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Cardiovascular End Points and Mortality Are Not Closer Associated With Central Than Peripheral Pulsatile Blood Pressure Components

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Abstract—Pulsatile blood pressure (BP) confers cardiovascular risk. Whether associations of cardiovascular end points are tighter for central systolic BP (cSBP) than peripheral systolic BP (pSBP) or central pulse pressure (cPP) than peripheral pulse pressure (pPP) is uncertain. Among 5608 participants (54.1% women; mean age, 54.2 years) enrolled in nine studies, median follow-up was 4.1 years. cSBP and cPP, estimated tonometrically from the radial waveform, averaged 123.7 and 42.5 mm Hg, and pSBP and pPP 134.1 and 53.9 mm Hg. The primary composite cardiovascular end point occurred in 255 participants (4.5%). Across fourths of the cPP distribution, rates increased exponentially (4.1, 5.0, 7.3, and 22.0 per 1000 person-years) with comparable estimates for cSBP, pSBP, and pPP. The multivariable-adjusted hazard ratios, expressing the risk per 1-SD increment in BP, were 1.50 (95% CI, 1.33–1.70) for cSBP, 1.36 (95% CI, 1.19–1.54) for cPP, 1.49 (95% CI, 1.33–1.67) for pSBP, and 1.34 (95% CI, 1.19–1.51) for pPP (P<0.001). Further adjustment of cSBP and cPP, respectively, for pSBP and pPP, and vice versa, removed the significance of all hazard ratios. Adding cSBP, cPP, pSBP, pPP to a base model including covariables increased the model fit (P<0.001) with generalized R^2 increments ranging from 0.37% to 0.74% but adding a second BP to a model including already one did not. Analyses of the secondary end points, including total mortality (204 deaths), coronary end points (109) and strokes (89), and various sensitivity analyses produced consistent results. In conclusion, associations of the primary and secondary end points with

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SBP and pulse pressure were not stronger if BP was measured centrally compared with peripherally. (*Hypertension***. 2020;76:350-358. DOI: 10.1161/HYPERTENSIONAHA.120.14787.)** • Data Supplement

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Blood pressure (BP) is the main modifiable cardiovascular risk factor.[1] Diastolic and mean arterial BP (MAP), the steady BP components, drive blood flow and are similar throughout the arterial tree from the ascending aorta up to the small arterioles, running through vital organs.[2] Systolic BP and pulse pressure (PP), the difference between systolic and diastolic BP oscillate around MAP, make up the pulsatile component of BP. Over half a century of research established systolic BP and PP as cardiovascular risk factor, in particular, in older adults.[2] Placebo-controlled randomized trials in patients with isolated systolic hypertension proved that lowering systolic BP reduced overall cardiovascular risk by over 30%.[3] Over the human lifespan, PP becomes wider because aging and age-related morbid conditions, such as hypertension, diabetes mellitus, or chronic kidney disease degrade the elastic properties of large arteries.[2] Widening of PP at any age is predominantly associated with a larger forward pressure wave,[4] thereby increasing the load on the left ventricle,[5] causing target organ damage,[6] and ultimately cardiovascular complications.[6]

Central systolic BP and central PP are lower than their peripheral counterparts are.[2] The perception that the pulsatile BP component confers risk and the anatomic proximity of the aorta to the heart, brain, and kidney, gave rise to the hypothesis that cardiovascular complications must be more closely associated with central than peripheral systolic BP and PP.[7] However, the evidence supporting a tighter association of cardiovascular end points with central than peripheral BP, remains controversial.[7] To address this knowledge gap, we constructed the IDCARS (International Database of Central Arterial Properties for Risk Stratification), in which data from nine prospective population studies were harmonized and analyzed. In this article, we compared associations of fatal and nonfatal cardiovascular end points with central and peripheral systolic BP and PP.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Participants

All population studies included in IDCARS received ethical approval in their country of origin and adhered to the principles of the Declaration of Helsinki. Participants provided written informed consent. The anonymized IDCARS database was constructed at the Studies Coordinating Centre in Leuven, Belgium. IDCARS cohorts qualified for inclusion in the present analysis, if peripheral and central BP and cardiovascular risk factors had been measured at baseline, and if follow-up included both fatal and nonfatal outcomes. The Data Supplement available online provide detailed information on the population sampling methods, timelines, and countries of recruitment (Table S1 in the Data Supplement). Initial enrollment took place from 1985 until 2015. For the present analysis, baseline refers to the first measurement of central and peripheral BP along with cardiovascular risk factors (October 2000 until February 2016). Across studies, the last follow-up took place from October 2012 to December 2018 (Table S1). References describing the nine cohorts are available in Table S2 and References S1 to S23 in the Data Supplement.

BP Measurement

Peripheral BP was measured immediately before the hemodynamic assessment after participants had rested for at least 5 minutes in the supine position, using standard mercury sphygmomanometers or validated oscillometric devices (Table S3). Peripheral BP was the average or the last of 2 consecutive readings. MAP was peripheral diastolic BP plus one-third of PP. Estimates of central BP were calibrated on peripheral systolic and diastolic BP. Experienced observers recorded the radial arterial waveform at the dominant arm during an 8-second period by applanation tonometry. They used a high-fidelity SPC-301 micromanometer (Millar Instruments Inc., Houston, TX), interfaced with a SphygmoCor CvMS device and a laptop computer running SphygmoCor software. Recordings were discarded if the systolic or diastolic variability of consecutive waveforms exceeded 5% or if the amplitude of the pulse wave signal was below 80 mV, or if the operator index was <70%. From the radial signal, the SphygmoCor software reconstructs the aortic pulse wave by means of a validated generalized transfer function.[8] The software returns systolic, diastolic, MAP, and PP in the ascending aorta.

Ascertainment of End Points

We ascertained vital status and the incidence of fatal and nonfatal end points from the appropriate sources in each country. Prespecified end points were coded according to the *International Classification of Diseases* (Table S4). The primary end point was a composite cardiovascular outcome consisting of cardiovascular mortality and nonfatal end points, including myocardial infarction, heart failure, stroke, and coronary revascularization. Secondary end points included total mortality, fatal and nonfatal coronary end points, and fatal and nonfatal stroke, not including transient ischemic attack. All end points were validated against hospital files or medical records held by primary care physicians or specialists. In all outcome analyses, only the first event within each category was considered. No participant was lost to follow-up.

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.4, maintenance level 5. For between-group comparison of means and proportions, we applied the large-sample Z test and the Fisher exact test, respectively. After stratification for cohort and sex, we interpolated missing values of body mass index, serum creatinine, and blood glucose from the regression slopes on age. In participants with unknown status of smoking or drinking, we set the indicator (dummy) variable to the cohort- and sex-specific mean of the codes (0, 1). For the cohort recruited in Buenos Aires, Argentina, we extrapolated alcohol consumption from national statistics stratified by sex and age.[9] To compute 95% CIs of rates, we applied the formula as $R \pm 1.96 \times \sqrt{(R/T)}$, where R and T are the rate and the number of individuals used to compute the rate.

In multivariable-adjusted Cox regression, we accounted for cohort (random effect), sex, and baseline characteristics including age, body mass index, smoking and drinking status, the ratio of total-to-HDL (high-density lipoprotein) serum cholesterol, the estimated glomerular filtration rate (Chronic Kidney Disease-Epidemiology Collaboration equation), antihypertensive drug intake, history of cardiovascular disease, and diabetes mellitus. To adjust for cohort, we pooled participants recruited in the framework of the European Project on Genes in Hypertension (Kraków, Pilsen, and Padova;

Table 1. Baseline Characteristics of Participants

Characteristic	Statistic (n=5608)
Number (%) with characteristic	
Women	3034 (54.1)
Europeans	2388 (42.6)
Asians	1823 (32.5)
South Americans	1397 (24.9)
Current smoking*	1179 (21.0)
Drinking alcohol*	2818 (50.3)
Office hypertension†	2987 (53.3)
On antihypertensive treatment*	1943 (34.7)
Diabetes mellitus*	338 (6.03)
History of cardiovascular disease*	792 (14.1)
Renal dysfunction‡	700 (12.5)
Mean (±SD) of characteristic	
Age, y	54.2±14.4
Body mass index, kg/m²	25.8±4.8
Peripheral blood pressure, mm Hg†	
Systolic / diastolic, mm Hg	134.1±21.0/80.2±10.7
Pulse pressure, mm Hg	53.9±16.3
Central blood pressure, mm Hg§	
Systolic / diastolic, mm Hg	123.7±21.2/81.2±10.9
Pulse pressure, mm Hg	42.5±16.1
Mean arterial blood pressure, mm Hg	99.3±13.8
Biochemistry‖	
Serum total cholesterol, mg/dL	195.4±38.9
Serum HDL cholesterol, mg/dL	57.5±15.2
Serum non-HDL cholesterol, mg/dL	137.9±39.2
Total-to-HDL cholesterol ratio	3.60±1.11
Serum creatinine, mg/dL	0.93±0.28
Glomerular filtration rate, mL/(min·1.73 m²)‡	82.5±19.6
Blood glucose, mg/dL	90.7±19.2

HDL indicates high-density lipoprotein.

*Assessed by questionnaire at baseline. Current smoking was inhaling tobacco smoke on a daily basis. Drinking alcohol was the occasional or daily consumption of ethanol-containing beverages. Diabetes mellitus was use of antidiabetic drugs, fasting blood glucose of ≥126 mg/dL, random blood glucose of ≥200 mg/dL, a self-reported diagnosis, or diabetes mellitus documented in practice or hospital records.

†Peripheral blood pressure was measured immediately before the hemodynamic assessment after participants had rested in the supine position for ≥5 min with participants, using standard mercury sphygmomanometers or validated oscillometric devices. Hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or use of antihypertensive drugs.

‡The glomerular filtration rate was derived from serum creatinine using the Chronic Kidney Disease–Epidemiology Collaboration formula. Renal dysfunction was a glomerular filtration rate <60 mL/(min/1.73 m²).

§Central blood pressure was measured tonometrically (Table S3).

‖Measured at baseline by automated enzymatic methods in certified laboratories.

Table S1). We checked the proportional hazards assumption by the Kolmogorov-type supremum test and by testing the interaction between follow-up duration and the BP variables. In Cox models, including 2 BP indexes, we uncorrelated the BP levels by regressing one index on the other and by using the residual of one BP index and the measured level of the other. The residual of one BP index is the part of this BP index, which is unrelated to its counterpart on which it was regressed.[10,11] We constructed heat maps to visualize the contribution of central and peripheral BP components to the associations with the end points.[10,11] Improvement in the fit of nested Cox models was assessed by the log-likelihood ratio and the generalized R^2 statistic.[12] Statistical significance was a 2-tailed α-level of ≤0.05.

Results

Baseline Characteristics of Participants

Of 6650 people qualifying for analysis, we excluded 1042 because they were younger than 30 years without end points (n=954), peripheral PP was >130 mm Hg (n=10), central systolic BP was <70 mm Hg (n=1) or >230 mm Hg (n=1), central diastolic BP was >150 mm Hg (n=1) or <55 mm Hg (n=15), or because the pulse wave analysis was missing (n=60). This left 5608 participants for statistical analysis (Table 1). Missing values of body mass index (n=26), smoking (n=245), drinking (n=1069), serum creatinine (n=192), and blood glucose (n=161) were interpolated. Mean age was 54.2 years (Table 1). The study population included 3034 women (54.1%), 2388 (42.6%), 1823 (32.5%), and 1397 (24.9%) Europeans, Asians, and South Americans, 1179 smokers (21.0%), and 2818

Table 2. Correlation Matrix Between Central and Peripheral BP

BP	pSBP	pDBP	pPP	cSBP	cDBP	cPP	MAP
Correlations between measured peripheral and transfer-function derived central BP							
pSBP	…						
pDBP	0.64	…					
pPP	0.87	0.17	…				
cSBP	0.97	0.66	0.81	…			
cDBP	0.65	0.99	0.18	0.67	…		
cPP	0.84	0.20	0.95	0.86	0.20	…	
MAP	0.89	0.89	0.56	0.91	0.90	0.59	…
Correlations of residual BP with measured peripheral and transfer-function derived central BP							
rpSBP	0.23	−0.08	0.34	0.00	−0.08	0.06	−0.04
rpPP	0.15	−0.14	0.29	−0.07	−0.14	0.00	−0.10
rcSBP	0.00	0.23	−0.15	0.23	0.24	0.14	0.25
rcPP	0.10	0.21	0.00	0.32	0.21	0.29	0.28

MAP was peripheral diastolic BP plus one-third of pulse pressure (the difference between pSBP and pDBP). All correlation coefficients were significant (P<0.001) except for the correlation coefficients between the residuals and the measured or transfer-function derived values of the counterpart. BP indicates blood pressure; cSBP/cDBP, central systolic/diastolic BP; MAP, mean arterial BP; pPP/cPP, peripheral/central pulse pressure; pSBP/pDBP, peripheral systolic/diastolic BP; rcSBP/rcPP, residuals derived by regressing cSBP/cPP on pSBP/pPP; and rpSBP/rpPP, residuals of pSBP/pPP derived by regressing pSBP/pPP on cSBP/cPP.

participants (50.3%) reporting alcohol consumption. Of 2987 participants (53.3%) with office hypertension, 1943 (65.0%) were taking antihypertensive drug treatment. The prevalence of diabetes mellitus and a history of cardiovascular disease was 338 participants (6.03%) and 792 (14.1%), respectively. Table S5 and Table S6 list the baseline characteristics of participants by fourths of the distribution of central and peripheral systolic BP. Risk factors, including male sex, the prevalence of hypertension, treated hypertension and renal dysfunction, age, body mass index, serum cholesterol, the total-to-HDL cholesterol ratio, and blood glucose consistently increased (P<0.001) across categories of central (Table S5) and peripheral (Table S6) systolic BP.

Peripheral and Central BP

Systolic/diastolic BP and PP averaged 134.1/80.2 mm Hg and 53.9 mm Hg peripherally and 123.7/81.2 mm Hg and 42.5 mm Hg centrally (Table 1). MAP averaged 99.3 mm Hg. On average, peripheral compared with central diastolic BP was 1.04 mm Hg lower (95% CI, 1.02–1.06 mm Hg; P<0.001). Women had higher heart rate and central and peripheral PP, but lower peripheral systolic BP and lower central and peripheral diastolic BP than men had (Table S7). The central and peripheral BP levels were highly correlated (Table 2). Using the residual approach reduced the correlation coefficients between the corresponding peripheral and central BP indexes from 0.97 for systolic BP and 0.95 for PP to association sizes, which were infinitesimally small (Table 2). The residual BP levels were correlated to their original BP indexes with correlation coefficients ranging from 0.23 to 0.29 and maintained their associations with sex (Table S7) and the continuous covariables, for which analyses were adjusted, that is, age, body mass index, the ratio of high to low-density cholesterol, and the estimated glomerular filtration rate (Table S8).

Absolute Risk Associated With Central and Peripheral BP

Median follow-up of 5608 participants amounted to 4.1 years (fifth–95th percentile interval, 2.2–12.1 years). Across cohorts (Table S1), median follow-up ranged from 2.3 years (fifth–95th percentile interval, 1.4–3.1 years) to 14.0 years (fifth–95th percentile interval, 8.5–14.4 years). During 31610 person-years of follow-up, the primary end point occurred in 255 participants (4.5%); 109 (1.9%) and 89 (1.6%) participants experienced a coronary end point or stroke, and 204 (3.6%) died. The corresponding rates expressed per 1000 person-years (95% CI) were 8.2 (95% CI, 7.2–9.2), 3.5 (95% CI, 2.8–4.1), 2.8 (95% CI, 2.2–3.4), and 6.5 (95% CI, 5.6–7.3), respectively.

Across increasing fourths of the central systolic BP distribution (Table S9), the primary end point occurred in 14 (1.0%), 36 (2.6%), 71 (5.1%), and 134 (9.6%) participants at

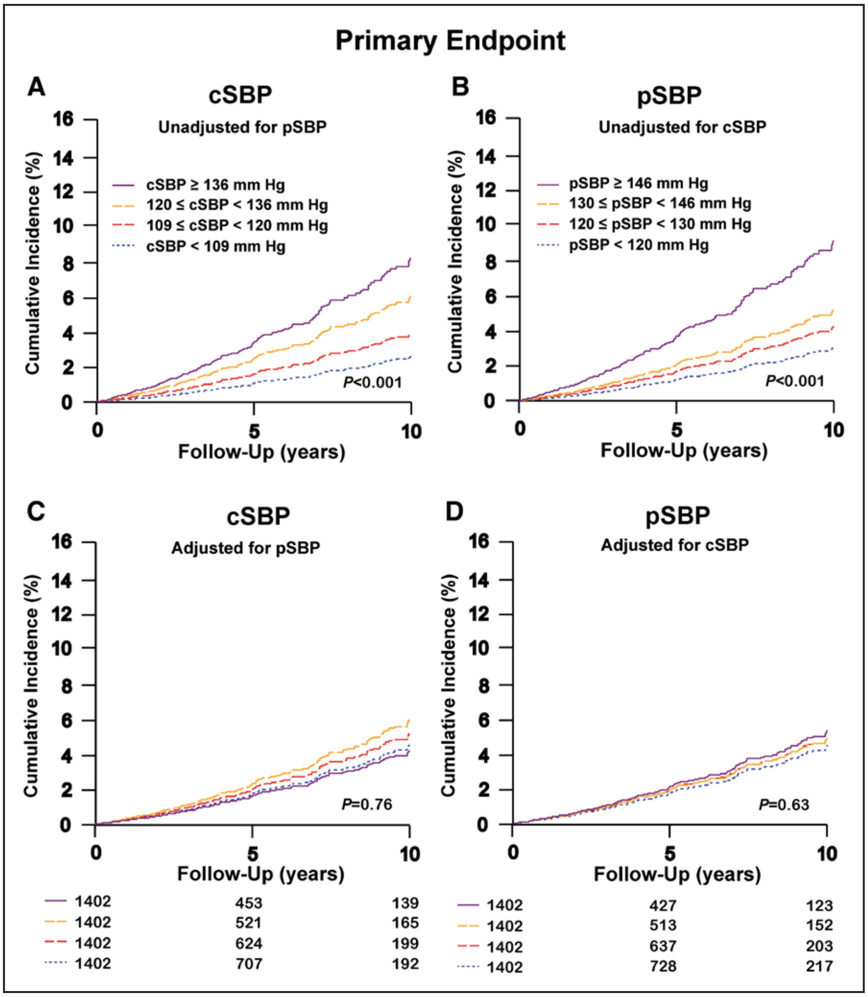

Figure 1. Cumulative incidence of the primary end point by fourths of the distributions of central systolic blood pressure (cSBP) and peripheral systolic blood pressure (pSBP). Tabulated data are the number of participants at risk at 5-y intervals. P values for trend were derived by Cox proportional hazards regression. Estimates accounted for sex and age (**A** and **B**). There were no differences in hazard ratios between cSBP (**A**) and pSBP (**B**; P=0.86). Additional adjustment for pSBP (**C**) or cSBP (**D**) removed the significance.

rates per 1000 person-years of 3.9, 5.1, 9.0, and 16.6, respectively. Similarly, across fourths of the central PP distribution (Table S10), the primary end point occurred in 21 (1.5%), 34 (2.4%), 54 (3.9%), and 146 (10.4%) participants at rates of 4.1, 5.0, 7.3, and 22.0 per 1000 person-years. These rate trends were consistent for the secondary end points across the categories of the central systolic BP and PP (Table S9 and Table S10).

In all Cox models that follow, the proportional hazards assumption was met and the residual method, as described in the statistical methods, was applied if models included two BP components. The sex- and age-adjusted cumulative incidence of the primary end point derived by Cox regression ran higher across increasing categories of central and peripheral systolic BP and PP. There were no differences in hazard ratios between central and peripheral BP components (*P*=0.86 for systolic BP and *P*=0.90 for PP, Figure 1A and 1B and Figure S1A and S1B). Additional adjustment of these BP components for their counterpart weakened these associations to a nonsignificant level (Figure 1C and 1D and Figure S1C and S1D). Findings for the cumulative incidence of the coronary end points (Figure S2) and stroke (Figure S3) in relation to systolic BP and PP were confirmatory.

Relative Risk Associated With the Central and Peripheral Pulsatile BP Components

In analyses adjusted for cohort, sex, age, body mass index, smoking and drinking status, the total-to-HDL serum cholesterol ratio, the estimated glomerular filtration rate, use of antihypertensive drugs, history of cardiovascular disease, and diabetes mellitus (Table 3), associations of the primary end point, total mortality, coronary end points, and stroke with systolic BP and PP were statistically significant (*P*≤0.037), irrespective of whether the pulsatile BP components were measured centrally or peripherally. The interaction terms between the pulsatile BP components and continent of recruitment were not significant in any model (*P*≥0.18).

Further adjustment of central for peripheral pulsatile BP, and vice versa, removed the significance of the associations of the primary end point, total mortality, coronary end points and

Table 3. Association of End Points With the Central and Peripheral Pulsatile BP Components

End Points (Number) BP Index*	Adjusted		Additionally Adjusted for cSBP or cPP*		Additionally Adjusted for pSBP or pPP*	
	HR (95% CI)†	*P* Value	HR (95% CI)†‡	*P* Value	HR (95% CI)†‡	*P* Value
Primary (255)						
cSBP	1.50 (1.33–1.70)	<0.001	…§	…§	1.01 (0.53–1.93)	0.97
cPP	1.36 (1.19–1.54)	<0.001	…§	…§	1.12 (0.67–1.89)	0.66
pSBP	1.49 (1.33–1.67)	<0.001	1.47 (0.79–2.74)	0.22	…§	…§
pPP	1.34 (1.19–1.51)	<0.001	1.20 (0.74–1.96)	0.47	…§	…§
Secondary						
Mortality (204)						
cSBP	1.16 (1.02–1.32)	0.025	…§	…§	0.63 (0.31–1.31)	0.22
cPP	1.18 (1.03–1.35)	0.017	…§	…§	0.77 (0.42–1.38)	0.37
pSBP	1.17 (1.04–1.33)	0.012	1.81 (0.90–3.65)	0.096	…§	…§
pPP	1.19 (1.05–1.36)	0.008	1.53 (0.87–2.66)	0.14	…§	…§
Coronary (109)						
cSBP	1.29 (1.05–1.58)	0.016	…§	…§	1.76 (0.64–4.84)	0.28
cPP	1.30 (1.05–1.60)	0.014	…§	…§	1.92 (0.85–4.33)	0.12
pSBP	1.25 (1.03–1.53)	0.028	0.74 (0.28–1.96)	0.47	…§	…§
pPP	1.23 (1.01–1.50)	0.037	0.68 (0.31–1.47)	0.33	…§	…§
Stroke (89)						
cSBP	1.65 (1.37–1.99)	<0.001	…§	…§	0.96 (0.32–2.88)	0.95
cPP	1.46 (1.19–1.79)	0.003	…§	…§	1.12 (0.46–2.70)	0.81
pSBP	1.64 (1.37–1.96)	<0.001	1.70 (0.59–4.89)	0.33	…§	…§
pPP	1.43 (1.18–1.74)	<0.001	1.30 (0.56–2.99)	0.81	…§	…§

BP indicates blood pressure; cPP, central pulse pressure; cSBP, central systolic BP; HDL, high-density lipoprotein; HR, hazard ratio; pPP, peripheral pulse pressure; and pSBP, peripheral systolic BP.

*pSBP/pPP, peripheral systolic blood pressure/pulse pressure; cSBP/cPP, central systolic blood pressure/pulse pressure.

†All HRs, given with 95% CI, expressed the relative risk associated with a 1-SD increment in BP and accounted for cohort, sex, age, body mass index, smoking and drinking, total-to-HDL serum cholesterol ratio, the estimated glomerular filtration rate, antihypertensive drug intake, history of cardiovascular disease, and diabetes mellitus.

‡HR were for the residual of the BP index.

§Not applicable.

stroke with both pulsatile BP components (Table 3). The log-likelihood ratios (Table 4) confirmed that adding a single pulsatile BP component to a base model including all covariables increased model fit ($P<0.001$) with an increment in the generalized R^2 statistic ranging from 0.37% to 0.74%. However, adding a second pulsatile BP index to a model including already one pulsatile BP component along with covariables did not. Heat maps associating the primary end point with central and peripheral systolic BP or with central and peripheral PP (Figure 2) provided a graphical confirmation of these findings. Heat maps relating the secondary end points to central and peripheral systolic BP (Figure S4) or to central and peripheral PP (Figure S5) were confirmatory.

Sensitivity Analysis

Hazard ratios relating to the primary end point to the central and peripheral pulsatile BP components (Table S11) remained significant when additionally adjusted for diastolic BP ($P\leq0.001$). Significance weakened when these hazard ratios were further adjusted for MAP ($0.026\leq P\leq0.32$) instead of diastolic BP. Sensitivity analyses of the primary end point in relation to central and peripheral pulsatile BP components in various subgroups (Table S12) delineated by treatment status, history of cardiovascular disease, or the presence of renal dysfunction at baseline confirmed the results reported in Table 3.

Discussion

The key point addressed by our study was whether the central pulsatile BP components, as exemplified by systolic BP or PP, provide statistically and clinically relevant improvement in risk stratification over and beyond their counterparts measured peripherally. The risk of the composite cardiovascular end point, total mortality, a coronary end point, and stroke increased with higher pulsatile BP, irrespective of whether pulsatile BP was measured centrally or peripherally. The strength of these associations was similar for central compared with peripheral pulsatile BP. The correlations close to unity ($P\geq0.95$) between the central and peripheral pulsatile BP levels provided the explanation (Table 2). The underlying physiological explanation is that the radial pulse wave is recorded and calibrated on brachial BP, whereas the central waveform, from which central systolic BP and PP are derived, is extrapolated using a transfer function.[8] Recalibration of the radial pulse wave on diastolic BP and MAP to reconstruct the aortic pulse wave did not weaken these correlations (Table S13). Adjustment of the central pulsatile BP for its peripheral counterpart and vice versa removed the significance of both central and peripheral pulsatile BP with gradients in the 5-year risks conferred across the BP scales (Figure 2). Furthermore, diastolic BP was similar centrally and peripherally (Table 1), and women had a higher heart rate and higher central and peripheral PP than men had (Table S7). These observations are in keeping with long-established hemodynamic principles[13] and represent an internal validation of our study results.

Our current findings must be placed within the context of the abundant literature, suggesting that the association of adverse health outcomes with central systolic BP and central PP must be closer than with their peripheral counterparts.

Table 4. Fit of Cox Models Relating the Primary End point to Central and Peripheral Pulsatile Blood Pressure Components

Models	−2 Log L	χ^2 Statistic	*P* Value	R^2 (%)*
Base model†	3661.5			
+cSBP	3621.4	40.1	<0.001	0.713
+cPP	3641.0	20.5	<0.001	0.365
+pSBP	3620.0	41.5	<0.001	0.737
+pPP	3640.7	20.9	<0.001	0.371
Base model including pSBP‡	3620.0			
+cSBP	3620.0	0.004	0.95	<0.001
Base model including pPP‡	3640.7			
+cPP	3640.5	0.18	0.67	0.003
Base model including cSBP§	3621.4			
+pSBP	3620.0	1.35	0.24	0.024
Base model including cPP§	3641.0			
+pPP	3640.5	0.52	0.47	0.009

cPP indicates central pulse pressure; cSBP, central systolic BP; HDL, high-density lipoprotein; pPP, peripheral pulse pressure; and pSBP, peripheral systolic BP.

*R^2 is an estimate of the additional variance explained (https://apha.confex.com/apha/134am/techprogram/paper_135906.htm).

†Included cohort (random effect), sex, and baseline characteristics including age, body mass index, smoking and drinking, total-to-HDL cholesterol ratio, estimated glomerular filtration rate, antihypertensive drug intake, history of cardiovascular disease, and diabetes mellitus.

‡Base model, including pSBP or pPP, respectively, extended by cSBP or cPP.

§Base model, including cSBP or cPP, respectively, extended by pSBP or pPP.

However, approximately half of the published studies had a cross-sectional design with preclinical outcomes.[14-19] The longitudinal studies related a broad spectrum of outcomes with central BP, but applied different technologies to quantify the risk marker and not always accounted for peripheral BP.[16,17,20-25] Other factors limiting the interpretation of the available literature are a sample size of <200,[14,15,26,27] a follow-up confined to 1 year or less,[20] selective enrollment of patients with hypertension,[14,19,22,26,28], renal dysfunction[15,18,29] or coronary heart disease.[20] In a meta-analysis of summary statistics extracted from 11 studies that included 5648 patients followed up for 3.8 years, central PP was only associated with a marginally higher relative risk of clinical end points ($P=0.057$).[30] Most patients were either elderly or had coronary arterial or end-stage renal disease.[30] In the Conduit Artery Function Evaluation Study,[22] the multivariable-adjusted hazard ratios relating peripheral and central PP to the composite cardiovascular end point were similar (1.10 [$P=0.050$] versus 1.11 [$P=0.048$]), again confirming our current findings, but in the setting of a randomized controlled trial.

Strengths and Limitations

From the perspective of generalizability, participants were enrolled in 9 countries and 3 continents. End points encompassed both fatal and nonfatal events, which were all validated against the source documents available in each country. Notwithstanding these strengths, our study has limitations.

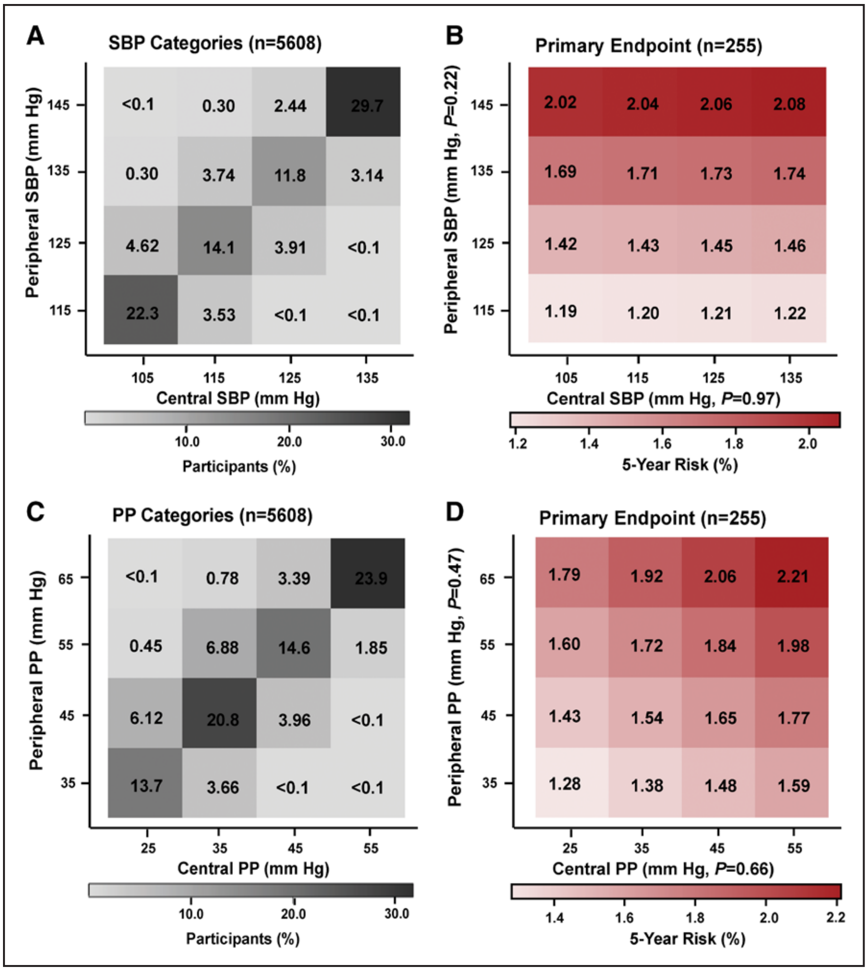

Figure 2. Heat maps depicting the 5-year risk of the primary end point in relation to central and peripheral systolic blood pressure (SBP) or pulse pressure (PP) in 5608 study participants. Heat maps were derived by Cox proportional hazard regression. Risk estimates were standardized to the average of the distributions in the whole study population (mean or ratio) of cohort identifier, sex, age, body mass index, smoking and drinking, the total-to-HDL (high-density lipoprotein) serum cholesterol ratio, the estimated glomerular filtration rate, intake of antihypertensive drug, history of cardiovascular disease, and diabetes mellitus. Numbers in grids **A** and **C** represent the percent of participants within each cross-classification category of central and peripheral SBP or PP. Numbers in grids **B** and **D** represent the 5-year risk of a primary end point.

First, we had no information on blacks of African descent or blacks born and living in Africa, who are more susceptible to the complications of hypertension than other ethnic groups. Second, the tonometric reconstruction of the aortic pulse wave from the radial pulse wave requires the application of a generalized transfer function, which has been criticized.[31] However, the tonometric approach, as applied in our current study, has been invasively validated.[8] Third, the tonometric method requires a 2-point calibration, either on peripheral systolic and diastolic BP or on peripheral diastolic BP and MAP. Whatever calibration was applied, the correlations between the central and peripheral systolic BP components were equally high (Table 2 and Table S13). In calculating peripheral MAP from systolic and diastolic BP, a form factor of 33 or 40 can be applied.[32] Whether MAP is computed using form factor 33 or 40 does not matter in Cox regression (data not shown). Indeed, the difference in calibration on MAP form factor 33 versus 40 involves a constant factor in each individual participant, that is, 7% of PP. This constant will not affect the significance of hazard ratios; if expressed per 1-SD increment in the pulsatile BP, hazard ratios will also be similar. Fourth, the rates of coronary revascularization, a component of the primary and coronary end points differed across cohorts, based on sample size and the age distribution: 2.31% (N=27/1171) in Noordkempen, Belgium; 0.05% (N=1/1823) in JingNing, China; 2.75 (N=35/1271) in Buenos Aires, Argentina; and 2.30% (N=10/435) in Finland. However, analyses were adjusted for cohort as a random effect. Finally, confounding factors, such as antihypertensive treatment, smoking and drinking status, or renal dysfunction, were only assessed at baseline so that they could not be accounted for in a time-dependent manner.

Perspectives

In a large population-based cohort, the strength of the associations of the primary and secondary end points with the central BP components was not stronger than with their peripheral counterparts. Thus, the concept that central systolic BP and central PP would refine risk stratification over and beyond peripheral systolic BP or peripheral PP could not be confirmed. In other words, a carefully recorded peripheral systolic BP or PP is accurate in risk stratification without need of measuring their central counterparts in adults aged ≥30 years. Our current analysis is relevant for clinical medicine but has no bearing on the key role of studying central hemodynamic measurements as a way to gain deeper insight into the pathophysiology of cardiovascular disease.

Appendix

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Disclosures

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Novelty and Significance

What Is New?

- In a population-based cohort of people aged ≥30 years, the risk of a composite cardiovascular end point, total mortality, a coronary end point and stroke increased with higher systolic blood pressure and pulse pressure, irrespective of whether these pulsatile blood pressure components were measured centrally or peripherally. Our study showed that central systolic blood pressure and pulse pressure did not improve risk stratification over and beyond their peripheral counterparts.
- Correlations close to unity between the central and peripheral pulsatile blood pressure levels provided the explanation.

What Is Relevant?

- A carefully recorded peripheral pulsatile blood pressure component is sufficient in risk stratification without the need of measuring their central counterparts to refine risk prediction in adults older than 30 years.
- Our observations are relevant for clinical medicine, but have no bearing on the key role of studying central hemodynamic measurements as a way to gain deeper insight in the pathophysiology of cardiovascular disease.

Summary

Associations of cardiovascular complications with systolic blood pressure and pulse pressure were not stronger if blood pressure was measured centrally, compared with peripherally. The emphasis in daily clinical practice should remain on the careful measurement of brachial blood pressure.