



# Risk Stratification by Cross-Classification of Central and Brachial Systolic Blood Pressure

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**BACKGROUND:** Whether cardiovascular risk is more tightly associated with central (cSBP) than brachial (bSBP) systolic pressure remains debated, because of their close correlation and uncertain thresholds to differentiate cSBP into normotension versus hypertension.

**METHODS:** In a person-level meta-analysis of the International Database of Central Arterial Properties for Risk Stratification (n=5576; 54.1% women; mean age 54.2 years), outcome-driven thresholds for cSBP were determined and whether the cross-classification of cSBP and bSBP improved risk stratification was explored. cSBP was tonometrically estimated from the radial pulse wave using SphygmoCor software.

**RESULTS:** Over 4.1 years (median), 255 composite cardiovascular end points occurred. In multivariable bootstrapped analyses, cSBP thresholds (in mm Hg) of 110.5 (95% CI, 109.1–111.8), 120.2 (119.4–121.0), 130.0 (129.6–130.3), and 149.5 (148.4–150.5) generated 5-year cardiovascular risks equivalent to the American College of Cardiology/American Heart Association bSBP thresholds of 120, 130, 140, and 160. Applying 120/130 mm Hg as cSBP/bSBP thresholds delineated concordant central and brachial normotension (43.1%) and hypertension (48.2%) versus isolated brachial hypertension (5.0%) and isolated central hypertension (3.7%). With concordant normotension as reference, the multivariable hazard ratios for the cardiovascular end point were 1.30 (95% CI, 0.58–2.94) for isolated brachial hypertension, 2.28 (1.21–4.30) for isolated central hypertension, and 2.02 (1.41–2.91) for concordant hypertension. The increased cardiovascular risk associated with isolated central and concordant hypertension was paralleled by cerebrovascular end points with hazard ratios of 3.71 (1.37–10.06) and 2.60 (1.35–5.00), respectively.

**CONCLUSIONS:** Irrespective of the brachial blood pressure status, central hypertension increased cardiovascular and cerebrovascular risk indicating the importance of controlling central hypertension. (*Hypertension*. 2022;79:1101–1111. DOI: 10.1161/HYPERTENSIONAHA.121.18773.) • Supplemental Material

**Key Words:** brachial blood pressure ■ central blood pressure ■ cardiovascular risk ■ hypertension ■ mortality ■ population science

In clinical practice, blood pressure (BP) is routinely measured at the brachial artery. The anatomic proximity of the heart, brain, and kidney to the central arteries and growing insights<sup>1,2</sup> in the role of arterial stiffening in cardiovascular disease led to the view

point that vascular risk must be more closely associated with central than brachial BP. However, the tighter association of cardiovascular risk with central compared with brachial BP remains controversial,<sup>3–6</sup> mainly because of the strong correlation between

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†A list of the International Database of Central Arterial Properties for Risk Stratification Investigators is given in the Appendix.

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## NOVELTY AND RELEVANCE

### What Is New?

In a person-level meta-analysis of the International Database of Central Arterial Properties for Risk Stratification, outcome-driven thresholds for central systolic blood pressure (cSBP) were derived, and risk stratification based on the cross-classification of cSBP with brachial SBP (bSBP) was investigated.

### What Is Relevant?

In multivariable bootstrapped analyses, cSBP thresholds (in mm Hg) of 110, 120, 130, and 150 generated 5-year cardiovascular risks equivalent to the American College of Cardiology/American Heart Association bSBP thresholds of 120, 130, 140, and 160.

Applying 120/130 mmHg as cSBP/bSBP thresholds delineated concordant central and brachial normotension (43.1%)

and hypertension (48.2%) versus isolated brachial hypertension (5.0%) and isolated central hypertension (3.7%).

With concordant normotension as reference, the multivariable hazard ratios for the cardiovascular end point were 1.30 for isolated brachial hypertension, 2.28 for isolated central hypertension, and 2.02 for concordant hypertension.

### Clinical/Pathophysiological Implications?

In the presence of brachial systolic normotension, central systolic hypertension increased cardiovascular and cerebrovascular risk. Women made up close to 70% of the patient with central systolic hypertension but normal bSBP. These findings highlight the role of cSBP in risk stratification, in particular in women, and the need to tailor antihypertensive drug treatment.

## Nonstandard Abbreviations and Acronyms

<b>ACC</b>	American College of Cardiology
<b>AHA</b>	American Heart Association
<b>BP</b>	blood pressure
<b>bSBP</b>	brachial systolic blood pressure
<b>CAFÉ</b>	Conduit Artery Function Evaluation
<b>cSBP</b>	central systolic blood pressure
<b>IDCARS</b>	International Database of Central Arterial Properties for Risk Stratification

central and brachial BP,<sup>5,6</sup> as measured on a continuous scale.

A categorical approach might avoid the incongruities in the published associations of target organ damage<sup>4,5</sup> or the incidence of adverse health outcomes<sup>3,6</sup> with central compared with brachial BP. Central and brachial BPs might be categorized into normotensive versus hypertensive levels, allowing study participants to be cross-classified as being consistently or incoherently normotensive or hypertensive based on their central versus brachial BP.<sup>7–11</sup> Previous studies that applies such approach focused on the prevalence of central versus brachial hypertension<sup>9,11</sup> or related target organ damage cross-sectionally<sup>8,10</sup> or total and cardiovascular mortality prospectively<sup>7</sup> to central hypertension on top of brachial BP. The cross-classification method critically depends on the applied thresholds separating normotension from hypertension. The 2017 US guideline established new brachial BP thresholds.<sup>12</sup> With regard to the central BP thresholds, diastolic BP being similar throughout the arterial tree,<sup>13</sup> only 1 study derived and validated thresholds for central systolic BP against the long-term risk of mortality.<sup>7</sup> In the current study, the

International Database of Central Arterial Properties for Risk Stratification (IDCARS)<sup>6,14</sup> was analyzed to establish an outcome-driven threshold for central systolic BP considering fatal as well as nonfatal cardiovascular end points and to explore whether the cross-classification approach added to risk stratification in the general population.

## METHODS

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

### Study Population

Previous publications describe the construction of the IDCARS database in detail.<sup>6,14</sup> The longitudinal studies extracted from the IDCARS data resource qualified for the current analysis, if information on brachial and central BP and cardiovascular risk factors was available at baseline, if the central BP had been tonometrically measured, if follow-up included both fatal and nonfatal end points, if study reports had been published in peer-reviewed articles, and if the study participants were representative for a population. All studies complied with the Helsinki Declaration on research in humans<sup>15</sup> and were approved by the competent Institutional Review Boards. Participants provided informed written consent. Before transfer to the coordinating office in Leuven, Belgium, the data were stripped from all personal identifiers, and if required by national legislations, additional ethical clearances were obtained. Study-specific information on the catchment areas, sampling strategies, timeframes of recruitment and follow-up, participation rates, and the related literature sources are available in the Table S1 and in the published study protocol.<sup>14</sup>

### BP Measurement

Brachial BP was measured immediately before the hemodynamic assessment after participants had rested for at least 5 minutes, up to 15 minutes, in the supine position, using standard

mercury sphygmomanometers or validated oscillometric devices.<sup>14</sup> Brachial BP was the average or the last of 2 consecutive readings. Estimates of central BP were calibrated on brachial systolic and diastolic BP and derived with the use of the SphygmoCor system.<sup>16</sup> Details of the central BP estimation were described in the Expanded Methods in the Supplemental Material.

### Ascertainment of End Points

Vital status of participants and the incidence of end points were ascertained from appropriate sources in each country. The primary end point was a composite cardiovascular outcome consisting of cardiovascular mortality and nonfatal end points, including death from ischemic heart disease, sudden death, nonfatal myocardial infarction, coronary revascularization, heart failure and fatal and nonfatal cerebrovascular end points. Secondary end points included total mortality, fatal and nonfatal cardiac end points, and fatal and nonfatal cerebrovascular end points. 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.

### Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.4, maintenance level 5. Interpolation of missing values were described in the Expanded Methods in the Supplemental Material.<sup>17</sup> We compared means and incidence rates using the large-sample  $z$  test and proportions by the  $\chi^2$  statistic, respectively.

We obtained diagnostic thresholds for central systolic BP in 5 steps, using a bootstrapped procedure<sup>18</sup> with the risk associated with the office BP categories according to the 2017 American hypertension guideline as reference standard.<sup>12</sup> For the details of the bootstrapped procedure, please refer to the Expanded Methods in the Supplemental Material. After having established the central systolic BP thresholds, the incidence rates of end points were cross-classified by the presence of central and brachial systolic hypertension, irrespective of treatment status. Henceforth, normotension and hypertension refer to the systolic BP status, disregarding the intake of antihypertensive drugs at baseline. The incidence rates of end points were standardized for cohort, sex, and age group ( $\leq 50$  versus  $>50$  years) by the direct method. We computed 95% CIs of rates as  $R \pm 1.96 \times \sqrt{(R/T)}$ , where  $R$  and  $T$  are the rate and the denominator used to calculate the rate.<sup>19</sup>

In multivariable-adjusted Cox models, hazard ratios were expressed for patients with isolated central or brachial hypertension or central combined with brachial hypertension, using participants with central and brachial systolic normotension as reference. Cox models accounted for cohort as random effect and a propensity score generated by a logistic procedure with LINK=GLOGIT option.<sup>20</sup> We checked the proportional hazards assumption by the Kolmogorov-type supremum test. Statistical significance was a 2-sided probability of 0.05 or less.

## RESULTS

### Characteristics of Participants

Of the 6650 participants from 9 cohorts, 1074 were excluded. The reasons of excluding were described in

the Expanded Results in the Supplemental Material. The number on interpolated values amounted to 23 (0.4%) for body mass index, 223 (4.0%) for smoking and 1171 (21.0%) for drinking, and 69 (1.2%) for history of cardiovascular disease.

In all participants, mean age at enrollment was 54.2 years (Table 1). Central compared with brachial systolic BP was on average 10.3 mmHg lower ([95% CI, 10.2–10.5];  $P < 0.001$ ). Accordingly, central pulse pressure was also 11.4 mmHg smaller ([95% CI, 11.2–11.5];  $P < 0.001$ ) than brachial pulse pressure. However, there was large interindividual variability in the differences between brachial minus central systolic BP and between central minus brachial pulse pressure (Figure S1). The Pearson correlation coefficients between central and brachial systolic BP and between central and brachial pulse pressure were 0.97 ( $P < 0.0001$ ) and 0.95 ( $P < 0.0001$ ), respectively (Table S2).

Among all participants, 3985 had hypertension, 1918 were on antihypertensive treatment, and 1809 patients reported the information on antihypertensive drugs, of whom 392 (7.0%) and 1417 (25.4%) were taking a single agent or combination therapy, respectively. Drug classes taken were diuretics in 647 (16.2%) patients,  $\beta$ -blockers in 747 (18.8%), inhibitors of the renin-angiotensin system in 1181 (29.6%), and vasodilators in 831 (20.9%). Between-sex comparisons in characteristics (Table 1) were described in the Expanded Results in the Supplemental Material.

### Thresholds for Central Systolic BP

In the overall study population, median follow-up time was 4.1 years (5th–95th percentile interval, 2.2–12.1 years). Over 31 481 person-years, 255 participants experienced the primary cardiovascular end point (8.3 per 1000 person-years), 203 died (6.4 per 1000 person-years), 164 had a cardiac end point (5.3 per 1000 person-years), and 89 a cerebrovascular event (2.8 per 1000 person-years). Table S3 provides details on the components of the primary cardiovascular end point.

The thresholds of central systolic BP yielding a 5-year probability of experiencing the primary cardiovascular end point corresponding with the 5-year risk at the guideline-endorsed brachial BP thresholds of 120, 130, 140, and 160 mmHg were determined by proportional hazard regression, while adjusting for cohort (random effect) and a propensity score that accounted for sex, age, heart rate, body mass index, smoking and drinking status, serum total cholesterol, antihypertensive drug treatment by class, history of cardiovascular disease, and diabetes (Table 2). These central systolic BP thresholds were 110.5, 120.2, 130.0, and 149.5 mmHg, respectively. The thresholds based on the full data set were similar to the means of the bootstraps. The central systolic

**Table 1. Baseline Characteristics of Participants**

Characteristic	Women	Men	All
No. with characteristic (%)	3015 (54.1)	2561 (45.9)	5576
Europeans	1241 (41.2)	1145 (44.7)*	2386 (42.8)
Asians	931 (30.9)	887 (34.6)*	1818 (32.6)
South Americans	843 (28.0)	529 (20.7)*	1372 (24.6)
Current smoking	310 (10.3)	868 (33.9)*	1178 (21.1)
Drinking alcohol	877 (29.1)	1929 (75.3)*	2806 (50.3)
Hypertension	2100 (73.6)	1885 (69.7)*	3985 (71.5)
On antihypertensive treatment	1140 (54.3)	778 (41.3)*	1918 (48.1)
Diabetes	185 (6.1)	175 (6.8)	360 (6.5)
History of CV disease	442 (14.7)	347 (13.6)	789 (14.2)
Mean characteristic ( $\pm$ SD)			
Age, y	54.9 $\pm$ 14.8	53.4 $\pm$ 14.0*	54.2 $\pm$ 14.4
Body mass index, kg/m <sup>2</sup>	25.8 $\pm$ 5.1	25.9 $\pm$ 4.5	25.8 $\pm$ 4.8
Heart rate, bpm	67.0 $\pm$ 11.2	63.7 $\pm$ 11.4*	65.5 $\pm$ 11.4
Central BP, mmHg			
Systolic	124.4 $\pm$ 22.0	123.0 $\pm$ 20.2*	123.8 $\pm$ 21.2
Diastolic	80.0 $\pm$ 10.8	82.6 $\pm$ 10.8*	81.2 $\pm$ 10.9
Pulse pressure	44.4 $\pm$ 17.5	40.4 $\pm$ 14.8*	42.6 $\pm$ 16.1
Brachial BP, mmHg			
Systolic	133.3 $\pm$ 22.0	135.0 $\pm$ 19.7*	134.1 $\pm$ 21.0
Diastolic	78.9 $\pm$ 10.6	81.7 $\pm$ 10.6*	80.2 $\pm$ 10.7
Pulse pressure	54.4 $\pm$ 10.8	53.3 $\pm$ 10.8*	54.0 $\pm$ 16.3
Biochemistry			
Total serum cholesterol, mmol/L	5.12 $\pm$ 1.02	5.00 $\pm$ 0.99*	5.06 $\pm$ 1.01
Blood glucose, mmol/L	5.05 $\pm$ 0.98	5.14 $\pm$ 1.30*	5.09 $\pm$ 1.14

Current smoking was inhaling tobacco smoke on a daily basis. Drinking alcohol was the occasional or daily consumption of ethanol containing beverages. Diabetes was use of antidiabetic drugs, fasting blood glucose of  $\geq 7.0$  mg/dL, random blood glucose of  $\geq 11.1$  mg/dL, a self-reported diagnosis, or diabetes documented in practice or hospital records. Brachial blood pressure was measured immediately before the hemodynamic assessment after participants had rested in the supine position for  $\geq 5$  min. Hypertension was a brachial blood pressure of  $\geq 130$  mmHg systolic or  $\geq 80$  mmHg diastolic, or use of antihypertensive drugs.

\*Significant sex difference.

BP thresholds for the secondary end points were similar to those derived for the primary cardiovascular end point (Table 2). In all these Cox models and all that follow later in this article, the proportional hazard regression assumption was met.

Sensitivity analyses from which 1918 participants on antihypertensive treatment at enrollment (Tables S4) or 789 with a history of cardiovascular disease (Table S5) were excluded produced consistent results. To obtain more easily recallable thresholds for central systolic BP, we rounded the point estimates obtained in Table 2 to an integer value ending in 0 or 5. These rounded thresholds indicating elevated BP, stage 1, stage 2 and severe hypertension based on central systolic BP were 110, 120, 130, and 150 mmHg, respectively, consistent with the mean difference between central and brachial systolic BP (Table 1). With increasing category of central or brachial systolic BP, the risk of the primary cardiovascular end point increased (Figure 1).

### Cross-Classification of Central and Brachial Systolic Hypertension

The currently derived threshold for central systolic BP (120 mmHg) and the American College of Cardiology/American Heart Association threshold for brachial systolic BP (130 mmHg) were applied for cross-classifying the IDCARS participants. In exploratory analyses, the number of primary cardiovascular end points amounted to 39/2403 (1.6%) in participants with concordant normotension, 20/486 (4.1%) in patients with discordant hypertension (central normotension combined with brachial hypertension or vice versa), and 196/2687 (7.3%) in patients with concordant hypertension, resulting in significantly increasing cohort-, sex- and age-standardized rates across the 3 groups of 2.66 (95% CI, 2.56–3.13), 8.33 (7.75–9.10), and 16.18 (15.81–16.83) end points per 1000 person-years, respectively (Figure S2). The trend in the primary cardiovascular end point was driven by cerebrovascular events, of which the numbers were 12/2403 (0.5%), 9/486 (1.9%), and



**Table 2. Central Systolic Blood Pressure Levels Yielding Similar 5-y Risks as the ACC/AHA Thresholds for Brachial Hypertension**

End points (n)	Brachial systolic BP, mm Hg	5-y absolute risk, %	Central systolic BP, mm Hg (95% CI)
Primary end point (255)	120	1.47	110.5 (109.1–111.8)
	130	1.79	120.2 (119.4–121.0)
	140	2.18	130.0 (129.6–130.3)
	160	3.25	149.5 (148.4–150.5)
Secondary end points			
Total mortality (203)	120	1.28	109.8 (100.2–119.3)
	130	1.38	120.0 (115.5–124.7)
	140	1.49	130.4 (129.1–131.8)
	160	1.76	151.0 (140.4–161.5)
Cardiac (164)	120	0.82	110.3 (107.3–113.4)
	130	0.93	120.1 (118.9–121.3)
	140	1.06	129.9 (128.6–131.1)
	160	1.38	149.4 (144.9–153.8)
Cerebrovascular (89)	120	0.48	110.3 (108.4–112.1)
	130	0.60	120.1 (119.0–121.2)
	140	0.75	130.0 (129.4–130.5)
	160	1.19	149.7 (148.1–151.3)

The 5-yr risks were determined by proportional hazard regression, while adjusting for cohort (random effect) and for a propensity score that accounted for sex, age, heart rate, body mass index, smoking and drinking status, serum cholesterol, antihypertensive drug treatment by class, history of cardiovascular disease, and diabetes. The point estimates and 95% CIs for the central systolic BP yielding equivalent risks compared with the corresponding brachial systolic BP were derived from the bootstrapped distribution of the regression results. ACC indicates American College of Cardiology; AHA, American Heart Association; and BP, blood pressure.

68/2687 (2.5%) in participants with concordant normotension and discordant and concordant hypertension, respectively; the corresponding rates expressed per 1000 person-years were 0.70 (0.68–1.18), 3.77 (3.51–4.25), and 5.40 (5.27–5.91;  $P$  for trend  $<0.001$ ), respectively.

To clarify whether the risk in the patients with discordant hypertension was associated with central or brachial hypertension, the following next analyses were stratified into 4 groups, by subdividing the discordantly hypertensive group into patients with central normotension but brachial hypertension and patients with central hypertension but brachial normotension. Thus, the so-demarcated categories (Table 3) included concordant central and brachial systolic normotension ( $n=2403$ ; 43.1% of the total IDCARS study population), isolated brachial hypertension ( $n=277$ ; 5.0%), isolated central systolic hypertension ( $n=209$ ; 3.7%), and concordant central and brachial hypertension ( $n=2687$ ; 48.2%). Table S6 provides the distribution of the 4 groups in each cohort contributing to the present analysis.

### Characteristics of the 4 Cross-Classified Groups

Compared with normotensive individuals, patients with isolated brachial hypertension were more likely to be

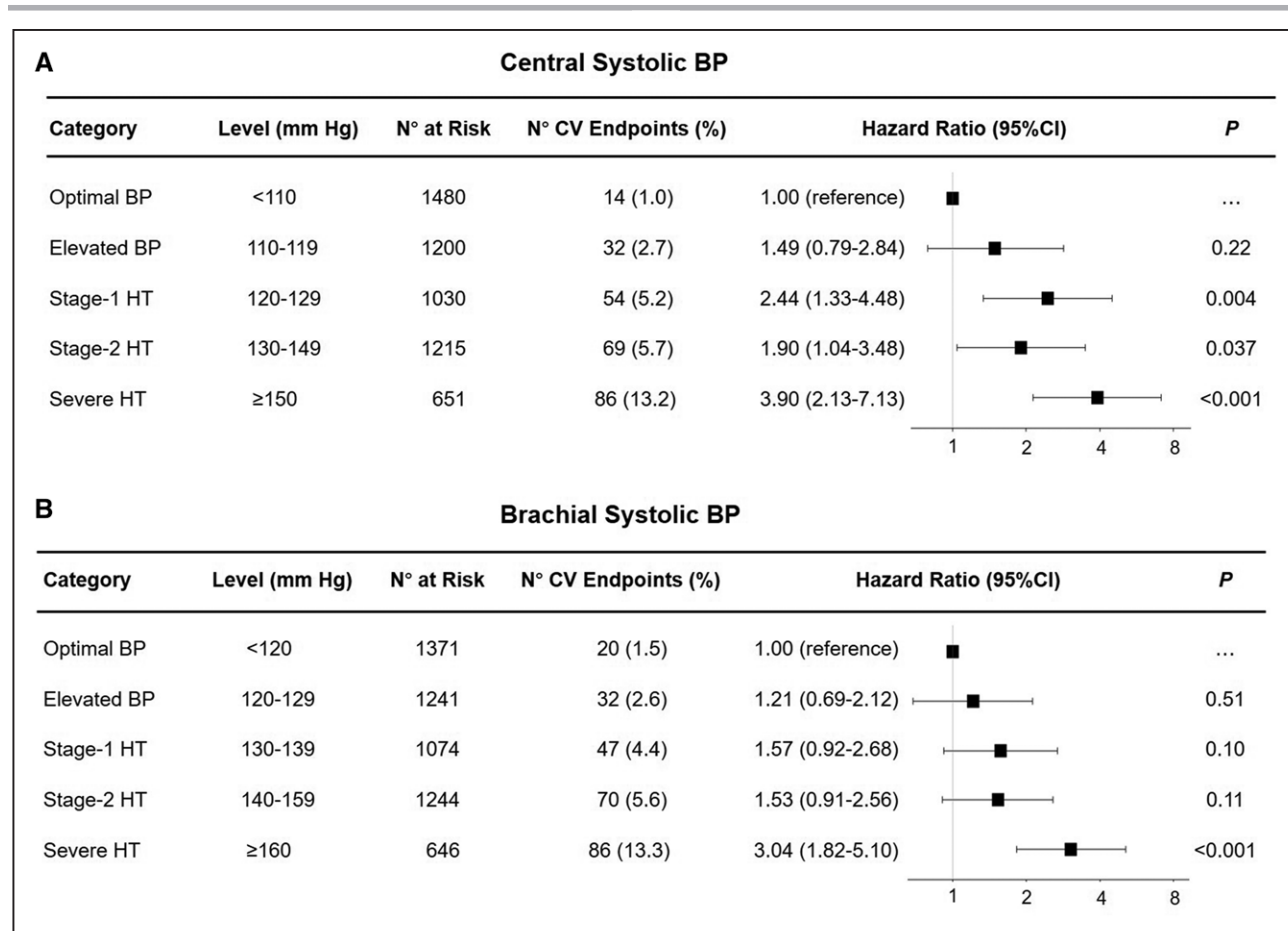
male and drinkers, were taller and heavier, and had faster heart rate and less central augmentation. Patients with isolated central and concordant hypertension shared similarities in characteristics. They were older, had higher body mass index, serum total cholesterol, and central augmentation, and were more likely to have history of cardiovascular disease or to be on antihypertensive drugs than subjects with concordant normotension (Table 3). Patients with isolated central hypertension were more likely to be female, had the slowest heart rate among the 4 groups (Table 3), and more frequently took  $\beta$ -blockers compared with the patients with isolated brachial hypertension (Table S7;  $P=0.008$ ). Table S7 presents detailed information on the antihypertensive drugs taken at baseline in the 4 cross-classified groups and Figure S3 on the distribution of central and brachial pulse pressure in the 4 groups.

### Absolute Risk by Cross-Classified Groups

Compared with concordant central and brachial normotension, the cohort-, sex- and age- standardized incidence rates of all end points were higher in patients with concordant central and brachial hypertension ( $P<0.001$ ; Table 4); the rates of the primary cardiovascular end point and cerebrovascular events were also significantly higher ( $P\leq 0.005$ ) in patients with central hypertension in the presence of brachial normotension (Table 4).

### Relative Risk by Cross-Classified Groups

The cumulative incidence of the primary end point increased gradually from concordant central and brachial normotension over isolated brachial hypertension to isolated central hypertension and onward to concordant central and brachial hypertension ( $P<0.001$ ) with no difference between isolated central hypertension and concordant hypertension ( $P=0.35$ ; Figure 2). With concordant normotension as reference, the multivariable-adjusted hazard ratios were 1.30 (95% CI, 0.58–2.94;  $P=0.52$ ) for isolated brachial hypertension, 2.28 (1.21–4.30;  $P=0.011$ ) for isolated central hypertension, and 2.02 (1.41–2.91;  $P<0.001$ ) for concordant hypertension (Table 4). Sensitivity analyses excluding patients with central and brachial diastolic hypertension ( $\geq 80$  mm Hg,  $n=2978$ , Table S8) or participants taking  $\beta$ -blockers at baseline ( $n=747$ , Table S9), or patients on antihypertensive drug treatment at enrollment ( $n=1918$ , Table S10) produced risk estimates, which confirmed the results presented in Table 4. In particular, in untreated participants, the incidence of the primary end points increased from concordant normotension over isolated brachial hypertension to isolated central hypertension and onwards to concordant hypertension ( $P$  for trend, 0.023). Among untreated participants, the hazard ratios were directionally similar compared with the main



**Figure 1. Forrest plots showing the risk of the primary composite cardiovascular end point by category.**

Central (A) and brachial (B) systolic blood pressure (BP) hazard ratios, given with 95% CI, were adjusted for cohort (random effect) and a propensity score that accounted for sex, age, heart rate, body mass index, smoking and drinking status, serum cholesterol, antihypertensive drug treatment by drug class, history of cardiovascular disease, and diabetes. The linear trend across increasing categories of central and brachial BP was significant ( $P < 0.001$ ).

analysis (Table 4), but in view of the smaller number of events and people at risk, formal statistical significance was only reached for the primary and cerebrovascular end points among patients with concordant central and brachial systolic hypertension.

## DISCUSSION

The IDCARS cohort included community-dwelling participants, representative for the country, where they had been recruited and followed up. Central systolic BP and central pulse pressure were on average 10 mm Hg lower than their brachial counterparts (Table 1). However, there was large interindividual variability around these average differences in systolic amplification (Figure S1). This observation justified the derivation of thresholds for central systolic BP with a 95% CI around the point estimates based on the equivalence of risk with the established American College of Cardiology/American Heart Association diagnostic thresholds for brachial BP.<sup>12</sup> The so-derived thresholds for central systolic BP, rounded to the closest integer were 110, 120, 130,

and 150 mmHg, respectively, for elevated BP, stage 1, stage 2, and severe hypertension. The gradual increase in fatal combined with nonfatal cardiovascular complications with higher categories of central and brachial BP provided the validation of this approach (Figure 1). The cross-classification of central hypertension (threshold 120 mmHg) versus brachial hypertension (threshold, 130 mmHg) demonstrated similar risks in patients with isolated brachial hypertension compared with concordant normotension (Figure 2; Table 4). Patients with isolated brachial hypertension, in the literature also referred to as spurious systolic hypertension, were predominantly tall men (Table 3) with no increased risk of adverse health outcomes (Table 4), a finding which is consistent with pulse wave dynamics and previous reports.<sup>21,22</sup> However, patients with isolated central hypertension showed hazards ratios of fatal combined with nonfatal cardiovascular and cerebrovascular end points approaching the risks in concordantly hypertensive patients. In a previous IDCARS analysis,<sup>6</sup> the associations of end points were similar for central and brachial systolic BP, because of the high correlation between both BP indexes ( $r = 0.97$ ).

**Table 3. Baseline Characteristics of Participants by Systolic Hypertension Categories**

Characteristic	Central systolic NT		Central systolic HT	
	Brachial systolic NT	Brachial systolic HT	Brachial systolic NT	Brachial systolic HT
Systolic BP thresholds, mm Hg				
Central	<120	<120	≥120	≥120
Brachial	<130	≥130	<130	≥130
N° with characteristic (%)	2403	277	209	2687
Women	1329 (55.3)	69 (24.9)*	144 (68.9)*	1473 (54.8)
Smokers	614 (25.6)	61 (22.0)	39 (18.7)†	464 (17.3)*
Drinking alcohol	1227 (51.1)	168 (60.7)‡	91 (43.5)†	1320 (49.1)
On antihypertensive medication	450 (18.7)	85 (30.7)*	72 (34.5)*	1311 (48.8)*
Diabetes	95 (4.0)	18 (6.5)†	8 (3.8)	239 (8.9)*
History of CV disease	188 (7.8)	25 (9.0)	30 (14.4)	546 (20.3)*
Mean characteristic (±SD)				
Age, y	47.8±12.4	47.3±15.3	57.1±10.7*	60.5±13.4*
Body height, cm	164.6±9.9	169.8±10.5*	162.2±9.9‡	162.3±10.7*
Body weight, kg	68.0±15.8	76.2±17.8*	69.1±16.2	70.9±17.8*
Body mass index, kg/m <sup>2</sup>	24.9±4.5	26.2±4.5*	26.1±4.9*	26.6±4.9*
Serum cholesterol, mmol/L	4.94±0.99	5.04±0.99	5.22±1.08*	5.16±1.01*
Heart rate, bpm	65.5±11.2	71.9±12.3*	60.8±9.7*	65.2±11.4
Central BP, mm Hg				
Systolic	106.0±8.5	115.1±3.4*	121.9±1.7*	140.7±17.0*
Diastolic	74.7±7.3	79.4±7.3†	81.3±7.2*	87.2±10.8*
Pulse pressure	31.3±6.7	35.7±7.2*	40.6±7.4*	53.5±15.8*
Brachial BP, mm Hg				
Systolic	116.4±8.1	133.6±4.0*	126.9±1.8*	150.5±17.4*
Diastolic	73.9±7.3	78.4±7.3†	80.3±7.2*	86.0±10.6*
Pulse pressure	42.5±7.5	55.2±8.7*	46.6±7.4*	64.5±16.1*
Central augmentation index, %	131.1±22.3	117.7±15.9*	158.3±19.5*	152.5±22.8*
Central augmentation ratio, %	21.6±12.7	12.3±11.8*	35.6±7.4*	32.7±9.5*

Values are number of subjects (%) or mean±SD. The systolic augmentation index was the absolute difference between the second and first peak of the central BP wave divided by central pulse pressure. The systolic augmentation ratio was the second divided by the first peak of the central BP. Both the augmentation index and ratio were expressed in per cent by multiplying the fraction by 100. Significance of the difference with concordant normotension (reference). BP indicates blood pressure; CV, cardiovascular; HT, hypertension; and NT, normotension.

\* $P<0.001$ .

† $P<0.05$ .

‡ $P<0.01$ .

Our current observations generated new insights by identifying small groups without or with increased cardiovascular risk based on the cross-classification of central and brachial systolic hypertension, thereby illustrating the clinical utility of measuring both central and brachial systolic BP.

The reference values for arterial measurements collaboration analyzed 18 183 health people and 29 605 patients with one or more cardiovascular risk factor, including hypertension.<sup>23</sup> All individuals were not on anti-hypertensive or lipid-lowering drug treatment and were free from cardiovascular disease and diabetes. In analyses stratified by the presence versus absence of cardiovascular risk factors, amplification decreased only slightly with age, whereas the overriding determinant of systolic

amplification was sex, given that the difference between brachial minus central systolic BP was 6.6 mm Hg (95% CI, 5.8–7.4 mm Hg) less in women than men. In the normal population, the 90th percentiles for optimal, normal, and high-normal central systolic BPs were 110, 125, and 135 mm Hg in women and 111, 122, and 132 mm Hg in men.<sup>23</sup> The currently proposed thresholds for central systolic BP were only stratified by brachial systolic BP, but sex and age were included in the propensity score used for their derivation. The rounded thresholds listed in Table 2 are therefore applicable, irrespective of sex facilitating their clinical application.

Only one previous study reported thresholds for central systolic BP based on adverse health outcomes.<sup>7</sup> Cheng et al<sup>7</sup> determined diagnostic thresholds for

**Table 4. End Point Rates and Corresponding Hazard Ratios by Systolic Hypertension Categories**

	Central systolic NT		Central systolic HT	
	Brachial NT	Brachial HT	Brachial NT	Brachial HT
Number at risk	2403	277	209	2687
Systolic BP thresholds, mm Hg				
Central	<120	<120	≥120	≥120
Brachial	<130	≥130	<130	≥130
Primary end point				
Number of end points	39	7	13	196
Rate per 1000 person-years	2.66 (2.56–3.13)	5.83 (5.11–6.91)	11.72 (10.53–13.16)*	16.18 (15.81–16.83)†
HR (95% CI)	1 (reference)	1.30 (0.58–2.94)	2.28 (1.21–4.30)‡	2.02 (1.41–2.91)†
Secondary end points				
Total mortality				
Number of deaths	52	6	4	141
Rate per 1000 person-year	4.15 (4.02–4.63)	5.26 (4.02–6.93)	2.94 (2.57–3.61)	10.61 (10.36–11.18)†
HR (95% CI)	1 (reference)	1.03 (0.44–2.43)	0.54 (0.20–1.51)	1.05 (0.74–1.48)
Cardiac end points				
Number of end points	26	4	8	126
Rate per 1000 person-years	1.88 (1.80–2.35)	3.51 (2.95–4.46)	6.36 (5.54–7.45)	10.33 (10.06–10.91)†
HR (95% CI)	1 (reference)	1.26 (0.62–2.60)	1.15 (0.56–2.36)	1.37 (0.97–1.91)*
Cerebrovascular end points				
Number of end points	12	3	6	68
Rate per 1000 patient-years	0.70 (0.68–1.18)	2.29 (2.00–3.01)	5.90 (5.24–6.83)*	5.40 (5.27–5.91)†
HR (95% CI)	1 (reference)	2.21 (0.62–7.97)	3.71 (1.37–10.06)*	2.60 (1.35–5.00)*

Incidence rates were standardized for cohort, sex and age group (<50 vs ≥50 y) by the direct method. Hazard ratios were adjusted for cohort (random effect) and a propensity score that accounted for sex, age, heart rate, body mass index, smoking and drinking status, serum cholesterol, antihypertensive drug treatment by drug class (diuretics, β-blockers, inhibitors of the renin-angiotensin system [angiotensin converting-enzyme inhibitor and angiotensin II type 1 receptor blockers] and vasodilators [calcium channel blocker and α-blockers]), history of cardiovascular disease, and diabetes. Significance of the difference with concordant central and brachial normotension (reference).

\* $P < 0.01$ .

† $P < 0.001$ .

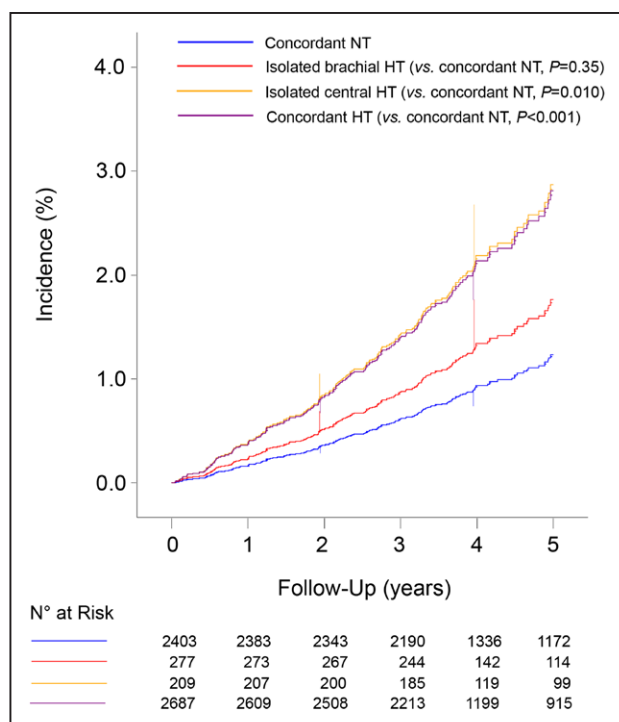
‡ $P < 0.05$ .

central systolic BP in a derivation cohort consisting of 1272 individuals followed up for a median of 15 years and replicated these thresholds in a test cohort comprising 2501 individuals with median follow-up of 10 years. All study participants were untreated for hypertension. The thresholds for central systolic BP were generated using the same bootstrapped approach as in the current study with as objective to determine the central systolic BP levels that yielded the same risk of cardiovascular mortality as associated with brachial systolic BP levels of 120 mmHg (optimal BP) and 140 mmHg (hypertension). After rounding, the systolic threshold was 110 mmHg for optimal BP and 130 mmHg for hypertension. Compared with optimal BP, the risk of cardiovascular mortality increased significantly in patients with hypertension (hazard ratio, 3.08 [95% CI, 1.05–9.05]). The present study extends Cheng's observations<sup>7</sup> in a multiethnic and multicultural context and by considering fatal combined with nonfatal end points as well as target organ-specific end points, such as cerebrovascular events. Thus, the Cheng's study<sup>7</sup> and IDCARS provided mutually replicative findings with the same rounded

thresholds for optimal and hypertensive levels of central systolic BP. Some differences between the 2 studies deserve to be highlighted. In the IDCARS analyses, diastolic BP was not considered and 48.1% of the IDCARS study population were on antihypertensive drug treatment at enrollment. Diastolic BP is similar throughout the arterial tree.<sup>13</sup> Thus, in the Cheng's study, the outcome-driven thresholds for central diastolic BP yielding a risk of cardiovascular mortality equivalent to brachial diastolic BP levels of 80 and 90 mmHg were of 80.92 and 90.98 mmHg, respectively. Sensitivity analyses of the IDCARS data addressed the issues of antihypertensive drug (Table S4), specific treatment with β-blockers (Table S9), and diastolic hypertension (Table S8).

While the IDCARS database is a powerful resource, some limitations in its exploitation must also be acknowledged. First, a single type-1<sup>24</sup> central BP monitoring (SphygmoCor) was used for the noninvasive assessment of the central hemodynamic traits. The SphygmoCor algorithm preserves the systolic amplification as evidenced by the 10 mmHg mean difference between the central and brachial arteries. Nevertheless, the accuracy of the





**Figure 2. Cumulative incidence of the primary composite cardiovascular end point by the cross-classification of central and brachial blood pressure categories.**

Vertical lines denote the SE. Tabulated data are the number of participants at risk by hypertension category at 1-year intervals. The survival functions and *P* were derived by proportional hazard regression with concordant normotension as the reference group and with cumulative adjustment for cohort, sex and age. The systolic BP thresholds delineating the 4 groups are given in Table 3. HT indicates hypertension; and NT, normotension.

SphygmoCor approach is vulnerable to errors in the measurement of brachial BP,<sup>25</sup> which is needed for calibration, and it does also not account for pulse wave amplification from the brachial to the radial artery.<sup>26</sup> However, as highlighted in the Methods, the quality control of the arterial phenotypes was rigorously standardized in IDCARS. In all but one cohort, the brachial BP used to calibrate the central pulse wave was obtained by automated oscillometric devices,<sup>14</sup> which to a large extent excludes observer bias. While the use of a single type-1 system might be considered as a strength in terms of the standardization, it might also limit generalizability. However, as suggested by a previous meta-analyses,<sup>3</sup> there is little device-dependent heterogeneity in the association of adverse health outcomes and central systolic BP. Second, the anthropometric characteristics, the period of recruitment, and the assessment of end point data differed between cohorts (Table S1). However, the present analyses were adjusted for cohort as a random effect. By design participant-level meta-analyses allow applying the same statistical methods to all contributing cohorts. Moreover, the diversity of the IDCARS cohorts strengthens the generalizability of our current results. Third, although the IDCARS participants currently analyzed were enrolled in 8 countries

and 3 continents, the analyses did not include people younger than 30 years, because they did not contribute to the incidence of the primary end point. Furthermore, Blacks show a steeper relation of adverse health effects with both central and brachial systolic BP, as for instance illustrated for left ventricular hypertrophy in a Sub-Saharan cohort.<sup>27</sup> Thus, the current observations cannot be extrapolated to people with Black ancestry. Fourth, risk factors and antihypertensive drug treatment were only quantified at enrollment, so that analyses could not be adjusted for time-varying covariables. Finally, cross-classifying the IDCARS participants into 4 groups led to a small number of cardiovascular and cerebrovascular end points in the discordant groups (Table 4). We addressed this issue by implementing the multivariable adjustment by a propensity score. The 95% confidence interval of the hazard ratios expressing the relative risk of a cardiovascular or cerebrovascular end point in patients with central hypertension but brachial normotension compared with concordant normotension were not exceedingly large, suggesting that the risk estimates were relatively precise.

## Perspectives

The patients with central systolic hypertension but brachial normotension are a minority, in IDCARS representing only 3.7% of the total study population. However, these patients include close to 70% of women (Table 3), in whom cardiovascular risk is often ignored<sup>28</sup> and close to 20% of patients on treatment with  $\beta$ -blockers (Table S7). The CAFÉ (Conduit Artery Function Evaluation) study<sup>29</sup> examined the impact of 2 different BP lowering-regimens (atenolol $\pm$ thiazide-based versus amlodipine $\pm$ perindopril-based therapy) on central aortic pressures as derived from the radial pulse wave by means of the SphygmoCor technology. Despite similar brachial systolic BPs between treatment groups (difference, 0.7 mmHg [95% CI, -0.4 to 1.7]; *P*=0.20), there were substantial reductions in central aortic pressures with the amlodipine-based regimen, amounting to 4.3 mmHg (95% CI, 3.3–5.4) for central systolic BP and 3.0 mmHg (95% CI, 2.1–3.9) for central pulse pressure. Thus, the CAFE investigators generated important evidence that should guide clinical practice in patients with central systolic hypertension but brachial normotension. Clinicians should become aware that even in the presence of brachial normotension, an assessment of central systolic BP might help in risk stratification and optimizing antihypertensive drug treatment.

## ARTICLE INFORMATION

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### Disclosures

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