Hypertension

ORIGINAL ARTICLE

Mortality and Cardiovascular End Points In Relation to the Aortic Pulse Wave Components: An Individual-Participant Meta-Analysis

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BACKGROUND: Wave separation analysis enables individualized evaluation of the aortic pulse wave components. Previous studies focused on the pressure height with overall positive but differing results. In the present analysis, we assessed the associations of the pressure of forward and backward (P_{for} and P_{ref}) pulse waves with prospective cardiovascular end points, with extended analysis for time to pressure peak (T_{for} and T_{ref}).

METHODS: Participants in 3 IDCARS (International Database of Central Arterial Properties for Risk Stratification) cohorts (Argentina, Belgium, and Finland) aged ≥20 years with valid pulse wave analysis and follow-up data were included. Pulse wave analysis was done using the SphygmoCor device, and pulse wave separation was done using the triangular method. The primary end points consisted of cardiovascular mortality and nonfatal cardiovascular and cerebrovascular events. Multivariable-adjusted Cox regression was used to calculate hazard ratios.

RESULTS: A total of 2206 participants (mean age, 57.0 years; 55.0% women) were analyzed. Mean±SDs for P_{for}, P_{ref}, T_{for}, and T_{for}/T_{ref} were 31.0±9.1 mm Hg, 20.8±8.4 mm Hg, 130.8±35.5, and 0.51±0.11, respectively. Over a median follow-up of 4.4 years, 146 (6.6%) participants experienced a primary end point. Every 1 SD increment in P_{for}, T_{for}, and T_{for}/T_{ref} was associated with 27% (95% CI, 1.07–1.49), 25% (95% CI, 1.07–1.45), and 32% (95% CI, 1.12–1.56) higher risk, respectively. Adding T_{for} and T_{for}/T_{ref} to existing risk models improved model prediction (ΔUno's C, 0.020; $P<0.01$).

CONCLUSIONS: Pulse wave components were predictive of composite cardiovascular end points, with T_{for}/T_{ref} showing significant improvement in risk prediction. Pending further confirmation, the ratio of time to forward and backward pressure peak may be useful to evaluate increased afterload and signify increased cardiovascular risk. ***(Hypertension.* 2024;81:1065–1075. DOI: 10.1161/HYPERTENSIONAHA.123.22036.)** • **Supplement Material**.

Key Words: cardiovascular diseases ■ heart disease risk factors ■ prospective studies ■ pulse wave analysis ■ risk factors

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

In International Database of Central Arterial Properties for Risk Stratification, the association of cardiovascular end points with time to forward and backward pressure peak and their ratio were analyzed in prospective cohorts.

What Is Relevant?

In addition to forward wave pressure, the forward pressure peak time and the forward-backward pressure peak time ratio were associated with composite cardiovascular end points.

The forward-backward pressure peak time ratio improved the overall model fit.

Clinical/Pathophysiological Implications?

Pulse wave analysis helps in identifying the underappreciated cardiovascular risk.

The amplitude and peak time of pulse wave contribute to cardiovascular risk.

The absolute value and ratio of forward-backward pressure peak times might reveal the extent to which wave reflection increases afterload.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CVD	cardiovascular disease
IDCARS	International Database of Central Arterial Properties for Risk Stratification
MAP	mean arterial pressure
MESA	Multiethnic Study of Atherosclerosis
P_{for}	forward aortic pulse wave
PP	pulse pressure
P_{ref}	reflected (backward) aortic pulse wave
RM	reflection magnitude
T_{for}	forward pressure peak time
T_{ref}	backward pressure peak time

Cardiovascular disease (CVD) is the leading cause of global mortality, with 85% attributable to myocardial infarction and stroke.[1] With advancing age, the pulsatile blood pressure (BP) components, systolic BP and pulse pressure (PP), override the steady components, diastolic BP and mean arterial pressure (MAP), in determining cardiovascular mortality and morbidity.[2–4] The arterial pressure wave consists of a forward component generated by the heart (P_{for}) and reflected waves returning from peripheral branching sites to the central aorta (P_{ref}).[2,5] In stiff compared with elastic arteries, reflected waves return faster, reach the proximal aorta during systole, augment late systolic BP,[2,5] and increase the work load of the left ventricle.[6,7]

However, the contributions of the aortic pulse wave components to cardiovascular risk are not uniform, with significant findings shown in P_{for}, P_{ref}, or both.[8–10] The issue is not trivial, because identifying the risk-carrying pulse wave components should be helpful in developing more effective therapeutic approaches to managing hypertension by choosing drugs with selective influence on the P_{ref} as compared with the P_{for}.[11,12] Notwithstanding the obvious merits of the previous publications, there are issues in the selection of end points, sometimes confined to mortality,[13] or overadjustment for multiple interrelated covariables,[14] or underadjustment by not considering brachial BP.[9] Moreover, the times to pressure peak of forward (T_{for}) and reflected (T_{ref}) waves were associated with higher risk groups in cross-sectional studies.[15,16] Although premature wave reflections were associated with outcomes in patients with heart failure with a reduced ejection fraction,[17] whether T_{for} and T_{ref} are predictive of cardiovascular end points in general populations is not known.

In the current study, 3 cohorts enrolled in the IDCARS (International Database of Central Arterial Properties for Risk Stratification)[18] were analyzed to assess the relationship of fatal and nonfatal adverse health outcomes with pressure and peak time components of the aortic pulse wave.

METHODS

Data Availability

All available data are shown within the article and the online Supplemental Material. Anonymized individual data are available from the corresponding author upon request, on condition that an analysis plan is accompanying the request and that the principal investigators of all IDCARS cohorts approve data sharing.

Study Cohorts

The population studies included in the current meta-analysis met the principles outlined in the Declaration of Helsinki for investigation of human participants.[19] The IDCARS study protocols and the secondary analyses of anonymized data were approved by the competent local institutional or national review boards. Participants gave written informed consent at recruitment and renewed consent at the time of the hemodynamic examination.

The anonymized IDCARS database is currently maintained by the Alliance for the Promotion of Preventive Medicine (https://www.appremed.org). IDCARS cohorts qualified for inclusion in the present analysis if peripheral and central BP and cardiovascular risk factors had been measured at baseline, if follow-up included both fatal and nonfatal outcomes, and if the raw pulse wave data were on file, allowing the separation of the aortic pulse wave into its P_{for} and P_{ref} components. Three cohorts met these eligibility criteria. Supplemental Material provides detailed information on the population sampling methods, timelines, and countries of recruitment (Table S1). Initial enrollment took place from 1985 until 2015. For the present analysis, baseline refers to the first measurement of pulse wave analysis along with cardiovascular risk factors (May 2005 to April 2015). The last follow-up took place from November 2014 to December 2018 (Table S1). Of the 3281 participants enrolled in the 3 cohorts, wave separation analysis was available in 2314 participants. Of them, 108 (4.7%) were discarded because they were teenagers (<20 years, n=45) or without follow-up data (n=63), leaving 2206 people for statistical analysis.

Measurement of BP

Brachial BP was measured immediately before the hemodynamic assessment after participants had rested for ≥5 minutes in the supine position using a validated oscillometric device (OMRON 705 CP).[20] Next, experienced observers recorded the radial arterial waveform at the dominant arm during an 8-second period by applanation tonometry, using a high-fidelity SPC-301 micromanometer (Millar Instruments Inc, Houston, TX), interfaced with a SphygmoCor CvMS device, and a laptop computer running SphygmoCor software (AtCor Medical, Australia, version 9.0). Estimates of central BP were calibrated on brachial systolic and diastolic BP. Recordings were discarded if the systolic or diastolic variability of consecutive waveforms exceeded 5%, if the amplitude of the pulse wave signal was <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.[21] The software returns systolic and diastolic BP, MAP, and PP in the ascending aorta. A triangular-flow pressure-based wave separation algorithm, which enables accurate calculation of wave reflection[22] and is implemented in the SphygmoCor software, allows computing the P_{for} and P_{ref} amplitudes and the duration (T_{for} and T_{ref}) to their peak height (Figure S1). The reflection index was the ratio of the backward to the forward PP amplitude expressed as a percentage. The central augmentation ratio was determined as the quotient of the second over the first systolic peak of the central arterial pressure wave. PP augmentation was determined as peripheral divided by central PP and expressed in percent.

Ascertainment of End Points

The vital status and the incidence of fatal and nonfatal cardiovascular end points were obtained from the appropriate sources in each country.[18] The prespecified primary end point was a composite cardiovascular end point, including cardiovascular death and nonfatal cardiovascular events, including myocardial infarction, coronary revascularization, heart failure, and stroke. The secondary end points included total mortality, fatal and nonfatal coronary events (sudden death, death from ischemic heart disease, nonfatal myocardial infarction, and coronary revascularization), and fatal and nonfatal stroke, not including transient ischemic attack. In all outcome analyses, only the first event within each category was considered.

Statistical Analysis

Database management and statistical analysis were done using SAS, version 9.4 (maintenance level 6), and R 4.3.0. The Kolmogorov-Smirnov test was applied to test the deviation from the normal distribution. The central tendency and spread of continuously distributed variables were presented as mean (SD) or median (interquartile range). The T_{for}/T_{ref} was log-transformed to reduce skewness. The group means and proportions were compared by the large-sample Z test or the Wilcoxon test, depending on the variable distribution, and the Fisher exact test, respectively. Pearson correlation coefficients were applied to express associations between aortic BP and pulse wave variables. Trends across tertiles were accessed by the Cochran-Armitage Trend test, the Cochran-Mantel-Haenszel test for categorical variables, or linear regression for continuous variables.

After stratification for cohort and sex, missing values of serum total cholesterol, the glomerular filtration rate estimated from serum creatinine,[23] and blood glucose were interpolated from the cohort- and sex-specific regression slopes on age. In participants with unknown status of smoking or drinking, the indicator (dummy) variable was set to cohort, sex, and age (<60 versus ≥60 years; specific mean of the codes [0, 1]). For the cohort recruited in Buenos Aires, Argentina, alcohol consumption was extrapolated from national statistics stratified by sex and age.[24]

In the analyses of end points, incidence rates were tabulated by thirds of the distributions of P_{for}, P_{ref}, reflection magnitude (RM), T_{for}, T_{ref}, and T_{for}/T_{ref} while applying the direct method for standardizing rates in IDCARS for cohort, sex, and age (<40, 40–59, and ≥60 years). The 95% CIs of rates were computed as $R \pm 1.96 \times \sqrt{(R \times [100-R]/T)}$, where R is the rate and T is the number of participants at risk of developing an adverse outcome. The cumulative incidence of the primary and secondary end points was plotted and compared using Log-rank test. We then utilized the multivariable-adjusted Cox models to evaluate the hazard ratios per 1 SD increment in aortic pulse wave components. The full model accounted for cohort, sex, age, MAP, heart rate, body mass index, total cholesterol, smoking, use of antihypertensive drugs, history of diabetes, and previous CVD. We also implemented simpler models by considering only cohort, sex, and age, or using backward elimination in the exploratory analyses. The proportional hazards assumption was checked by the Kolmogorov-type supremum test. Sensitivity analyses were further conducted in participants stratified by sex, age (<60 versus ≥60 years), hypertension status (all hypertension, isolated systolic hypertension, and normotension), peripheral PP (<60 versus ≥60 mm Hg), and in participants free of chronic kidney disease (glomerular filtration rate estimated from serum creatinine ≥60 mL/min/1.73 m^2) or previous CVD.

To evaluate whether aortic pulse wave components refined the association of adverse health outcomes over and beyond the other risk factors, we compared the bootstrapped Uno's C statistic, integrated discrimination improvement, and net

Table 1. Baseline Characteristics of 2206 Participants

Categorical variables	n (%)	Continuously distributed variables	Mean (SD)
Ethnicity		Age, y	57.0 (16.6)
White Europeans	1019 (46.2)	BMI, kg/m^2	27.4 (4.72)
South Americans	1187 (53.8)	Brachial systolic BP, mm Hg	134.5 (18.8)
Women	1214 (55.0)	Central systolic BP, mm Hg	123.5 (18.8)
Overweight or obese		Brachial pulse pressure, mm Hg	55.4 (16.1)
BMI ≥25 to <30 kg/m^2	975 (44.2)	Central pulse pressure, mm Hg	43.9 (16.0)
BMI ≥30 kg/m^2	521 (23.6)	Diastolic blood pressure, mm Hg	78.3 (10.6)
		Mean arterial pressure, mm Hg	97.2 (11.1)
Hypertension	1423 (64.5)	Heart rate, bpm	65.0 (11.9)
Systolic hypertension	1395 (63.2)	P_{for}, mm Hg	31.0 (9.09)
Diastolic hypertension	1284 (58.2)	T_{for}, ms	130.8 (35.5)
Mixed hypertension	1256 (56.9)	P_{ref}, mm Hg	20.8 (8.42)
Treated hypertension	1182 (53.6)	T_{ref}, ms	257.5 (24.4)
		Reflection magnitude	0.67 (0.17)
Total serum cholesterol ≥4.90 mmol/L	1296 (58.7)	T_{for}/T_{ref}	0.51 (0.11)
Diabetes	163 (7.39)	Pulse pressure augmentation ratio	1.31 (0.19)
History of cardiovascular disease	386 (17.5)	eGFR, mL/min/1.73 m^2	82.1 (18.5)
Current smokers	320 (14.5)	Total serum cholesterol, mmol/L	5.14 (0.99)
Alcohol use	770 (34.9)	Blood glucose, mmol/L	5.48 (0.96)

BMI was weight in kilograms divided by height in meters squared. Hypertension was a BP of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or being on antihypertensive treatment. Mean arterial pressure was diastolic BP plus one-third of pulse pressure. Diabetes was a self-reported diagnosis, use of antidiabetic drugs, fasting blood glucose of ≥7 mmol/L, random blood glucose of ≥11.1 mmol/L, or diabetes documented in practice or hospital records. Smoking was the use of smoking materials on a daily basis. Drinking was an average daily alcohol intake of ≥5 g/day. eGFR is estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. Unit conversion factors: to convert cholesterol from mmol/L to mg/dL, multiply by 38.67; glucose from mmol/L to mg/dL, multiply by 18. BMI indicates body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate derived from serum creatinine; P_{for}, aortic forward wave pressure; P_{ref}, aortic reflected wave pressure; T_{for}, forward pressure peak time; and T_{ref}, backward pressure peak time.

reclassification improvement for the primary end point at 5 years.[25,26] We also evaluated whether these parameters added to conventional risk factors and pulse wave velocity in a subset of 1741 subjects.[19] In all analyses, a 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The sites included in the current analyses were in Belgium (n=537, 24.3%), Finland (n=482, 21.9%), and Argentina (n=1187, 53.8%). The baseline difference between included and excluded participants is shown in Table S2. Missing values of smoking (n=230), drinking (n=988), serum creatinine (n=168), and blood glucose (n=135) were interpolated.

The study population included 1214 women (55.0%), 1019 White Europeans (46.2%), 1187 South Americans (53.8%), and 320 smokers (14.5%). Of 1423 participants (64.5%) with hypertension, 1182 (83.1%) were taking antihypertensive treatment. The number of participants with overweight, obesity, hypercholesterolemia, diabetes, or a history of CVD amounted to 975 (44.2%), 521 (23.6%), 1296 (58.7%), 163 (7.39%), and 386 (17.5%), respectively. The mean age (±SD) was 57.0±16.6 years. Table 1 lists the mean values in the whole study population of the anthropometric measurements, the brachial and central pulsatile BP components, MAP, and diastolic BP, which are similar throughout the arterial tree, the amplitudes (P_{for} and P_{ref}) and peak times (T_{for} and T_{ref}) of pulse wave, and the biochemical measurements.

The correlation matrix between BP components (Table S3) revealed significant correlations between brachial and central systolic BP and PP with P_{for} and P_{ref} ($r \geq 0.73$) and less closer correlations with T_{for} and T_{ref} ($r \leq 0.34$). Significant negative correlations were noted for heart rate and PP amplification with P_{ref}, RM, T_{for}, and T_{ref} ($r \leq -0.24$). Interestingly, RM was mainly determined by P_{ref}, whereas T_{for}/T_{ref} was determined by T_{for} (Table S3).

Characteristics by thirds of the studied parameters are shown in Tables S4 through S9. Overall, participants with increases in the tertiles of P_{for}, P_{ref}, and RM had higher risk profiles. Of note, there are inverted participants' profiles for T_{for} (Table S7) and T_{ref} (Table S8), with participants in the highest tertile of T_{for} and the lowest of T_{ref} having profiles with higher cardiovascular risk.

Incidence of End Points

Over a median follow-up of 4.39 years (interquartile range, 3.14–6.94 years; 5th–95th percentile interval,

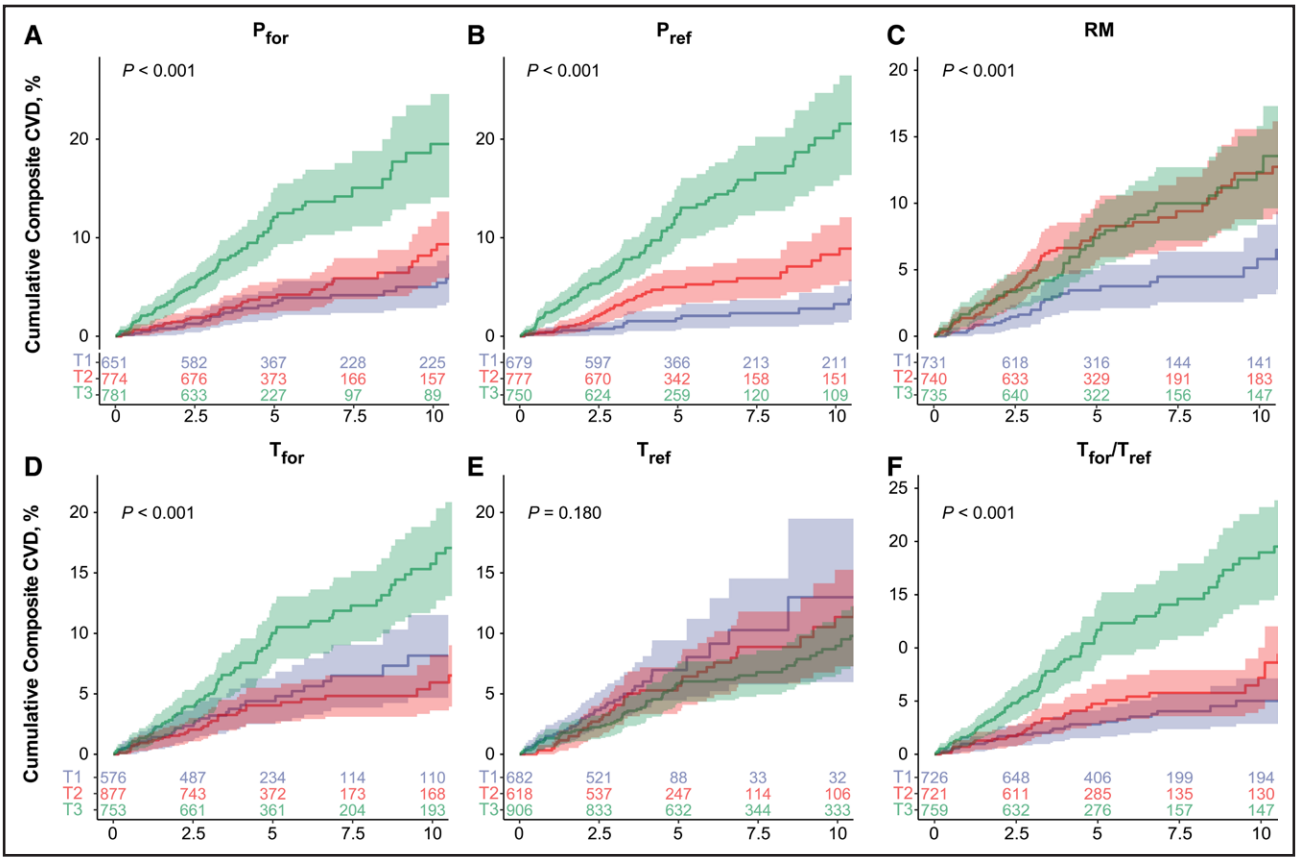

Figure 1. Cumulative incidence of the composite cardiovascular end point by thirds of aortic pulse wave components. Shown are the amplitude and time to pressure peak of the forward (P_{for} and T_{for}; **A** and **D**) and reflected (P_{ref} and T_{ref}; **B** and **E**) aortic pulse wave components, the reflection magnitude (RM; **C**), and the ratio of forward and backward pressure peak time (T_{for}/T_{ref}; **F**). Tabulated data are the number of participants at risk at 2.5-year intervals. *P* values were derived from Log-rank test. CVD indicates cardiovascular disease.

1.64–12.1 years; Table S10), 86 participants (3.90%) died, 25 (1.13%) because of CVD. Considering fatal combined with nonfatal events, the primary end point occurred in 146 individuals (6.62%), coronary events in 70 (3.17%), and stroke in 39 (1.77%). The incidence rates of end points by overall and by thirds of the studied parameters showed significant linear trends (Tables S11 and S12). Similar to baseline profiles, all studied parameters except T_{ref} had positively incremental event rates for 4 end points.

We then plotted the cumulative incidence end points by tertiles of the studied parameters. As shown in Figure 1, for the primary composite end point, there were significant differences across all tertiles ($P<0.001$) except T_{ref}. A similar trend for secondary end points is shown in Figure S2 and S3.

Multivariable-Adjusted Analyses

Multivariable-adjusted Cox regressions were conducted to evaluate aortic pulse wave components with adjusted baseline. As shown in Table 2, every 1 SD increment in P_{for}, T_{for}, and T_{for}/T_{ref} was associated with 27% (95% CI, 1.07–1.49), 25% (95% CI, 1.07–1.45), and 32% (95% CI, 1.12–1.56) higher risk of primary end point. T_{for}, T_{ref}, and T_{for}/T_{ref} were also associated with secondary end points (Table 2). Considering the close correlation between forward and backward pulse wave components, we determined the population composition and absolute 5-year risk of the primary end point for P_{for} and P_{ref} and T_{for} and T_{ref} (Figure 2). When entering the same model, forward pulse wave components were significant for pressure and time, with a higher risk for primary end point observed among participants with high T_{for}/T_{ref}. We further conducted fully adjusted subgroup analyses (Figure 3). P_{for} remained significant in women, with high BP regardless of treatment status (≥140/90 mm Hg), isolated systolic hypertension, and high peripheral PP (≥60 mm Hg). T_{for} and T_{for}/T_{ref} were significant with advanced age (≥60 years), normal systolic and diastolic BP, and PP, or without apparent chronic kidney disease (glomerular filtration rate estimated from serum creatinine ≥60 mL/min/1.73 m^2) or CVD, with T_{for}/T_{ref} also significant in both sexes. There were significant interactions of age ($P=0.027$) and peripheral PP ($P=0.010$) with P_{for}, and hypertension with T_{for} and T_{for}/T_{ref} ($P=0.014/0.017$).

Table 2. End Points in Relation to Pulse Wave Components (Starts)

Pulse wave component End point	Ne (%)	Model 1		Model 2	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
P_{for}					
Primary end point	146 (6.62)	1.26 (1.07–1.49)	0.005	1.27 (1.07–1.49)	0.005
Total mortality	86 (3.90)	1.11 (0.90–1.38)	0.335	1.06 (0.85–1.31)	0.604
Coronary events	70 (3.17)	1.24 (0.97–1.57)	0.082	1.23 (0.97–1.57)	0.090
Stroke	39 (1.77)	1.08 (0.78–1.48)	0.660	1.04 (0.76–1.43)	0.807
P_{ref}					
Primary end point	146 (6.62)	1.10 (0.93–1.32)	0.266	0.98 (0.81–1.19)	0.821
Total mortality	86 (3.90)	1.06 (0.84–1.35)	0.612	1.13 (0.89–1.44)	0.327
Coronary events	70 (3.17)	1.20 (0.93–1.55)	0.154	1.21 (0.93–1.56)	0.160
Stroke	39 (1.77)	1.05 (0.74–1.48)	0.791	1.00 (0.71–1.41)	>0.999
Reflection magnitude					
Primary end point	146 (6.62)	0.85 (0.70–1.03)	0.100	0.84 (0.69–1.01)	0.065
Total mortality	86 (3.90)	0.99 (0.76–1.28)	0.930	1.17 (0.89–1.54)	0.271
Coronary events	70 (3.17)	1.00 (0.76–1.31)	0.979	0.99 (0.75–1.31)	0.946
Stroke	39 (1.77)	1.01 (0.69–1.47)	0.976	0.97 (0.67–1.40)	0.860
T_{for}					
Primary end point	146 (6.62)	1.28 (1.10–1.49)	0.001	1.25 (1.07–1.45)	0.005
Total mortality	86 (3.90)	1.08 (0.90–1.30)	0.417	1.15 (0.94–1.40)	0.189
Coronary events	70 (3.17)	1.36 (1.09–1.70)	0.007	1.37 (1.09–1.73)	0.008
Stroke	39 (1.77)	1.04 (0.78–1.38)	0.804	0.97 (0.73–1.28)	0.827
T_{ref}					
Primary end point	146 (6.62)	1.03 (0.86–1.24)	0.749	1.01 (0.84–1.22)	0.892
Total mortality	86 (3.90)	0.68 (0.53–0.87)	0.003	0.68 (0.53–0.87)	0.002
Coronary events	70 (3.17)	1.30 (1.01–1.69)	0.045	1.33 (1.02–1.73)	0.033
Stroke	39 (1.77)	0.89 (0.62–1.28)	0.536	0.84 (0.59–1.20)	0.340
T_{for}/T_{ref}					
Primary end point	146 (6.62)	1.36 (1.16–1.60)	<0.001	1.32 (1.12–1.56)	<0.001
Total mortality	86 (3.90)	1.22 (1.00–1.48)	0.047	1.25 (1.01–1.54)	0.037
Coronary events	70 (3.17)	1.36 (1.07–1.72)	0.011	1.37 (1.07–1.74)	0.013
Stroke	39 (1.77)	1.08 (0.80–1.45)	0.605	1.01 (0.76–1.35)	0.941

Ne indicates number of events in 2206 individuals at risk. HRs express the relative risk for a 1 SD increment in the explanatory variables. Model 1 accounted for cohort, sex, and age. Model 2 additionally accounted for mean arterial pressure, heart rate, body mass index, the total to high-density lipoprotein serum cholesterol ratio, smoking, use of antihypertensive drugs, history of diabetes, and previous cardiovascular disease with backward elimination. HR indicates hazard ratio; P_{for}, forward aortic pulse wave; P_{ref}, reflected (backward) aortic pulse wave; T_{for}, forward pressure peak time; and T_{ref}, backward pressure peak time.

Predictive Performance

To further assess the incremental predictive value of significant P_{for}, T_{for}, and T_{for}/T_{ref}, we further compared model performance for 5-year primary end point prediction. As shown in Table 3, adding T_{for} and T_{for}/T_{ref} to the full model consisting of established cardiovascular risk factors resulted in significant improvement in Uno's C statistic (0.829 versus 0.812; difference: 0.020±0.007 and 0.022±0.008 for T_{for} and T_{for}/T_{ref}, all $P<0.01$). Integrating T_{for}/T_{ref} further improved net reclassification improvement (0.159 [95% CI, 0.019–0.260]; $P=0.027$) and had marginally improved net reclassification improvement for T_{for} ($P=0.053$). Importantly, T_{for}/T_{ref} had predictive value beyond pulse wave velocity (net reclassification improvement of 0.184 [95% CI, 0.032–0.322; $P=0.027$; Table 3).

DISCUSSION

In a large outcome-based population study across a wide age range (20–93 years), consisting of 3 cohorts from different countries and continents, we provide evidence that the forward, but not the backward traveling pressure wave, is the component of aortic PP that predicts cardiovascular outcomes. We also showed that, to the first of our knowledge, the ratio of forward-to-reflected pressure peak time improves cardiovascular outcome prediction in a multivariable model consisting of established risk factors.

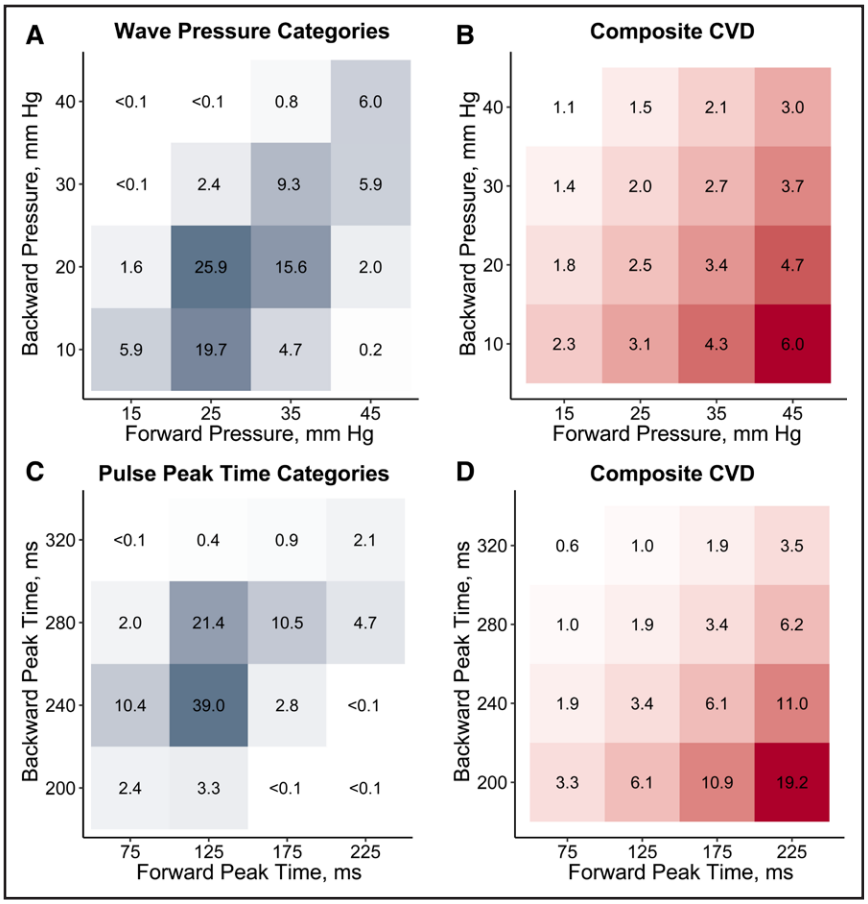

Figure 2. Heat plots for the composition of aortic pulse wave components and the 5-year risk of the primary composite end point. Forward and backward pulse wave components (**A** and **C**) are mutually included in the multivariable adjusted models (**B** and **D**) with covariables of sex, age, body mass index, mean arterial pressure, heart rate, total cholesterol, current smoking, antihypertensive treatment, history of diabetes, and previous cardiovascular disease (CVD) with backward elimination and adjusted for cohort.

Currently, there is controversy as to whether P_{for}, P_{ref}, or both predict cardiovascular events and if this is beyond brachial BP. In this regard, in the Framingham study, P_{for} but not P_{ref} was associated with increased cardiovascular events independent of brachial systolic BP.[9] In comparison, in the MESA (Multiethnic Study of Atherosclerosis), RM (P_{ref}/P_{for}) was an independent (beyond brachial BP) predictor of cardiovascular outcomes.[8] The main differences between the Framingham study and MESA are the types of cardiovascular outcomes. In the Framingham study, the cardiovascular outcomes were driven by myocardial infarction or stroke (59.1%), with only 31.9% of cardiovascular outcomes being due to heart failure.[9] The majority of cardiovascular events in the Framingham study were therefore due to vascular pathology rather than cardiac pathology. In comparison, in MESA, although RM was predictive of all cardiovascular events (hazard ratio, 1.34 [95% CI, 1.08–1.67]; P=0.009), the strongest predictive power was with incident congestive heart failure (hazard ratio, 2.69 [95% CI, 1.79–4.04]; P<0.0001).[8] Hence, in MESA, the predictive ability of RM (P_{ref}/P_{for}) was driven by cardiac functional pathology. It is likely that the ability of RM (P_{ref}/P_{for}) to predict events in MESA is due to the relationship between P_{ref} and cardiac function.[27,28] Indeed, P_{ref} is associated with left ventricular mass[27] and indices of diastolic function.[28] The association of P_{ref} but not P_{for} with left ventricular mass[27] and indices of diastolic function[28] may be explained by the fact that backward wave pressures are derived from local rather than distal regions. Consequently, backward wave pressures measured at the aorta (P_{ref}) would be poor indices of backward wave effects in peripheral sites.[29,30] Hence, P_{ref} is unlikely to be the component of aortic PP that is associated with vascular effects. Indeed, our data, similar to the Framingham study, where outcomes were driven by vascular and not cardiac events, indicate that P_{for} is the component of aortic PP that is an index of atherosclerotic risk or small vessel effects independent of peripheral pressure. However, our results diverge from the CARTaGENE study,[10] which found that both P_{for} and P_{ref} were significantly associated with major adverse cardiovascular events, highlighting the complexity of pulse wave components in cardiovascular risk prediction.

Whether independent associations between central pressure components and cardiovascular events are dependent on sex is also uncertain. In a community-based study in Taiwan, P_{for} was shown to predict outcomes in women but not in men, whereas P_{ref} was weakly associated with outcomes in both men and women.[13] However, no adjustments for peripheral BP were made in this study.[13] In comparison, in a small study of patients undergoing coronary angiography, P_{ref} but not P_{for} was shown to predict events independent of peripheral systolic BP.[14] Although no sex-specific analyses were

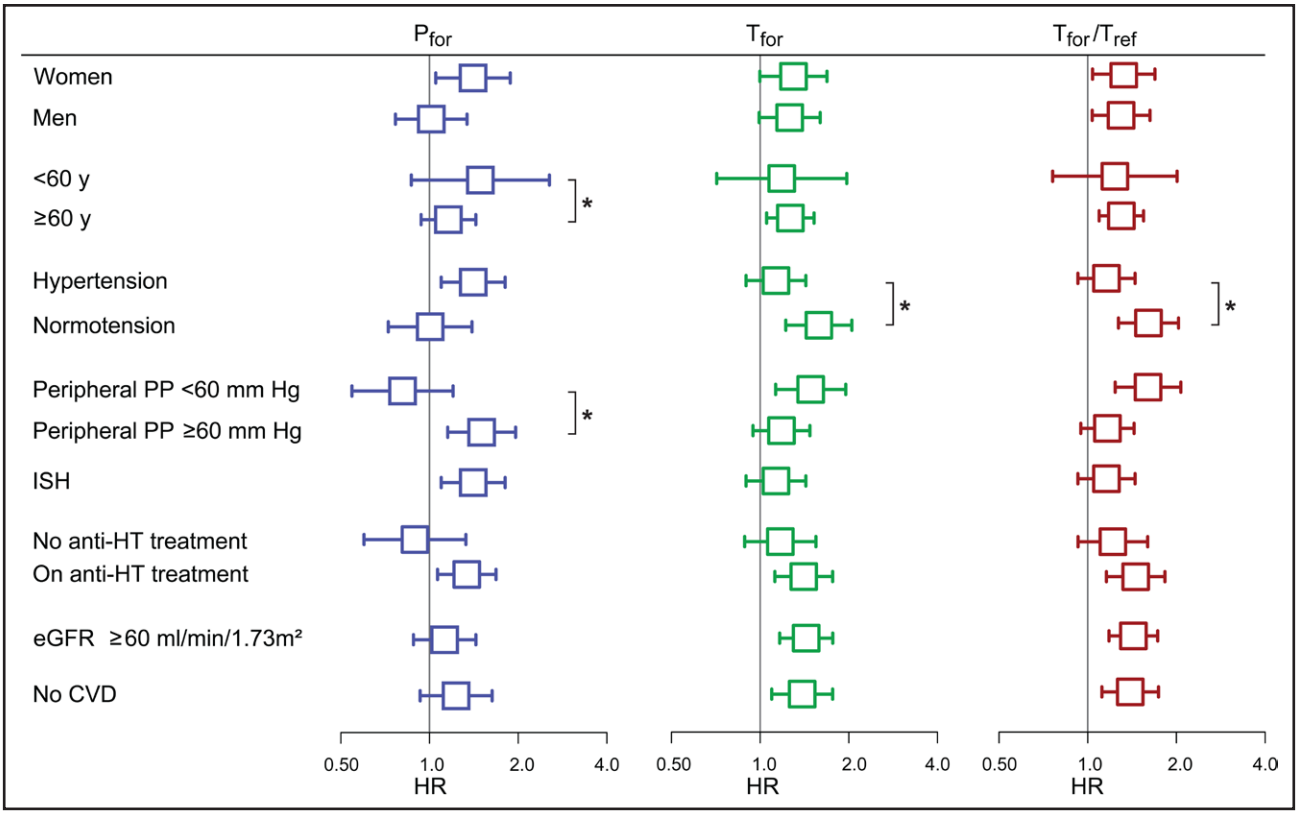

Figure 3. Subgroup analysis of selected aortic pulse wave components for primary end point.
Hazard ratios in subgroups adjusted for cohort, sex, age, body mass index, mean arterial pressure, heart rate, total cholesterol, current smoking, antihypertensive treatment, history of diabetes, and previous cardiovascular disease. CVD indicates cardiovascular disease; eGFR, glomerular filtration rate estimated from serum creatinine; HR, hazard ratio; HT, hypertension; ISH, isolated systolic hypertension; P_{for}, aortic forward wave pressure; PP, pulse pressure; T_{for}, forward pressure peak time; and T_{ref}, backward pressure peak time.

done in this small study,[14] a large proportion (58%) of the patients were men. Hence, it is possible that the lack of an independent association between P_{for} and cardiovascular outcomes in patients undergoing coronary angiography, is driven by relationships observed in men. In this regard, in our study, the ability of P_{for} to independently predict cardiovascular events, although consistent across various subgroups is not significant in men with marginally significant interaction (*P* for interaction=0.052). It should also be considered that

Table 3. Integrated Discrimination Improvement and Net Reclassification Improvement by Adding Aortic Pulse Wave Components to the Base Model

	IAUC and difference in Uno's C			Integrated discrimination improvement		Net reclassification improvement	
Pulse wave component	Base	Added	Δ (SE)	IDI (95% CI)	*P*	NRI (95% CI)	*P*
Full (n=2206)							
P_{for}	0.812	0.826	0.013 (0.008)	0.003 (−0.002 to 0.024)	0.346	−0.022 (−0.184 to 0.139)	0.824
T_{for}	0.812	0.829	0.020 (0.007)*	0.006 (−0.002 to 0.023)	0.113	0.170 (−0.006 to 0.272)	0.053
T_{for}/T_{ref}	0.812	0.829	0.022 (0.008)*	0.008 (0.000 to 0.024)	0.073	0.159 (0.019 to 0.260)	0.027
With PWV (n=1741)							
P_{for}	0.811	0.828	0.014 (0.229)	0.001 (−0.001 to 0.018)	0.319	−0.003 (−0.188 to 0.179)	>0.999
T_{for}	0.811	0.826	0.023 (0.011)†	0.013 (0.001 to 0.040)	0.027	0.195 (−0.018 to 0.314)	0.066
T_{for}/T_{ref}	0.811	0.825	0.025 (0.011)†	0.016 (0.003 to 0.044)	0.007	0.184 (0.032 to 0.322)	0.027

C statistic, IDI, and NRI calculations were performed for the 5-year risk with bootstrapping. The base model was adjusted for cohort and included, sex, age, mean arterial pressure, heart rate, body mass index, serum total cholesterol, smoking, diabetes, and history of cardiovascular disease. For the subset including carotid-femoral pulse wave velocity (PWV), PWV was also included in the base model. Added model additionally includes P_{for}, T_{for}, and T_{for}/T_{ref}. IDI and NRI estimates are given with 95% CI. IAUC indicates integrated area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement; P_{for}, forward aortic pulse wave; T_{for}, forward pressure peak time; and T_{ref}, backward pressure peak time.

*$P<0.01$.

†$P<0.05$.

the possible sex differences with regard to pulse wave components in relation to outcome could be partly due to the shorter pulse wave traveled distance in women as compared with men due to the average body height difference.[31]

Importantly, we show that P_{for} predicts cardiovascular outcomes in both systolic/diastolic hypertension and isolated systolic hypertension, independent of confounders, including brachial MAP. Hence, P_{for} provides information about cardiovascular risk beyond brachial BP measurements. In this regard, prior studies showing an impact of P_{for} on outcomes did not adjust for brachial BP.[9]

The association of the timing of pulse wave components with cardiovascular end points in the current study is clinically relevant as the timing of arterial waves influences ventricular-vascular interactions and impacts cardiac afterload. In this regard, a prolonged QRS (duration of mechanical systole) is a well-established predictor of mortality in patients with heart failure with reduced ejection fraction,[32–34] and a greater T_{for} reflects a prolonged mechanical systole.[35] The consequences of a greater T_{for} and hence T_{for}/T_{ref} would be an enhanced chance of overlap of P_{for} and P_{ref}, thereby augmenting central systolic pressure[2,5] and increasing hemodynamic load on the left ventricle.[6,7] Indeed, in patients with heart failure with reduced ejection fraction, premature wave reflections are associated with adverse clinical outcomes.[17]

Importantly, our study is the first to show the ability of peak-time components of the aortic pulse wave to predict outcomes in general population. A previous study reporting associations between premature wave reflections and adverse clinical outcomes was conducted in a cohort of patients with heart failure.[17] In this regard, we showed that the timing of aortic pressure wave components predicted cardiovascular events across various subgroups, including those without apparent chronic kidney disease or CVD. Indeed, the T_{for}/T_{ref} significantly improved the risk prediction of adverse cardiovascular events over and beyond the other risk factors.

Clinical Implications

As the pulsatile components (PP) of BP predict cardiovascular events better than steady pressures,[9] identifying the primary components of PP that determine cardiovascular events independent of brachial BP could be helpful in developing more effective therapeutic approaches to managing hypertension, thereby preventing cardiovascular events. Furthermore, assessing the role of T_{for}/T_{ref} in predicting cardiovascular events is important as the relative timing of the aortic pressure wave components influences the extent of overlap of P_{for} and P_{ref}, and hence peak PP. In the current study, we show that P_{for} is independently associated with increased cardiovascular risk. Moreover, T_{for}/T_{ref} significantly improved cardiovascular risk prediction beyond conventional risk factors and pulse wave velocity. As a key determinant of P_{for} and T_{for}/T_{ref} is arterial stiffness, reducing arterial stiffness may assist in lowering cardiovascular events. In this regard, intensive pharmacological management of BP (target systolic BP <120 mm Hg) compared with usual treatment (<140 mm Hg) has been shown to attenuate increases in pulse wave velocity over an 18-month follow-up period.[36] Consequently, a more stringent control of BP is imperative to reduce the impact of increased P_{for} on the vasculature and hence on cardiovascular events. Moreover, antihypertensive agents that specifically prolong T_{ref} and shorten T_{for} may be beneficial to reduce cardiovascular events. One such agent would be vasodilators,[37] which have been shown to increase T_{ref}, thereby decreasing aortic BP and cardiac afterload.[12]

Limitations

The results of the current study should be interpreted in the context of its potential limitations. Although the current study was performed in participants over a wider age range than previous studies, the limited number of events and the heterogeneity of study cohorts may limit study power for the detection of these less pronounced aortic pulse wave components. That said, the analyses were adjusted for cohort, and we found P_{for} and T_{for}/T_{ref} showed significant associations with primary and some secondary end points. Second, it is important to note that although IDCARS was a multiethnic cohort, Blacks and Asians were not represented in the data sets analyzed in this study. It would therefore be desirable to replicate the findings in other populations to better establish their generalizability. Third, T_{for}/T_{ref} was not measured repeatedly, thus the repeatability and change over time require further study. However, our study aligns with previous cross-sectional studies in different populations, showing T_{for}/T_{ref} was associated with cardiovascular parameters. Lastly, the significant improvement in the C statistic is moderate in terms of size; however, pulse wave analysis enables the unmasking of hidden risk factors in patients with high P_{for} and T_{for}/T_{ref}.

Perspectives

In a large outcome-based study representing a wide age range (20–93 years) and 3 different countries and 2 continents, we show that the forward traveling pressure wave, not the backward traveling pressure wave, is the component of aortic PP that predicts cardiovascular outcomes. Moreover, T_{for}/T_{ref} is independently associated with cardiovascular events and shows significant improvement in prediction of cardiovascular events beyond conventional risk factors. Future research is necessary to evaluate the intervention modifying these components on cardiovascular outcomes.

ARTICLE INFORMATION

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G.R. Norton spent a considerable proportion of his scientific research career, from 1987 until a few weeks before his death, unraveling the central hemodynamics in animal models and humans and making, as evidenced by his impressive publication list, important contributions to this field. The IDCARS investigators gratefully dedicate this article to his memory. Gavin R. Norton died on December 9, 2022.

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Disclosures

None.

Supplemental Material

Tables S1–S12
Figures S1–S3

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