Central Aortic Reservoir-Wave Analysis Improves Prediction of Cardiovascular Events in Elderly Hypertensives

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Abstract

Several morphological parameters based on the central aortic pressure waveform are proposed as cardiovascular risk markers, yet no study has definitively demonstrated the incremental value of any waveform parameter in addition to currently accepted biomarkers in elderly, hypertensive patients. The reservoir-wave concept combines elements of wave transmission and Windkessel models of arterial pressure generation, defining an excess pressure superimposed on a background reservoir pressure. The utility of pressure rate constants derived from reservoir-wave analysis in prediction of cardiovascular events is unknown. Carotid blood pressure waveforms were measured prerandomization in a subset of 838 patients in the Second Australian National Blood Pressure Study. Reservoir-wave analysis was performed and indices of arterial function, including the systolic and diastolic rate constants, were derived. Survival analysis was performed to determine the association between reservoir-wave parameters and cardiovascular events. The incremental utility of reservoir-wave parameters in addition to the Framingham Risk Score was assessed.
Baseline values of the systolic rate constant were independently predictive of clinical outcome (hazard ratio, 0.33; 95% confidence interval, 0.13–0.82; \( P=0.016 \) for fatal and nonfatal stroke and myocardial infarction and hazard ratio, 0.38; 95% confidence interval, 0.20–0.74; \( P=0.004 \) for the composite end point, including all cardiovascular events). Addition of this parameter to the Framingham Risk Score was associated with an improvement in predictive accuracy for cardiovascular events as assessed by the integrated discrimination improvement and net reclassification improvement indices. This analysis demonstrates that baseline values of the systolic rate constant predict clinical outcomes in elderly patients with hypertension and incrementally improve prognostication of cardiovascular events.

**Keywords**

aging; blood pressure; cardiovascular diseases; hypertension; pulse wave analysis; vascular stiffness

**Introduction**

Central aortic blood pressure and morphological parameters derived from central aortic pressure wave analysis have been proposed as potentially better predictors of cardiovascular risk than traditional brachial blood pressure.1,2 Two clinical trials in hypertensive patients with independent adjudication of clinical end points—the arterial mechanics substudy of the Second Australian National Blood Pressure Study (ANBP2)3 and the Conduit Artery Functional Evaluation (CAFE)4 have reported on associations between central arterial parameters and the subsequent occurrence of cardiovascular events. CAFE assessed on-treatment central aortic blood pressure parameters in a subgroup of the Anglo Scandinavian Cardiac Outcomes Trial5,6 and found that derived central aortic pulse pressure was independently associated with a post hoc defined secondary end point.4 As all measurements were made postrandomization, CAFE could not elucidate the relationship between baseline values of these parameters and outcomes. ANBP2 was a prospective, randomized, open-label, blinded end point study of the effect of angiotensin-converting enzyme inhibitors (ACEi) versus diuretic-based regimens in the treatment of elderly hypertensives.7,8 The full protocol and results have been reported.7,8 The arterial mechanics substudy of ANBP2 participants examined the influence of baseline central aortic function on treatment responsiveness and cardiovascular outcome.3,9 There was no association between any index of central aortic blood pressure or arterial stiffness and outcome, nor was a treatment-related (ACEi-based versus diuretic-based) influence on arterial mechanics demonstrated.3,9,10 ANBP2 remains the only outcome study performed in arterial hypertension that has reported baseline (prerandomization) measurements of central blood pressure parameters.

Reservoir-wave analysis is based on the premise that not all changes in aortic pressure and flow can be ascribed to forward and backward traveling waves.11–14 It attempts to unify wave propagation and 3-element Windkessel models, thereby accounting for the distributed capacitive function of conduit arteries. In reservoir analysis, pressure waveforms are separated into 2 components: a reservoir pressure that relates to arterial compliance and is
temporally uniform throughout the large arterial system but shows a time lag that depends on the location and the wave properties of the arteries; and an excess pressure that is the difference between the total pressure waveform and the reservoir pressure waveform (Figure A). The areas under the reservoir and excess pressure curves as well as their amplitudes have been shown to predict survival in a large cohort of patients undergoing coronary angiography and in a recent analysis from the CAFE study.

Pressure waveform separation into reservoir and excess pressures. A, Calculation of the reservoir pressure waveform permits separation of the pressure waveform into excess (wave-related) and reservoir (conduit-related) pressures with diastolic pressure taken as a baseline. The excess pressure integral (XSPI) and reservoir pressure integral (RPI) are defined by the areas enclosed as shown. B, Effect of changes in $k_s$ and $k_d$ on the final reservoir pressure waveform. The reservoir pressure waveform is represented by the solid blue line. An increase in $k_s$ results in an upward shift of the waveform (represented by the upper blue dashed line), whereas a decrease in $k_s$ results in a downward shift of the waveform (represented by the lower blue dashed line).

If wave reflections are assumed to be of minimal intensity, the rate constant for reservoir filling ($k_s$) will be inversely related to the product of aortic characteristic impedance and total arterial compliance ($k_s = (Z_0 C)^{-1}$). Similarly, the rate constant for reservoir emptying ($k_d$) is inversely related to the product of systemic arterial resistance and total arterial compliance ($k_d = (RC)^{-1}$) and is the reciprocal of the diastolic time constant $\tau$ (Figure B; online-only Data Supplement). The utility of these rate constants for predicting benefit from antihypertensive therapy or clinical outcome is unknown. We therefore applied reservoir-wave analysis to the baseline data from the arterial mechanics substudy of ANBP2 to (1) investigate the prognostic value of reservoir pressure model parameters on cardiovascular outcome in elderly hypertensive subjects and (2) examine any drug-class effects between treatment arms in the cohort.

Methods

The study design and patient recruitment methodology used in ANBP2 have been published previously. Briefly, ANBP2 used a prospective, randomized, open label design with adjudicated and blinded assessment of end points to determine whether an ACEi-based regimen was superior to a diuretic-based regimen in 65 to 84-year-old hypertensive patients. A detailed description of inclusion and exclusion criteria may be found in the online-only Data Supplement. After confirmation of eligibility and before randomization, patients were invited to participate in the arterial mechanics substudy. This substudy comprised participants recruited from the Melbourne sites of the left ventricular hypertrophy substudy cohort of ANBP2. All studies were approved by the Royal Australian College of General Practitioners Ethics Committee, the institutional review committees of participating centers, and conformed to the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Data acquisition in the arterial mechanics substudy has been described previously and is detailed in the online-only Data Supplement. Briefly, carotid arterial waveforms were
acquired by applanation tonometry of the proximal right carotid artery with a pencil-type
tonometer (Millar Micro-tip SPT-301 transducer, 200 Hz sampling rate) calibrated to
brachial mean and diastolic blood pressure. Patients were followed for a mean of 4.4 years
(range 1.3–5.4 years). End points and adjudication processes have been previously
described— the composite end point of the ANPB2 study included fatal and nonfatal
stroke, fatal and nonfatal myocardial infarction, sudden or rapid death from cardiac causes,
other deaths from coronary causes or coronary events associated with coronary intervention,
incident heart failure, acute occlusion of a major feeding artery in any vascular bed other
than cerebral or coronary, death from noncoronary cardiac causes, dissecting or ruptured
aortic aneurysm, or death from vascular causes.8 The primary end point for the current
analysis comprised hard cardiovascular events (fatal and nonfatal myocardial infarction and
stroke), whereas the combined cardiovascular event end point included all events as defined
in the ANBP2 study.

Statistics

Group data are presented as means (±SD) or medians (and interquartile range) for non-
normally distributed data. Normality was investigated by visual inspection of histograms and
confirmed with the Shapiro–Wilk test. Nonparametrically distributed continuous variables
were natural log transformed for multivariate analysis. Chi-square and t tests for independent
samples were used with categorical and continuous variables, respectively. IBM SPSS
Statistics version 22 was used for statistical analyses.

Cox Proportional hazards modeling was applied with the simultaneous entry of covariates
using the ENTER function. First, the independent association of reservoir-wave and central
blood pressure morphological parameters with the primary and combined cardiovascular
outcomes after adjustment for age and sex was assessed (Model 1). Parameters found to
significantly predict outcomes were subsequently entered in a more comprehensive model
adjusted for recognized cardiovascular risk predictors in addition to age and sex, including
brachial systolic blood pressure (SBP), total cholesterol, high-density lipoprotein
cholesterol, heart rate, smoking status, presence of diabetes mellitus, treatment
randomization, and presence of left ventricular hypertrophy according to
electrocardiographic criteria (Model 2). Pulse pressure amplification (PPA), defined as
brachial pulse pressure (PP)/central PP, was also tested in this model. The proportional
hazards assumption was tested by inspection of Schoenfeld residuals. Subgroup analyses
were performed to determine whether associations between reservoir wave parameters and
outcomes were altered by sex, treatment allocation, or age. The incremental utility of
reservoir-wave parameters when added to the Framingham Risk Score (FRS) was assessed
with the integrated discrimination improvement (IDI) and net reclassification improvement
(NRI) indices. Data for patients who were lost to follow-up were censored at the time of the
last contact.

Results

Baseline, prerandomization demographic characteristics are shown in Table 1. Patients who
subsequently experienced events were older, more commonly male, with higher brachial
systolic blood pressures, elevated plasma creatinine with a greater prevalence of previous angina, or myocardial infarction (all \( P < 0.05 \)). There were no relevant differences between the patients recruited in the substudy compared with those in the ANBP2 cohort. Recorded waveforms were not suitable for reservoir-wave analysis in 33 patients (3.8% of the initial 871 patient cohort) leaving 838 includible for further analysis. Baseline reservoir pressure parameters are shown in Table 1. Mean peak reservoir pressure, \( k_s \), and \( k_d \) values were lower in the group experiencing subsequent cardiovascular events compared with those who did not (\( P < 0.05 \) for all comparisons).

**Relationship Between Reservoir Parameters and Central/Brachial Blood Pressure Parameters**

The systolic rate constant \( k_s \) was moderately positively correlated with \( k_d \) (\( R = 0.68, P < 0.001 \)) and weakly correlated with cSBP (\( R = 0.15, P < 0.01 \)), cDBP (\( R = 0.10, P = 0.01 \)), and cPP (\( R = 0.13, P = 0.01 \)). \( k_s \) was not correlated with the central A1x or augmentation pressure. The diastolic rate constant \( k_d \) was weakly positively correlated with both cSBP (\( R = 0.30, P < 0.001 \)) and brachial SBP (\( R = 0.24, P < 0.01 \)) but not with other indices. Reservoir pressure parameters were strongly correlated with central and brachial blood pressures (see online-only Data Supplement).

**Predictors of Cardiovascular Events During Follow Up**

The primary end point comprising fatal and nonfatal stroke and myocardial infarction was observed in 43 patients representing 5.1% of the total 838 patient cohort, whereas the combined cardiovascular end point was reached in 81 patients or 9.7% of the cohort. After adjustment for age and sex (Model 1), only the systolic rate constant \( k_s \) was independently predictive of the incidence of the primary end point (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.18–0.99; \( P = 0.049 \); see Table S1). No other reservoir-wave or central pressure waveform parameter was found to significantly predict the incidence of the primary end point after accounting for age and sex. \( k_s \) also independently predicted the incidence of the combined cardiovascular end point (HR, 0.41; 95% CI, 0.22–0.77; \( P = 0.006 \)) after adjustment for age and sex (see Table S2). Higher values of \( k_s \) were associated with a reduced incidence of both end points. Additionally, PPA ratio was predictive of the combined cardiovascular end point (HR, 1.95; 95% CI, 1.22–3.11; \( P = 0.005 \)). Conversely, higher values of PPA were associated with a higher incidence of the combined cardiovascular end point. Treatment allocation was not associated with differences in the overall incidence of the primary or the combined cardiovascular end points.

**Predictors of Outcome After Adjustment for Known Risk Markers**

Reservoir wave and central aortic pressure waveform parameters found to significantly predict either end point in Model 1 were subsequently entered into Model 2, which adjusted for multiple a priori identified cardiovascular risk markers in addition to age and sex. The systolic rate constant \( k_s \) remained independently associated with the primary end point (HR, 0.33; 95% CI, 0.13–0.82; \( P = 0.016 \); Table 2). Female sex was associated with a significantly reduced rate (HR, 0.38; 95% CI, 0.19–0.75; \( P = 0.006 \)), whereas increasing age (HR, 1.10; 95% CI, 1.03–1.17; \( P = 0.004 \)) and brachial blood pressure (HR, 1.02; 95% CI, 1.01–1.04; \( P = 0.008 \)) were associated with an increased risk of the primary end point.
The systolic rate constant $k_s$ also predicted the combined cardiovascular end point in Model 2 (HR, 0.38; 95% CI, 0.20–0.74; $P=0.004$; Table 2). Age, female sex, brachial SBP, and PPA also predicted the combined cardiovascular end point in this model. Both $k_s$ and PPA remained significant predictors of outcome, despite simultaneous inclusion in Model 2. Increasing values of $k_s$ were predictive of a reduced incidence of both the primary and combined cardiovascular outcomes, whereas the converse was observed with PPA values. A higher PPA (indicating higher brachial PP relative to central PP) was associated with a higher incidence of the combined cardiovascular end point. In this context, increased PPA was driven by higher brachial SBP in patients subsequently experiencing an event (mean brachial SBP 166 mm Hg versus 161 mm Hg in patients not experiencing an event, $P=0.028$) rather than a decrease in central SBP. These findings are consistent with those observed previously in this cohort.9

**Effect of Treatment Allocation, Age, and Patient Sex**

We separated the 838 patients by randomized treatment into diuretic- and ACEi-treated subgroups. $k_s$ was significantly associated with both end points among diuretic-treated patients (HR, 0.13; 95% CI, 0.04–0.50; $P=0.003$ for the primary end point and HR, 0.21; 95% CI, 0.08–0.54; $P=0.001$ for the combined cardiovascular end point), whereas no significant association was observed among the ACEi-treated patients (see Table S3). Similarly, after separation into male and female subgroups, $k_s$ was found to be significantly associated with both end points among male patients (HR, 0.26; 95% CI, 0.08–0.83; $P=0.024$ for the primary end point and HR, 0.30; 95% CI, 0.13–0.70; $P=0.005$ for the combined cardiovascular end point), whereas this was not observed among female. No significant interaction between $k_s$ and age was evident for either end point.

**Incremental Predictive Utility of $k_s$**

The c-statistic for $k_s$ was lower than that for the FRS in prediction of the primary end point (0.58 versus 0.66, $P=0.03$). However, there was no significant difference noted between the c-statistics for $k_s$ and the FRS in predicting the combined cardiovascular end point (0.60 versus 0.62; $P=0.99$). Addition of $k_s$ to the FRS resulted in a nonsignificant increase in the c-statistic from 0.66 to 0.68 ($P=0.280$) with regard to the primary end point with a nonsignificant increase from 0.62 to 0.66 ($P=0.084$) noted with the combined cardiovascular end point (see Figures S1 and S2). As comparison of c-statistics is known to underestimate improvements in discrimination with the addition of novel biomarkers,17 we tested the incremental utility of $k_s$ added to the FRS with the IDI and NRI statistics.

The systolic rate constant $k_s$ significantly improved discrimination of the FRS for the primary end point as assessed by IDI (IDI=0.0072; $P=0.003$). Similarly, with regard to the combined cardiovascular end point, addition of $k_s$ to the FRS resulted in a significant improvement in discrimination (IDI=0.015; $P=0.001$). A significant improvement in NRI was observed with the addition of $k_s$ to the FRS in predicting the combined cardiovascular end point, but not with regard to the primary end point (NRI=0.27; $P=0.02$ for the combined cardiovascular end point versus NRI=0.14; $P=0.37$ for the primary end point).
Discussion

This analysis represents the first application of the reservoir-wave model in a large hypertensive patient cohort in whom prerandomization, direct measurements of central (carotid) BP were available and in whom outcome was formally documented. The systolic rate constant $k_s$ was independently associated with incident cardiovascular events over a mean 4.4-year follow-up period and significantly improved the discriminative power of the FRS to predict incident cardiovascular events. These findings highlight the potential utility of reservoir-wave analysis applied to noninvasive tonometric recordings of central arterial pressure in risk prognostication.

The compliance ($C$) of the proximal ascending aorta is known to decrease with advancing age caused by elastin fatigue, increasing atherosclerosis, and other factors. Changes in $k_s$ in all probability represent manifestations of large artery stiffening, with the increased incidence of adverse cardiovascular outcomes in patients with a low $k_s$ explainable as a consequence of major organ system exposure to ill-matched rates of pressure transmission. As derived, the systolic rate constant $k_s$ is inversely proportional to the product of $Z_0$ and $C$ (see online-only Data Supplement). This cohort of elderly hypertensive patients is likely to represent a group with uniformly low aortic compliance. Although it is difficult to separate individual contributions of each constituent parameter, from the water hammer equation $Z_0$ is proportional to pulse wave velocity; therefore, lower values of pulse wave velocity (representing lower $Z_0$) may account for higher $k_s$ values, potentially explaining the protective effect of this parameter on outcomes in our analysis. Against this background, a high $k_s$ may identify a cohort of patients with lower aortic characteristic impedance and arterial stiffening who subsequently have a lower incidence of cardiovascular events. The lack of an independent association between the diastolic rate constant $k_d$ and primary hard outcomes highlights the potential predominance of systolic aspects of ventriculo–vascular interaction, aortic systolic pressure generation, and transmission with regard to end-organ damage and cardiovascular events in elderly hypertensives.

Interactions between $k_s$, randomized treatment, and sex were observed in subgroup analyses. Although these results should be considered hypothesis generating only, possible pathophysiological explanations may relate to differing mechanisms of antihypertensive action and to sex-related differences in ventriculo–vascular coupling. Diuretic therapy, particularly with longer acting agents, has been shown to reduce rates of cerebrovascular and coronary events. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial demonstrated the superiority of diuretic therapy over either lisinopril or amlodipine in hypertensive patients aged $>$55 years. A higher $k_s$ value may identify patients with lower baseline characteristic impedance, relatively less fixed large vessel stiffness, and a greater potential to respond to diuretic-induced volume depletion. With respect to sex differences, the lower incidence of both end points in females may have resulted in reduced power to detect a significant association between $k_s$ and outcomes. Alternatively, this disparity may relate to the recognized differences in markers of arterial stiffness between age-matched males and females. Our findings merit further investigation in an adequately powered study.
Higher PPA was associated with a higher subsequent incidence of the combined cardiovascular end point. Although this may seem to run counter to currently accepted dogma, it is important to recognize that increased PPA in our population was driven by higher brachial SBP with relatively uniform central SBP in the population experiencing events. Previous analyses linking lower PPA with cardiovascular outcomes typically report higher central SBP values for a given brachial SBP value. This distinction is pertinent as greater transmission of pulsatile pressure may be operative in the former setting (resulting in greater end-organ exposure to pulsatile stress), whereas relatively increased wave reflection may be responsible for the latter (resulting in greater LV afterload). As a simple ratio of peripheral PP to central PP, PPA is unable to distinguish between these distinct scenarios.

The novel aspect of the aortic reservoir-wave model is its inclusion of aortic Windkessel function in accounting for the relationship between aortic blood pressure and blood flow. In particular, the model accounts for the relative absence of diastolic blood flow that has traditionally been explained by the influence of reverse travelling pressure and flow waves. Our results are consistent with the hypothesis that the central aortic pressure waveform is principally influenced by local ventriculo-vascular interactions involving stroke volume, aortic diameter, and stiffness of the vascular compartment into which the stroke volume is ejected (ie, a more or less compliant proximal aorta) than by reflection of discrete waves. These observations could account for the noted lack of predictive association between pulse wave analysis parameters and cardiovascular outcomes in ANBP2 and the weak associations seen in CAFE and Strong Heart and suggests that the relevance of wave reflection may be no greater in elderly hypertensives (with presumably stiffer aortas) than in the younger groups included in the other 2 studies.

Hametner and colleagues recently reported that peak reservoir pressure was independently and positively correlated with clinical outcome. Davies et al, however, found the excess pressure integral, but not peak reservoir pressure, when measured directly from radial tonometric pressure waveforms was predictive of events in a subanalysis of the CAFE cohort. These divergent results may be a consequence of multiple methodological differences between studies. We used tonometric carotid pressure waveforms as a surrogate for the central aortic pressure waveform, and the study performed by Hametner and colleagues used radial tonometry with the Sphygmocor generalized transfer function to estimate the central aortic waveform after application of a transfer function, whereas Davies et al used untransformed radial tonometric traces. Additionally, the patient groups differed significantly with an inclusive definition of cardiovascular events applied in the ANBP2 cohort. Our findings may be of particular applicability to older patients (>65 years of age) where vascular stiffening and generalized reductions in compliance may be well established.

**Limitations and Strengths**

As this is a post hoc analysis performed in a subgroup of the larger ANBP2, the results as described are hypothesis generating and require prospective confirmation in a larger cohort of patients. Conclusions relating to subgroups, including those defined by sex or treatment allocation, should be interpreted within this context. Additionally, echocardiographic data
relating to left ventricular function as assessed by ejection fraction was not available for this cohort. As ventricular function is an important determinant of prognosis, we cannot exclude the possibility that inclusion of left ventricular ejection fraction in the survival analysis could have altered our results. Conversely, important strengths of this analysis include its large size and the prospective collection of end point events and subsequent independent adjudication by an end point committee blinded to treatment allocation.

**Perspectives**

Although these findings can be considered as hypothesis generating, the clear differences in clinical outcome seen between patients with varying $k_s$ and the incremental prognostic benefit seen with this parameter strongly suggests that the reservoir-wave hypothesis applied to noninvasively obtained carotid pressure waveforms is of potential clinical utility. From a practical standpoint, acquisition of the carotid pressure waveform from the common carotid pulsation with a hand-held tonometer is safe and easily performed, with acquisition typically complete within 5 to 10 minutes. The tonometer is widely commercially available and the analysis required to estimate $k_s$ is easily performed with computational software. These findings support the concept that the time course of aortic pressure rise and fall in the proximal conduit vessels may be of greater importance than traditional pulse wave morphological parameters, including pulse pressure and AIx that assess pressure amplitude only.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**References**


Novelty and Significance

What Is New?

- This study demonstrates the prognostic utility of a systolic rate constant (ks), derived from reservoir wave analysis, in a large, prospectively evaluated cohort of patients with rigorously adjudicated follow-up of clinical events.
- Addition of ks to the Framingham risk score incrementally improves predictive accuracy for cardiovascular events.
- Measurement of ks from noninvasively acquired carotid pressure waveforms is straightforward, without the need for pressure calibration or vascular transfer functions.
- First demonstration of conduit artery systolic function predicting cardiovascular outcomes.

What Is Relevant?

- Calculation of ks from the central aortic pressure waveform enhances prediction of cardiovascular risk and provides important insights into ventricular–vascular interaction.
- Aortic systolic behavior is an important determinant of outcomes in hypertension.

Summary

The systolic rate constant ks measured from the central aortic blood pressure waveform indicates disturbed cardiovascular function and independently predicts cardiovascular outcomes.
A. Calculation of the reservoir pressure waveform permits separation of the pressure waveform into excess (wave-related) and reservoir (conduit-related) pressures with diastolic pressure taken as a baseline. The excess pressure integral (XSPI) and reservoir pressure integral (RPI) are defined by the areas enclosed as shown.

B. Effect of changes in $k_s$ and $k_d$ on the final reservoir pressure waveform. The reservoir pressure waveform is represented by the solid blue line. An increase in $k_s$ results in an upward shift of the waveform (represented...
by the upper blue dashed line), whereas a decrease in $k_s$ results in a downward shift of the waveform (represented by the lower blue dashed line).
### Table 1

Baseline Demographic Characteristics and Reservoir-Wave Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SEM)</th>
<th>Event (n=81)</th>
</tr>
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<tbody>
<tr>
<td><strong>Baseline Demographic Characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>71.6 (0.17)</td>
<td>73.47 (0.55)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.0 (0.32)</td>
<td>165.9 (1.10)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.9 (0.46)</td>
<td>73.8 (1.34)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6 (0.14)</td>
<td>26.73 (0.35)</td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td>161.8 (1.10)</td>
<td>161.2 (3.00)</td>
</tr>
<tr>
<td>Central DBP, mm Hg</td>
<td>81.0 (0.39)</td>
<td>82.8 (1.29)</td>
</tr>
<tr>
<td>Central PP, mm Hg</td>
<td>80.8 (0.99)</td>
<td>78.4 (2.95)</td>
</tr>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>160.9 (0.75)</td>
<td>166.2 (2.25)</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>81.7 (0.39)</td>
<td>83.6 (1.25)</td>
</tr>
<tr>
<td>Brachial PP, mm Hg</td>
<td>79.2 (0.63)</td>
<td>82.6 (2.20)</td>
</tr>
<tr>
<td>Brachial MBP, mm Hg</td>
<td>113.1 (0.56)</td>
<td>114.1 (1.61)</td>
</tr>
<tr>
<td>Heart Rate, bpm</td>
<td>69.9 (0.37)</td>
<td>69.5 (1.41)</td>
</tr>
<tr>
<td>Alx, %</td>
<td>34.5 (0.45)</td>
<td>33.1 (1.31)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.6 (0.04)</td>
<td>5.6 (0.11)</td>
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<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4 (0.02)</td>
<td>1.3 (0.06)</td>
</tr>
<tr>
<td>Non-fasting glucose</td>
<td>5.4 (0.07)</td>
<td>5.3 (0.154)</td>
</tr>
<tr>
<td>Plasma creatinine, μmol/L</td>
<td>87.2 (0.71)</td>
<td>94.5 (2.35)</td>
</tr>
<tr>
<td>Male sex, % (N)</td>
<td>42 (332)</td>
<td>64 (56)</td>
</tr>
<tr>
<td>Randomized to ACEi, % (N)</td>
<td>50 (389)</td>
<td>55 (48)</td>
</tr>
<tr>
<td>Ex smoker/current smoker, % (N)</td>
<td>43.7 (342)</td>
<td>58.0 (51)</td>
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<td>Hypertension history, % (N)</td>
<td>73.6 (576)</td>
<td>73.9 (65)</td>
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<td>Myocardial infarction history, % (N)</td>
<td>2.2 (17)</td>
<td>8.6 (7)</td>
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<tr>
<td>Angina history, % (N)</td>
<td>3.3 (25)</td>
<td>11.0 (8)</td>
</tr>
<tr>
<td>Diabetes mellitus, % (N)</td>
<td>6.0 (47)</td>
<td>6.8 (6)</td>
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| Reservoir-wave parameter        |                                   |              |
| Peak reservoir pressure, mm Hg  | 136.1 (0.86)                      | 133.2 (2.09) |
| Peak reservoir pressure (less diastolic pressure), mm Hg | 54.6 (0.71) | 50.6 (1.36) |
| $k_s$ (Natural Log transformed) | -2.78 (0.015)                     | -2.92 (0.039) |
| $k_d$ (10^-2)                   | 1.82 (0.029)                      | 1.64 (0.077) |
| Reservoir pressure integral (above diastole), mm Hg s | 20.1 (0.26) | 19.6 (0.85) |
| Excess pressure integral, mm Hg s | 8.1 (0.12)                      | 8.6 (0.43)   |

Results are presented as mean (SD) or n (%) for categorical data. ACEi indicates angiotensin-converting enzyme inhibitors; Alx, augmentation index; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; $k_s$, rate constant of systolic aortic filling; $k_d$, rate constant of diastolic aortic emptying; PP, pulse pressure; and SBP, systolic blood pressure. * P<0.05 and † P<0.001 comparing those experiencing a

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cardiovascular event with those not experiencing an event by Student’s $t$ test/Mann–Whitney U test for continuous variables or chi-square test for categorical variables.
### Table 2
Multivariate Cox Proportional Hazards Analysis: Primary and Combined Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
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<td>Primary end point</td>
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<td></td>
</tr>
<tr>
<td>Systolic rate constant $k_s$</td>
<td>0.33</td>
<td>0.13–0.82</td>
<td>0.016</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.10</td>
<td>1.03–1.17</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>0.38</td>
<td>0.19–0.75</td>
<td>0.006</td>
</tr>
<tr>
<td>Brachial SBP</td>
<td>1.02</td>
<td>1.01–1.04</td>
<td>0.008</td>
</tr>
<tr>
<td>Combined cardiovascular end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic rate constant $k_s$</td>
<td>0.38</td>
<td>0.20–0.74</td>
<td>0.004</td>
</tr>
<tr>
<td>Pulse pressure amplification ratio</td>
<td>1.76</td>
<td>1.05–2.93</td>
<td>0.03</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.09</td>
<td>1.04–1.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>0.34</td>
<td>0.21–0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Brachial SBP</td>
<td>1.01</td>
<td>1.003–1.024</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Hazard ratios for the primary or secondary end points following adjustment for known risk factors (sex, age, total and HDL cholesterol, brachial SBP, smoking, diabetes mellitus, heart rate, ECG evidence of LVH and treatment allocation). ACEi indicates angiotensin-converting enzyme inhibitor; AIx, augmentation index; CI, confidence interval; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; and SBP, systolic blood pressure.