.23) and DBP (P = 0.21) but there were differences in AIx (P = 0.0002), Pb (P = 0.023) and RI (P < 0.0001). AIx, $\log_e$(EPI), Pb and RI were consistently higher in regimens containing βBs (shaded rows) compared to regimens without βBs. This was both true for monotherapies and combination therapies. Therefore, whether alone or combined with other drugs, the presence of βBs appear to be a potential reason for differences in wave reflection measures and $\log_e$(EPI) between the regimens.

Pairwise comparisons between beta-blockers and other antihypertensives

Given the differences between βBs and non-βBs, forest plots were constructed, which more closely compare differences in BP variables between those on these two regimen groups (Supplementary Fig. S1). Each forest plot compares βBs (the reference group) with one other antihypertensive class. Drugs from other antihypertensive classes are controlled for as they are either absent (in the case of monotherapy comparisons, such as βB-versus-CCB) or are present in both of the regimens being compared (in the case of polytherapy comparisons, such as ACEI/βB-versus-ACEI/CCB comparisons and D/ACEI/βB-versus-D/ACEI/CCB comparisons, which both compare βBs with CCBs, controlling for other antihypertensive classes). Compared to participants on βBs, those on CCBs did not differ in brachial SBP (P = 0.69) and DBP (P = 0.63) but had lower AIx (pooled effect = 3.90, P < 0.0001), $\log_e$(EPI) (pooled effect = 0.10 $\log_e$(mm Hg · s), P = 0.001), Pb (pooled effect = 2.16 mm Hg, P < 0.0001) and RI (pooled effect = 0.019, P < 0.0001). Similarly, compared to participants on βBs, those on ACEIs did not differ in brachial SBP (P = 0.58) and DBP (P = 0.80) but had lower AIx (pooled effect = 4.16, P < 0.0001), $\log_e$(EPI) (pooled effect = 0.12 $\log_e$(mm Hg · s), P = 0.002), Pb (pooled effect = 1.71 mm Hg, P = 0.001) and RI (pooled effect = 0.014, P < 0.0001). Compared to participants on βBs, those on diuretics did not differ in brachial SBP (P = 0.23) and DBP (P = 0.93) but had lower $\log_e$(EPI) (pooled effect = 0.09 $\log_e$(mm Hg · s), P = 0.01) and RI (pooled effect = 0.0138, P = 0.010). In a similar manner, compared to participants on βBs, those on ARBs did not differ in brachial SBP (P = 0.10) and DBP (P = 0.05) but had lower AIx (pooled effect = 5.59, P < 0.0001), $\log_e$(EPI) (pooled effect = 0.13 $\log_e$(mm Hg · s), P = 0.004) and RI (pooled effect = 0.017, P < 0.0001).

The samples of individual regimens in each forest plot were then combined – an aggregated sample for those based on βBs (which appear second in the pair of regimens listed in each forest plot) and a separate aggregated sample for those based on the antihypertensive class they were compared to (which appear first in the pair of regimens listed in each forest plot). Differences in BP variables between these combined samples are shown in Table 3. These values are analogous (similar) to the pooled estimates in the forest plots as both comparisons are based on the same samples. This table shows that, compared to participants on βBs, those on other antihypertensives did not differ in brachial SBP and DBP but had lower $\log_e$(EPI), AIx, Pb and/or RI. These results are similar to those from the forest plots, despite the fact that the βB-other antihypertensive comparisons are calculated differently.

Contribution of heart rate, SEP and diastolic duration to waveform parameter differences

To understand the contribution of heart rate to differences in parameter levels across βB and non-βB regimens, heart rate differences were firstly determined. These differences are shown in Table 3, which indicates that βBs were associated with slower heart rates than ACEIs, CCBs, diuretics and ARBs. Secondly, correlations between heart rate and waveform parameters were examined and these revealed negative relationships ($r = -0.04$ to -0.39). This suggests that a slower heart rate associated with βBs could contribute to higher levels of waveform parameters, which was confirmed by adjusting the initial models shown in Table 3 for heart rate. Thus, correction for heart rate reduced (by 34–57%) or in some cases eliminated differences between βB and non-βB regimens (Table 3).

Similar analyses were applied to explore the effect of the length of systole and diastole. SEP and diastolic duration were longer among those on βB regimens (Table 3). Further, SEP was positively associated with all parameters ($r = 0.12$ to 0.53) except brachial DBP ($r = -0.04$); while diastolic duration was positively correlated with all parameters ($r = 0.05$ to 0.35) except brachial SBP ($P = 0.91$) and DBP ($r = -0.17$). This implied that SEP and diastolic duration should contribute to the differences between βB and other antihypertensives, which was verified by adjusting the initial models shown in Table 3 for these variables. Thus, controlling for the length of systole or diastole attenuated or removed differences in parameter levels across βB and non-βB regimens (Table 3).

Effect of vasodilating beta-blockers and non-thiazide(− like) diuretics

Vasodilating beta-blockers and non-thiazide(-like) diuretics (sample sizes shown in Supplementary Table S1) were subsequently excluded from the analyses for Table 2 and Table 3 and the modified results are shown in Supplementary Tables S2–S4. Removal of vasodilating βBs slightly reduced differences with untreated (Table S2) and slightly increased differences with non-βBs (Table S3). Exclusion of loop and/or potassium-sparing diuretics had minor effects on differences with untreated (Table S2) and βBs (Table S4).

Discussion

Compared to other antihypertensives, βBs were associated with similar levels of brachial SBP and DBP. Despite this, they were associated with higher AIx, $\log_e$(EPI), Pb and RI, suggesting that they have weaker relationships with these parameters. Variation in heart rate between βB and non-βB regimens contributed to these parameter differences.

Compared with untreated hypertensive participants, people receiving antihypertensives had lower brachial SBP, brachial DBP, aortic SBP, AIx and PWV, which is in agreement with findings of clinical trials [7, 9, 16, 17, 18, 35]. Our study builds on these studies by quantifying the magnitude of these effects in a real-world setting, over a wider range of antihypertensive regimens and by showing that several antihypertensive regimens also may reduce Pb and RI (Table 2). Another original finding is that, in several cases, EPI varied between untreated and treated participants (Table 2), suggesting that it could be modified with regimens. Clinical trials are required to confirm this.

The weaker AIx associations with the use of βBs compared to other antihypertensives concurs with clinical trials [7, 16, 17, 18]. We extend this prior work by showing that this is also true for polytherapies including βBs, and by demonstrating that βBs additionally have weaker associations with other waveform parameters – EPI, Pb and RI – particularly when compared with ACEIs and CCBs. Some meta-analyses and large clinical trials have shown βBs to be inferior to other antihypertensives in preventing CV events [36]. This may be explained by these weaker associations with waveform parameters. Altogether, this supports the view that βBs are not optimal drug choices in antihypertensive monotherapy and polytherapy.

Little is known about how much of antihypertensive effects on waveform parameters are mediated through effects on heart rate and SEP. Clinical trials have reported antihypertensive effects on heart rate and/or SEP but did not quantify the contribution of these to effects on BP variables [8, 10, 16, 17, 37, 38, 39]. An exception to this is the finding from the CAFE study

that differential effects of amlodipine- and atenolol-based regimens on aortic BP were predominantly mediated by influences on heart rate [11]. We build on this prior research in two ways. First, by showing that heart rate and SEP largely account for differential relationships with AIx, Pb and RI. Second, by demonstrating that this not only applies to comparisons between a βB and CCB (which was the focus of the CAFE study [11]), but additionally to differences that βBs have with diuretics, ACEIs and ARBs (Table 3). But heart rate is not the only factor accounting for variation between βBs and non-βBs as some differences remained after it was adjusted for (Table 3). Vasodilators (such as CCBs) may reduce the magnitude of the reflected wave by attenuating the vascular tone of peripheral muscular arteries and improving impedance matching [9, 15]. Our results are consistent with this as we observed differences in RI between βBs and vasodilators (CCBs, ACIs and ARBs) after adjustment for heart rate (Table 3).

It has been proposed that a slower heart rate increases the filling time of the ventricles, increasing preload, stroke volume and consequently aortic pulse pressure [12]. Whether this accounts for effects of antihypertensives on aortic waveform parameters has not been previously explored. Therefore, as recommended [40], we investigated whether influences on the diastolic filling period account for associations between antihypertensives and these parameters. Our results support this possibility (Table 3).

Given that βBs were associated with higher levels of aortic waveform parameters yet similar levels of brachial BP variables than non-βBs, effects on the former may be overestimated by brachial BP responses to βB therapy. This is important since brachial SBP and DBP are routinely used as targets in antihypertensive therapy, yet aortic waveform parameters may be more strongly or independently related to CV events [26, 31]. Clinical trials have found that, compared to their impact on brachial SBP, βBs have less favourable effects on AIx [14]. Our findings build on from this prior research by showing that, in addition to AIx, this may be true for EPI, Pb, RI and aortic PWV. Thus, our results support implementing the measurement of central waveform parameters to monitor their responses to antihypertensive therapy rather than reliance on brachial BP alone.

The use of two antihypertensives is often inadequate to control BP but there is little data assessing the efficacy of specific combinations of three or more drugs on brachial and central BP [41]. Our finding that a ACEI/CCB combination was associated with the most favourable (lowest) aortic waveform parameter profile out of all dual therapies is in accordance with clinical trials which have suggested that this is one of the preferred combination therapies for reducing brachial BP and preventing cardiovascular morbidity [42]. Out of all polytherapies

of at least three medicines, the ACEI/CCB/D combination had the lowest levels of aortic waveform parameters. This supports the use of this regimen in polytherapy to achieve optimal benefits on waveform parameters. Clinical trials are required to verify whether this approach is also optimal in terms of CV events.

Diuretics and beta-blockers predominantly comprised the thiazide(-like) diuretic and non-vasodilating beta-blocker subgroups (Supplementary Tables S1–S4), respectively, so their results are mostly applicable to these subgroups. The small reductions in differences in parameter levels compared to untreated (Table S2) and small increases in the differences compared to non-βBs (Table S3) when vasodilating βBs were excluded from analyses are consistent with the view that these drugs are associated with greater decrements in parameter levels than non-vasodilating βBs. A few intervention studies (which measured brachial and central SBP) support this [21] but additional trials are required to confirm whether this is true for the new parameters we measured (such as Pb and RI).

The observational nature of this analysis means that the findings are prone to confounding and cannot establish causal links. However, as demonstrated above, our results are consistent with those from clinical trials. For example, brachial SBP was 9–18 mm Hg lower in treated participants than in untreated people, which concurs with effect sizes reported in clinical trials [43]. In addition, we adjusted for indication bias by controlling for diabetes and heart failure. While residual confounding cannot be excluded, confounding from reverse causation does not seem to be a major explanation for the findings for the following reasons. First, as previously explained (Section 2.5), the inclusion of untreated normotensives introduces reverse causation, but this was reduced by excluding these participants from analyses. Second, reverse causation would create positive antihypertensive-brachial BP relationships since clinicians would prescribe antihypertensives to counter increases in brachial BP, but we did not observe such associations. Third, comparisons were made within regimens with the same number of drugs but reverse causation would more likely arise when comparing regimens with different numbers of drugs since additional drugs would be administered to counter difficulties in reducing brachial SBP and/or DBP. Therefore, forward causation (medicines influencing BP variables) appears to have dominated instead. Strengths of this study are the large sample size, the wide range of waveform parameters and the ability to investigate the potential benefit of polytherapy.

In summary, compared to other antihypertensives, βBs had the same associations with brachial BP variables but weaker associations with wave reflection measures and EPI, even when used in polytherapy. Thus, using brachial SBP and DBP as targets for antihypertensive

therapy may, in the case of βBs, overestimate effects on central haemodynamic measures (such as AIx) which are independently related to risk of CV events [2, 3, 26, 31]. This supports the measurement of central waveform parameters to assess their responsiveness to antihypertensive therapy rather than reliance on brachial BP alone.

Competing interest

Andrew Lowe is a shareholder in and has consulted for Uscom Limited.

Acknowledgements

The Health Research Council of New Zealand funded the ViDA study (HRC 10-400) and supported Dr. Sluyter with a postdoctoral fellowship (HRC 13-604).

References

[1] C.M. McEniery, J.R. Cockcroft, M.J. Roman, S.S. Franklin, I.B. Wilkinson. Central blood pressure: current evidence and clinical importance. Eur. Heart J., 35 (2014), pp. 1719–1725b

[2] C. Vlachopoulos, K. Aznaouridis, M.F. O'Rourke, M.E. Safar, K. Baou, C. Stefanadis Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur. Heart J., 31 (2010), pp. 1865–1871

[3] C. Vlachopoulos, K. Aznaouridis, C. Stefanadis. Prediction of cardiovascular events and all-cause mortality with arterial stiffness. A systematic review and meta-analysis. J. Am. Coll. Cardiol., 55 (2010), pp. 1318–1327.

[4] J.R. Kizer, B. Dahlöf, S.E. Kjeldsen, *et al.*Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: the Losartan Intervention for Endpoint reduction in hypertension study. Hypertension, 45 (2005), pp. 46–52

[5] S. Yusuf. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N. Engl. J. Med., 342 (2000), pp. 145–153

[6] R.G. Asmar, G.M. London, M.E. O'Rourke, M.E. Safar. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. Hypertension, 38 (2001), pp. 922–926.

[7] P. Boutouyrie, A. Achouba, P. Trunet, S. Laurent. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. Hypertension, 55 (2010), pp. 1314–1322

[8] G.M. London, R.G. Asmar, M.F. O'Rourke, M.E. Safar. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. J. Am. Coll. Cardiol., 43 (2004), pp. 92–99.
[9] Y. Matsui, K. Eguchi, M.F. O'Rourke, *et al.* Differential effects between a calcium channel blocker and a diuretic when used in combination with angiotensin II receptor blocker on central aortic pressure in hypertensive patients. Hypertension, 54 (2009), pp. 716–723
[10] B. Williams, P.S. Lacy, S.M. Thom, *et al.*Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation, 113 (2006), pp. 1213–1225
[11] B. Williams, P.S. Lacy. Impact of heart rate on central aortic pressures and hemodynamics. Analysis from the CAFE (Conduit Artery Function Evaluation) study: CAFE-Heart Rate. J. Am. Coll. Cardiol., 54 (2009), pp. 705–713.
[12] T. Nieminen, M. Kähönen, T. Kööbi. Letter by Nieminen et al regarding article, "Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study". Circulation, 114 (2006)
[13] J.E. Sharman, J.E. Davies, C. Jenkins, T.H. Marwick. Augmentation index, left ventricular contractility, and wave reflection. Hypertension, 54 (2009), pp. 1099–1105
[14] C.H. Manisty, A.D. Hughes. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. Br. J. Clin. Pharmacol., 75 (2013), pp. 79–92
[15] C.H. Manisty, A. Zambanini, K.H. Parker, *et al.*Differences in the magnitude of wave reflection account for differential effects of amlodipine- versus atenolol-based regimens on central blood pressure: an anglo-scandinavian cardiac outcome trial substudy. Hypertension, 54 (2009), pp. 724–730.
[16] C.H. Chen, C.T. Ting, S.J. Lin, *et al.* Different effects of fosinopril and atenolol on wave reflections in hypertensive patients. Hypertension, 25 (1995), pp. 1034–1041.
[17] K. Hirata, C. Vlachopoulos, A. Adji, M.F. O'Rourke. Benefits from angiotensin-converting enzyme inhibitor 'beyond blood pressure lowering': beyond blood pressure or beyond the brachial artery? J. Hypertens., 23 (2005), pp. 551–556.
[18] T. Morgan, J. Lauri, D. Bertram, A. Anderson. Effect of different antihypertensive drug classes on central aortic pressure. Am. J. Hypertens., 17 (2004), pp. 118–123.
[19] R. Scragg, A. Stewart, C. Lawes, L. Toop, K.T. Khaw, C.A. Camargo Jr. The vitamin D assessment (ViDA) study: Design of a Randomised Controlled Trial of vitamin D

supplementation to prevent cardiovascular disease, respiratory infection, falls and fractures. J. Steroid Biochem. Mol. Biol. (2015) (e-pub ahead of print)
[20] P.A. James, S. Oparil, B.L. Carter, *et al.* 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA, 311 (2014), pp. 507–520.
[21] M.E. Pedersen, J.R. Cockcroft. The vasodilatory beta-blockers. Curr. Hypertens. Rep., 9 (2007), pp. 269–277.
[22] M.E. Ernst, M. Moser. Use of diuretics in patients with hypertension. N. Engl. J. Med., 361 (2009), pp. 2153–2164
[23] A.C.W. Lin, A. Lowe, K. Sidhu, W. Harrison, P. Ruygrok, R. Stewart. Evaluation of a novel sphygmomanometer, which estimates central aortic blood pressure from analysis of brachial artery suprasystolic pressure waves. J. Hypertens., 30 (2012), pp. 1743–1750
[24] R.E.D. Climie, M.G. Schultz, S.B. Nikolic, K.D.K. Ahuja, J.W. Fell, J.E. Sharman. Validity and reliability of central blood pressure estimated by upper arm oscillometric cuff pressure. Am. J. Hypertens., 25 (2012), pp. 414–420.
[25] J.E. Davies, J. Baksi, D.P. Francis, *et al.* The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. Am. J. Physiol. Heart Circ. Physiol., 298 (2010), pp. H580–H586.
[26] J.E. Davies, P. Lacy, T. Tillin, *et al.* Excess pressure integral predicts cardiovascular events independent of other risk factors in the Conduit Artery Functional Evaluation (CAFE) sub-study of Anglo-Scandanavian Cardiac Outcomes Trial (ASCOT). Hypertension, 4 (2014), pp. 60–68.
[27] J.E. Davies, N. Hadjiloizou, D. Leibovich, *et al.* Importance of the aortic reservoir in determining the shape of the arterial pressure waveform — the forgotten lessons of Frank. Artery Res., 1 (2007), pp. 40–45.
[28] B. Hametner, S. Wassertheurer, A.D. Hughes, K.H. Parker, T. Weber, B. Eber. Reservoir and excess pressures predict cardiovascular events in high-risk patients. Int. J. Cardiol., 171 (2014), pp. 31–36
[29] B. Hametner, S. Wassertheurer, J. Kropf, *et al.*Wave reflection quantification based on pressure waveforms alone-methods, comparison, and clinical covariates. Comput. Methods Prog. Biomed., 109 (2013), pp. 250–259
[30] K.L. Wang, H.M. Cheng, S.H. Sung, *et al.*Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. Hypertension, 55 (2010), pp. 799–805.

[31] T. Weber, S. Wassertheurer, M. Rammer, A. Haiden, B. Hametner, B. Eber. Wave reflections, assessed with a novel method for pulse wave separation, are associated with end-organ damage and clinical outcomes. Hypertension, 60 (2012), pp. 534–541
[32] B. Hametner, S. Wassertheurer, J. Kropf, C. Mayer, B. Eber, T. Weber. Oscillometric estimation of aortic pulse wave velocity: comparison with intra-aortic catheter measurements. Blood Press. Monit., 18 (2013), pp. 173–176.
[33] T. Weber, S. Wassertheurer, B. Hametner, *et al.*Aortic stiffness, measured invasively, or estimated from radial waveforms, predicts severe cardiovascular events. Eur. Heart J., 34 (2013), p. 515.
[34] Review Manager (RevMan). [Computer Program]. Version 5.2. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen (2012).
[35] R. Kelly, J. Daley, A. Avolio, M. O'Rourke. Arterial dilation and reduced wave reflection. Benefit of dilevalol in hypertension. Hypertension, 14 (1989), pp. 14–21
[36] L.H. Lindholm, B. Carlberg, O. Samuelsson. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet, 366 (2005), pp. 1545–1553.
[37] Z. Dhakam, C.M. McEniery, C.J.R. Yasmin, M.J. Brown, I.B. Wilkinson. Atenolol and eprosartan: differential effects on central blood pressure and aortic pulse wave velocity. Am. J. Hypertens., 19 (2006), pp. 214–219.
[38] A.J. Deary, A.L. Schumann, H. Murfet, S. Haydock, R.S. Foo, M.J. Brown. Influence of drugs and gender on the arterial pulse wave and natriuretic peptide secretion in untreated patients with essential hypertension. Clin. Sci., 103 (2002), pp. 493–499
[39] J. Davies, E. Carr, M. Band, A. Morris, A. Struthers. Do losartan and atenolol have differential effects on BNP and central haemodynamic parameters? J. Renin-Angiotensin-Aldosterone Syst., 6 (2005), pp. 151–153.
[40] B. Williams, P.S. Lacy, H. Thurston, *et al.* Response to letters regarding article, "Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study". Circulation, 114 (2006), pp. e540–e541
[41] D.A. Calhoun, D. Jones, S. Textor, *et al.*Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension, 51 (2008), pp. 1403–1419.
[42] P.S. Sever, F.H. Messerli. Hypertension management 2011: optimal combination therapy. Eur. Heart J., 32 (2011), pp. 2499–2506.

[43] J.P. Baguet, B. Legallicier, P. Auquier, S. Robitail. Updated meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure. Clin. Drug Investig., 27 (2007), pp. 735–753.

Table 1. Demographic characteristics of participants across monotherapies and polytherapies.

Medicine regimen	**n**	**Age (y)***	**Male (%)**	**European/Other (%)**	**Maori (%)**	**Pacific (%)**	**South Asian (%)**
Untreated hypertensives	1292	66.3 (0.2)	57	83	4	8	4
1 drug							
ACEI	355	66.4 (0.4)	67	77	7	10	6
αB	51	70.3 (1.1)	98	96	2	2	0
ARB	77	68.2 (0.9)	61	90	3	3	5
βB	134	69.2 (0.7)	64	84	7	0	10
CCB	125	70.1 (0.7)	60	86	8	2	5
D	86	69.3 (0.9)	36	91	3	6	0
2 drugs							
ACEI + βB	73	69.7 (0.9)	81	84	4	8	4
ACEI + CCB	81	70.5 (0.9)	67	73	9	14	50
ACEI + D	199	67.4 (0.6)	54	84	5	9	3
ARB + D	44	70.2 (1.2)	36	93	2	5	0

Medicine regimen	**n**	**Age (y)***	**Male (%)**	**European/Other (%)**	**Maori (%)**	**Pacific (%)**	**South Asian (%)**
βB + D	54	70.1 (1.1)	36	87	6	4	4
CCB + D	34	71.4 (1.4)	32	88	6	3	3
3 drugs							
ACEI + βB + CCB	43	69.2 (1.2)	81	81	7	9	2
ACEI + βB + D	82	68.6 (0.9)	56	76	9	10	6
ACEI + CCB + D	108	68.1 (1.0)	59	79	9	8	4
4 drugs							
ACEI + βB + CCB + D	62	69.6 (1.0)	69	77	10	11	2
***P-value*†**		**< 0.0001**	**< 0.0001**	**0.0029**			

ACE = ACE inhibitor; αB = Alpha blocker; ARB = Angiotensin receptor blocker; βB = Beta-blocker; CCB = Calcium channel blocker; D = Diuretic. *Values are mean (standard error); †P-values test for differences across all-drug regimens (those < 0.05 are in bold).

Table 2. Variation in blood pressure variables across monotherapies and polytherapies[1].

Medicine regimen	n	Brachial SBP (mmHg)	Brachial DBP (mmHg)	Aortic SBP (mmHg)	Augmentation index	loge (excess pressure integral (mmHg.s))	Backward pressure amplitude (mmHg)	Reflection index (x 10^{-3})	Pulse wave velocity (m/s)
Untreated hypertensives	1292	152.7 (1.5)	85.0 (0.4)	144.0 (1.4)	33.0 (1.0)	1.46 (0.02)	24.8 (0.3)	386.9 (1.4)	10.4 (0.1)
1 drug [#]		P = 0.23	P = 0.21	P = 0.22	**P = 0.0002**	P = 0.10	**P = 0.023**	**P < 0.0001**	P = 0.17
ACEI	355	−13.6 (1.0)[‡]	−6.1 (0.6)[‡]	−13.5 (0.9)[‡]	−4.8 (0.7)[‡]	−0.12 (0.2)[‡]	−3.2 (0.4)[‡]	−6.8 (1.9)[‡]	−0.5 (0.1)[‡]
αB	51	−16.8 (2.3)[‡]	−7.4 (1.4)[‡]	−16.4 (2.2)[‡]	−4.0 (1.6)[†]	−0.11 (0.5)[*]	−3.7 (0.8)[‡]	−1.0 (4.6)	−0.8 (0.1)[‡]
ARB	77	−8.8 (1.9)[‡]	−3.4 (1.1)[†]	−9.2 (1.8)[‡]	−6.0 (1.3)[‡]	−0.14 (0.04)[†]	−2.7 (0.7)[‡]	−8.1 (3.7)[*]	−0.3 (0.1)[‡]
βB	134	−13.4 (1.5)[‡]	−5.8 (0.9)[‡]	−12.2 (1.4)[‡]	0.8 (1.0)	−0.03 (0.03)	−1.4 (0.5)[†]	9.7 (3.0)[†]	−0.6 (0.1)[‡]
CCB	125	−13.9 (1.5)[‡]	−5.9 (0.9)[‡]	−14.2 (1.5)[‡]	−3.9 (1.0)[‡]	−0.16 (0.03)[‡]	−3.8 (0.6)[‡]	−10.9 (3.0)[‡]	−0.6 (0.1)[‡]
D	86	−11.5 (1.8)[‡]	−4.0 (1.1)[‡]	−11.0 (1.7)[‡]	−3.7 (1.2)[†]	−0.15 (0.04)[‡]	−2.6 (0.7)[‡]	−1.2 (3.6)	−0.4 (0.1)[‡]
2 drugs[#]		P = 0.15	**P = 0.026**	P = 0.067	P = 0.21	P = 0.21	P = 0.21	**P = 0.0050**	P = 0.13
ACEI + βB	73	−18.2 (1.9)[‡]	−8.7 (1.1)[‡]	−17.4 (1.8)[‡]	−3.8 (1.3)[‡]	−0.07 (0.04)	−4.3 (0.7)[‡]	0.7 (3.9)	−1.3 (0.1)[‡]
ACEI + CCB	81	−15.9 (1.8)[‡]	−8.8 (1.1)[‡]	−17.5 (1.8)[‡]	−6.5 (1.3)[‡]	−0.12 (0.4)[†]	−4.5 (0.7)[‡]	−14.5 (3.7)[‡]	−0.6 (0.1)[‡]
ACEI + D	199	−13.9 (1.2)[‡]	−5.8 (0.7)[‡]	−13.7 (1.2)[‡]	−3.8 (1.3)[‡]	−0.15 (0.3)[‡]	−3.1 (0.5)[‡]	−5.6 (2.5)[*]	−0.5 (0.1)[‡]
ARB + D	44	−10.6 (2.5)[‡]	−4.1 (1.4)[†]	−10.8 (2.4)[‡]	−7.0 (1.7)[‡]	−0.13 (0.06)[*]	−3.1 (0.9)[‡]	−10.2 (5.0)[*]	−0.4 (0.2)[‡]
βB + D	54	−13.3 (2.2)[‡]	−6.1 (1.3)[‡]	−11.9 (2.2)[‡]	−2.3 (1.5)	−0.03 (0.05)	−2.3 (0.8)[†]	7.2 (4.5)	−0.7 (0.1)[‡]
CCB + D	34	−16.9 (2.8)[‡]	−8.0 (1.6)[‡]	−16.7 (2.7)[‡]	−7.0 (1.9)[‡]	−0.10 (0.06)	−3.6 (1.0)[‡]	−6.1 (5.6)	−0.6 (0.2)[‡]
3 drugs[#]		P = 0.85	P = 0.87	P = 0.36	**P < 0.0001**	P = 0.20	**P = 0.0048**	**P < 0.0001**	P = 0.97
ACEI + βB + CCB	43	−9.5 (2.5)[‡]	−6.7 (1.4)[‡]	−7.9 (2.4)[‡]	1.8 (1.7)	0.04 (0.06)	−0.0 (0.9)	13.0 (5.0)[†]	−0.4 (0.2)[‡]
ACEI + βB + D	82	−13.3 (1.8)[‡]	−7.7 (1.1)[‡]	−12.8 (1.8)[‡]	−1.4 (1.3)	0.06 (0.04)	−1.0 (0.7)	7.7 (3.7)[*]	−0.5 (0.1)[‡]
ACEI + CCB + D	108	−12.8 (1.6)[‡]	−7.5 (0.9)[‡]	−14.3 (1.6)[‡]	−6.6 (1.1)[‡]	−0.04 (0.04)	−3.3 (0.6)[‡]	−13.3 (3.2)[‡]	−0.5 (0.1)[‡]
4 drugs									
ACEI + βB + CCB + D	62	−13.5 (2.1)[‡]	−8.8 (1.2)[‡]	−12.9 (2.0)[‡]	−1.0 (1.4)	0.08 (0.05)	−1.4 (0.8)	9.0 (4.2)[*]	−0.7 (0.1)[‡]
All drugs[#]		P = 0.17	**P = 0.013**	P = 0.053	**P < 0.0001**	**P < 0.0001**	**P = 0.0001**	**P < 0.0001**	P = 0.21

[1]Values are means (standard error) for untreated hypertensives (reference group) and differences in means (standard error) for all other values (adjusted for age, sex and ethnicity). ACE = ACE inhibitor; αB = Alpha blocker; ARB = Angiotensin receptor blocker; βB = Beta-blocker; CCB = Calcium channel blocker; D = Diuretic. *P < 0.05, [†]P < 0.01 and [‡]P < 0.001 compared to untreated hypertensives; [#]P-values test for differences within 1-, 2-, 3- and all-drug regimens (those < 0.05 are in bold). Results for βB regimens are shaded.

Table 3. Differences in blood pressure (BP) variables between participants on beta-blockers and those on drugs from other antihypertensive classes.

Comparison group	Reference group (βB regimens)	BP variable	Difference (standard error)[†]			
			Initial model (IM)	IM + heart rate	IM + SEP	IM + DD
CCB regimens **CCB or (CCB + ACEI) or (CCB + D) or (CCB + D + ACEI)**	βB or (βB + ACEI) or (βB + D) or (βB + D + ACEI)	bSBP	− 0.1 (1.4)	0.7 (1.5)	1.5 (1.4)	0.6 (1.5)
		bDBP	− 0.3 (0.8)	− 1.4 (0.8)	− 0.4 (0.8)	− 1.4 (0.8)
		aSBP	− 1.9 (1.4)	− 0.3 (1.4)	0.2 (1.4)	− 0.7 (1.4)
		AIx	− 4.1 (0.9)*	− 0.7 (0.8)	− 1.8 (0.8)*	− 1.0 (0.8)
		$\log_e$(EPI)	− 0.10 (0.03)*	0.01 (0.03)	− 0.02 (0.03)	− 0.01 (0.03)
		Pb	− 2.1 (0.5)*	− 0.5 (0.5)	− 0.8 (0.5)	− 0.6 (0.5)
		RI	− 19.3 (2.6)*	− 12.5 (2.6)*	− 12.7 (2.4)*	− 13.3 (2.6)*
		PWV	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)
		HR	6.8 (0.8)*	.	.	.
		SEP	− 12.7 (2.1)*	.	.	.
		DD	− 90.0 (11.6)*	.	.	.
ACEI regimens **ACEI or (ACEI + D)**	βB or (βB + D)	bSBP	− 0.9 (1.5)	− 0.3 (1.6)	1.2 (1.5)	− 0.7 (1.6)
		bDBP	0.1 (0.9)	− 0.4 (0.9)	0.3 (0.9)	− 0.6 (0.9)
		aSBP	− 1.8 (1.5)	− 0.6 (1.5)	1.0 (1.5)	− 1.1 (1.5)
		AIx	− 4.3 (0.9)*	− 1.9 (0.9)*	− 1.3 (0.8)	− 2.0 (0.9)*
		$\log_e$(EPI)	− 0.12 (0.03)*	− 0.05 (0.03)	− 0.02 (0.03)	− 0.05 (0.03)
		Pb	− 1.7 (0.5)*	− 0.65 (0.50)	− 0.2 (0.5)	− 0.8 (0.5)
		RI	− 14.0 (2.8)*	− 8.9 (2.7)*	− 4.7 (2.5)	− 9.5 (2.8)*
		PWV	− 0.0 (0.1)	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)
		HR	5.1 (0.9)*	.	.	.
		SEP	− 13.9 (2.2)*	.	.	.

Comparison group	Reference group (βB regimens)	BP variable	Difference (standard error)[†]			
			Initial model (IM)	IM + heart rate	IM + SEP	IM + DD
D regimens **D or (D + ACEI) or (D + CCB + ACEI)**	βB or (βB + ACEI) or (βB + CCB + ACEI)	DD	− 73.3 (12.0)[*]	.	.	.
		bSBP	1.0 (1.5)	1.2 (1.6)	2.8 (1.6)	0.8 (1.6)
		bDBP	1.0 (0.8)	0.2 (0.9)	1.0 (0.9)	0.0 (0.8)
		aSBP	− 0.2 (1.5)	0.8 (1.6)	2.2 (1.5)	0.2 (1.5)
		AIx	− 4.5 (1.0)[*]	− 1.6 (0.9)	− 1.5 (0.9)	− 2.0 (0.9)[*]
		$\log_e$(EPI)	− 0.09 (0.03)[*]	− 0.01 (0.03)	− 0.00 (0.03)	− 0.02 (0.03)
		Pb	− 1.5 (0.5)[*]	− 0.4 (0.5)	− 0.1 (0.5)	− 0.6 (0.5)
		RI	− 14.4 (2.6)[*]	− 9.0 (2.6)[*]	− 7.1 (2.4)[*]	− 10.4 (2.6)[*]
		PWV	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)[*]	0.1 (0.1)
		HR	5.6 (0.9)[*]	.	.	.
		SEP	− 13.7 (2.2)[*]	.	.	.
ARB regimens **ARB or (ARB + D)**	βB or (βB + D)	DD	− 72.3 (12.2)[*]	.	.	.
		bSBP	3.4 (2.1)	4.3 (2.3)	5.6 (2.2)[*]	3.9 (2.3)
		bDBP	2.3 (1.2)	0.1 (1.3)	1.5 (1.3)	0.4 (1.3)
		aSBP	2.0 (2.0)	3.6 (2.2)	5.0 (2.1)[*]	3.0 (2.2)
		AIx	− 5.8 (1.3)[*]	− 2.0 (1.3)	− 2.0 (1.3)	− 2.5 (1.3)
		$\log_e$(EPI)	− 0.13 (0.05)[*]	0.02 (0.05)	0.01 (0.04)	− 0.01 (0.05)
		Pb	− 1.3 (0.8)	1.1 (0.8)	1.1 (0.7)	0.6 (0.8)
		RI	− 16.5 (3.8)[*]	− 8.2 (4.0)[*]	− 3.3 (3.6)	− 9.8 (4.0)[*]
		PWV	0.2 (0.1)	0.3 (0.1)[*]	0.3 (0.1)[*]	0.2 (0.1)[*]
		HR	9.0 (1.2)[*]	.	.	.
		SEP	− 21.6 (3.1)[*]	.	.	.

Comparison group	Reference group (βB regimens)	BP variable	Difference (standard error)†			
			Initial model (IM)	IM + heart rate	IM + SEP	IM + DD
		DD	− 121.8 (16.9)*	.	.	.

SEP = systolic ejection period (ms); DD = diastolic duration (ms); bSBP = brachial systolic BP (mm Hg); bDBP = brachial diastolic BP (mm Hg); aSBP = aortic systolic blood pressure (mm Hg); AIx = augmentation index; $\log_e$(EPI) = $\log_e$(excess pressure integral (mm Hg · s)); Pb = backward pressure (mm Hg); RI = Reflection index ($\times 10^{-3}$); PWV = pulse wave velocity (m/s); HR = heart rate (beats/min); ACEI = ACE inhibitor; ARB = angiotensin receptor blocker; βB = beta-blocker; CCB = calcium channel blocker; D = diuretic. Initial model = BP variable regressed on antihypertensive comparison, age, sex and ethnicity.

† Comparison group minus reference group. * $P < 0.05$.