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# Association of Total Mortality and Cardiovascular Endpoints With the Timing of the First and Second Systolic Peak of the Aortic Pulse Wave

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The International Database of Central Arterial Properties for Risk Stratification Investigators is listed in the Appendix.

**ABSTRACT**

Prognostic significance of the timing in the cardiac cycle of the first (TP1) and second (TP2) systolic peak of the central aortic pulse wave is ill-defined. Incidence rates and standardized multivariable-adjusted hazard ratios (HRs) of adverse health outcomes associated with TP1 and TP2, estimated by the SphygmoCor software, were assessed in the International Database of Central Arterial Properties for Risk Stratification (IDCARS) ($n = 5529$). Model refinement was assessed by the integrated discrimination (ID) and net reclassification (NR) improvement. Over 4.1 years (median), 201 participants died and 248 and 159 patients experienced cardiovascular or cardiac endpoints. Mean TP1 and TP2, standardized for cohort, sex, age, and heart rate, were 103 and 228 ms. Shorter TP1 and TP2 were associated with higher mortality and shorter TP1 with a higher risk of cardiovascular and cardiac endpoints (trend $p \leq 0.004$). The HRs relating total mortality and cardiovascular endpoints to TP2 were 0.82 (95% confidence interval [CI]: 0.72–0.94) and 0.87 (0.77–0.98), respectively. The HR relating cardiac endpoints to TP1 was 0.81 (0.68–0.97). For total mortality and cardiovascular endpoints in relation to TP2, NRI was significant ($p \leq 0.010$), but not for cardiac endpoints in relation to TP1. Integrated discrimination improvement (IDI) was not significant for any endpoint. The HRs relating total mortality to TP2 were smaller ($p \leq 0.026$) in women than men (0.67 vs. 0.95) and in older ($\geq 60$ years) versus younger ($< 60$ years) participants (0.80 vs. 0.88). Our study adds to the evidence supporting risk stratification based on aortic pulse analysis by showing that TP2 and TP1 carry prognostic information.

## 1 | Introduction

The arterial pressure wave consists of a forward component generated by left ventricular ejection and reflected waves returning from peripheral branching sites to the central aorta [1]. Using radial tonometry and a validated transfer function [2], the contour of the central aortic pulse wave can be reconstructed. The first systolic peak (P1) corresponds with the blood ejected by the left ventricular, while the second systolic peak (P2) is generated by the summation of the forward and the reflected wave. Stiffening of the aorta, mainly driven by aging, hypertension and dyslipidemia, increases the speed of the reflected wave, so that it reaches the proximal aorta during systole, augments late systolic blood pressure, and increases the workload of the left ventricle.

Several studies in populations [3–6] and in patients with coronary heart disease [7–10] or end-stage renal disease [11, 12] investigated the association between adverse health outcomes and the characteristics of the central aortic pulse wave, including the amplitude of P1 and P2, the reflection index, and the augmentation index. Of these studies, four [7, 8, 10, 11] reported a higher risk associated with shorter TP1, also known as the inflection point, while in one study [3] the adjusted association of all-cause and cardiovascular mortality with TP1 was not significant. None of these studies [3, 7, 8, 10, 11] assessed the prognostic value of TP2. To address this knowledge gap, we analyzed the International Database of Central Arterial Properties for Risk Stratification (IDCARS), which includes nine population cohorts recruited in Europe, Asia, and South America.

## 2 | Methods

### 2.1 | Study Population

Previous publications describe the construction of the IDCARS database in detail [13]. The longitudinal studies extracted from the IDCARS data resource qualified for the current analysis, if information on brachial and central blood pressure and cardiovascular risk factors was available at baseline, if the arterial pulse waveform had been tonometrically measured, if follow-up included both fatal and nonfatal endpoints, if study reports had been published in peer-reviewed journals, and if the study participants were representative for a population. All studies complied with the Helsinki Declaration on research in humans [14] and were approved by the competent Institutional Review Boards. Participants provided written informed consent. All data were stripped from personal identifiers, and if required by national legislation, additional ethical clearance was obtained. Study-specific information on the catchment areas, sampling strategies, timeframes of recruitment and follow-up, and participation rates, are listed in Table S1.

### 2.2 | Blood Pressure and Pulse Wave Analysis

Brachial blood pressure was measured immediately prior to the hemodynamic assessment after participants had rested for at least 5 min, up to 15 min, in the supine position, using standard mercury sphygmomanometers or validated oscillometric devices [13]. Brachial blood pressure was the average of two consecutive readings. Experienced observers recorded the radial arterial waveform at the dominant arm during an 8-s 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 (CARDIEX Pty., Ltd., Sydney, New South Wales, Australia). 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 less than 70%. From the radial signal, the SphygmoCor software reconstructs the aortic pulse wave by means of a validated generalized transfer function [2], and computed the forward and backward pulse pressure amplitudes and the timing of their peak height (Figure 1), relative to the electrocardiographic QRS complex by a pressure-based triangular-flow wave separation algorithm as implemented in the SphygmoCor software. Estimates of central blood pressure were calibrated on brachial systolic and diastolic blood pressure. Left

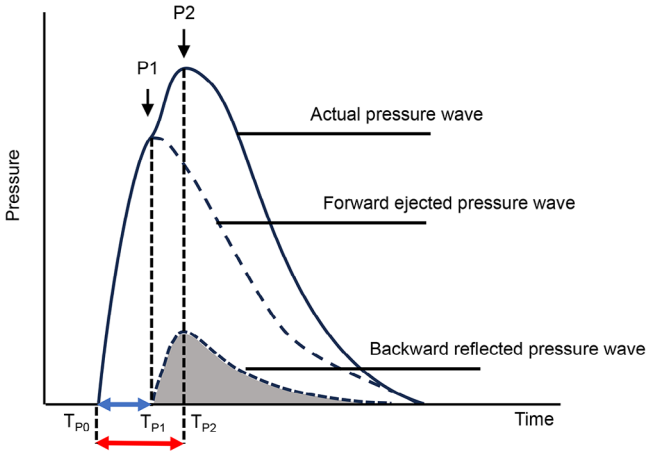


**FIGURE 1** | Pulse wave analysis. P1 and P2 indicate the first and second peaks of the waveform. The pressure waveform can be separated in its forward and backward components, using a pressure-based triangular-flow wave separation algorithm. P1 indicates the first systolic peak attributed to the forward wave. P2 is the late systolic peak attributed to the augmentation by the reflected pressure wave. TP0 is the onset of left ventricular ejection. The time intervals from P0 to P1 and to P2 are TP1 (blue arrow) and TP2 (red arrow), respectively.

ventricular contraction by ejecting blood into the aorta produces an early forward pressure wave (P1). The backward pressure wave originating from reflection points in the peripheral arterial system further augments systolic blood pressure and generates a second pressure peak (P2). TP1 and TP2 are the time intervals from the start of left ventricular ejection to the first (P1) and the second (P2) systolic peak of the aortic pulse wave.

### 2.3 | Carotid-Femoral Pulse Wave Velocity (PWV)

In all IDCARS cohorts included in the current analysis, carotid-femoral PWV was measured by sequential electrocardiographically gated recordings of the arterial pressure waveform at the carotid and femoral arteries. The observers measured the distance from the suprasternal notch to the carotid sampling site (distance A), and from the suprasternal notch to the femoral sampling site (distance B). Pulse wave travel distance was calculated as distance B minus distance A [13]. Pulse transit time was the average of 10 consecutive beats [13]. PWV is the ratio of the travel distance in meters to transit time in seconds. PWV measurements were discarded if the standard error of the mean of 10 beats was more than 10% [13].

### 2.4 | Ascertainment of Endpoints

Vital status of participants and the incidence of endpoints were ascertained from the appropriate sources in each country. The endpoints studied were total mortality, a composite cardiovascular outcome, and fatal plus nonfatal cardiac events, including death from ischemic heart disease, sudden death, nonfatal myocardial infarction, coronary revascularization, and heart failure. The composite cardiovascular endpoint also included fatal and nonfatal stroke. All endpoints 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.

### 2.5 | Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.4. 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 [15]. We compared means and incidence rates using the large-sample $z$-test and proportions by the $\chi 2$ statistic, respectively.

In the first step of our analyses, we standardized TP1 and TP2 to the average in the whole study population (mean or ratio) of sex, age, and heart rate. We then tabulated the endpoint rates by quartiles of TP1, TP2, and the TP2/TP1 ratio. We computed 95% confidence intervals (CIs) of rates as $R \pm 1.96 \times \sqrt{(R/T)}$, where $R$ and $T$ are the rates and the denominator used to calculate the rate [16]. Next, we applied multivariable-adjusted Cox models, in which the risk associated with TP1, TP2, and the TP2/TP1 ratio was expressed by per 1-SD increment. The covariables accounted for were cohort (random effect), body mass index, smoking and drinking, serum cholesterol, antihypertensive drug treatment, history of cardiovascular disease, diabetes mellitus, and brachial systolic and diastolic blood pressure. To adjust for cohort, we pooled participants recruited in the framework of the European Project on Genes in Hypertension (Kraków, Pilsen, and Padova; Table S1) [17]. We checked the proportional hazards assumption by the Kolmogorov-type supremum test and by testing the interaction between follow-up duration and the timing parameters. Statistical significance was a two-sided probability of 0.05 or less.

## 3 | Results

### 3.1 | Characteristics of Participants

Of 6650 participants available in the IDCARS database (Table S1), 1121 were excluded, 954 because they were younger than 30 years with a low incidence of endpoints (rates less than 0.5 events per 1000 person-years); 60 because the radial pulse wave had not been recorded; 75 because TP1 and TP2 were missing; and 32 because their treatment status for hypertension was not on file. Among the 5529 participants left for analysis, missing values were interpolated for body mass index ($n = 23$), total serum cholesterol ($n = 157$), current smoking ($n = 221$), use of alcoholic beverages ($n = 1140$), and history of cardiovascular disease ($n = 69$). A sensitivity analysis including PWV as an additional covariable included 3366 individuals, in whom PWV had been measured along with TP1 and TP2.

Table 1 lists the main characteristics of the participants kept in the analyses. Mean age at enrollment was 54.2 years. The correlation coefficient between TP1 and TP2 was 0.11 ($p < 0.001$). Among

**TABLE 1** | Baseline characteristics of participants.

| Characteristic | Women | Men | All |
|---|---|---|---|
| N° with characteristic (%) | 2998 (54.2) | 2531 (45.8) | 5529 |
| Europeans | 1238 (41.3) | 1140 (45.0)* | 2378 (43.0) |
| Asians | 931 (31.1) | 888 (35.1)* | 1819 (32.9) |
| South Americans | 829 (27.7) | 503 (19.9)* | 1332 (24.1) |
| Current smoking | 312 (10.4) | 865 (34.2)* | 1177 (21.3) |
| Drinking alcohol | 882 (29.4) | 1905 (75.3)* | 2787 (50.4) |
| Hypertension | 2084 (69.5) | 1858 (73.4)* | 3942 (71.3) |
| On antihypertensive treatment | 1126 (54.0) | 757 (40.7)* | 1883 (47.8) |
| Diabetes mellitus | 186 (6.2) | 166 (6.6) | 352 (6.4) |
| History of cardiovascular disease | 437 (14.6) | 340 (13.4) | 777 (14.1) |
| Mean characteristic (± SD) | | | |
| Age, y | 54.9 ± 14.8 | 53.3 ± 14.0* | 54.2 ± 14.4 |
| Body mass index, kg/m2 | 25.8 ± 5.1 | 25.8 ± 4.5 | 25.8 ± 4.8 |
| Heart rate, bpm | 67.0 ± 11.2 | 63.4 ± 11.1* | 65.5 ± 11.3 |
| Brachial BP, mm Hg | | | |
| Systolic | 133.3 ± 22.0 | 135.1 ± 20.0* | 134.2 ± 21.6 |
| Diastolic | 78.9 ± 10.6 | 81.6 ± 10.7* | 80.1 ± 10.8 |
| Central BP, mm Hg | | | |
| Systolic | 124.4 ± 22.0 | 123.2 ± 20.4* | 124.0 ± 21.6 |
| Diastolic | 80.0 ± 10.8 | 82.5 ± 10.8* | 81.1 ± 11.0 |
| Biochemistry | | | |
| Serum cholesterol, mmol/L | 5.12 ± 1.02 | 5.00 ± 0.99* | 5.06 ± 1.01 |
| Blood glucose, mmol/L | 5.05 ± 0.98 | 5.12 ± 1.30* | 5.08 ± 1.14 |
| TP1, ms | 101.0 ± 13.5 | 105.0 ± 15.4* | 102.8 ± 14.5 |
| TP2, ms | 230.5 ± 21.9 | 225.6 ± 22.9* | 228.3 ± 22.5 |
| TP2/TP1 ratio | 2.32 ± 0.35 | 2.19 ± 0.38* | 2.26 ± 0.37 |

*Note:* 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 ≥ 7.0 mg/dL, random blood glucose of ≥ 11.1 mg/dL, a self-reported diagnosis, or diabetes documented in practice or hospital records. Brachial blood pressure was measured immediately prior to the hemodynamic assessment after participants had rested in the supine position for ≥ 5 min. Hypertension was a brachial blood pressure of ≥ 130 mm Hg systolic or ≥ 80 mm Hg diastolic, or use of antihypertensive drugs. An asterisk indicates a significant sex difference.

all participants 3942 (71.3%) had hypertension, 1883 (47.8%) were on antihypertensive treatment, and 1773 patients reported the information on antihypertensive drugs, of whom 387 (21.8%) and 1386 (78.2%) were taking a single agent or combination therapy, respectively. Drug classes taken were diuretics in 634 (35.8%) patients, $\beta$-blockers in 742 (41.9%), inhibitors of the renin-angiotensin system in 1150 (64.9%), and vasodilators in 808 (45.6%). Among the 5529 study participants (Table 1), 2998 (54.2%) were women. The distributions of TP1, TP2, and the TP2/TP1 ratio are shown in Figure S1. Across continents, there were small but significant differences in the sex distribution with proportionally less women than men among Europeans (41.3% vs. 45.0%) and Asians (31.1% vs. 35.1%), but a greater percentage of women among South Americans (27.7% vs. 19.9%). Compared to women, more men reported smoking cigarettes (10.4% vs. 34.2%) or consuming alcoholic beverages (29.4% vs. 75.3%).

### 3.2 | Absolute Risk

Median follow-up time was 4.1 years (5th–95th percentile interval: 2.2–12.1 years). Over 31 267 person-years, 201 died (6.4 deaths per 1000 person-years) and 248 participants experienced a cardiovascular endpoint (8.1 events per 1000 person-years) and 159 a cardiac endpoint (5.2 events per 1000 person-years). Table S2 lists the components of the cardiovascular and cardiac endpoints.

In exploratory analyses, TP1 and TP2 were standardized for cohort, sex, age, and heart rate. The crude incidence rates of total mortality and cardiovascular and cardiac endpoints were examined across quartiles of TP1, TP2, and the TP2/TP1 ratio (Table S3). Considering TP1, the incidence of total mortality and cardiovascular and cardiac endpoints significantly decreased from the shortest to the longest TP1 interval ($p$ for trend ≤ 0.004;

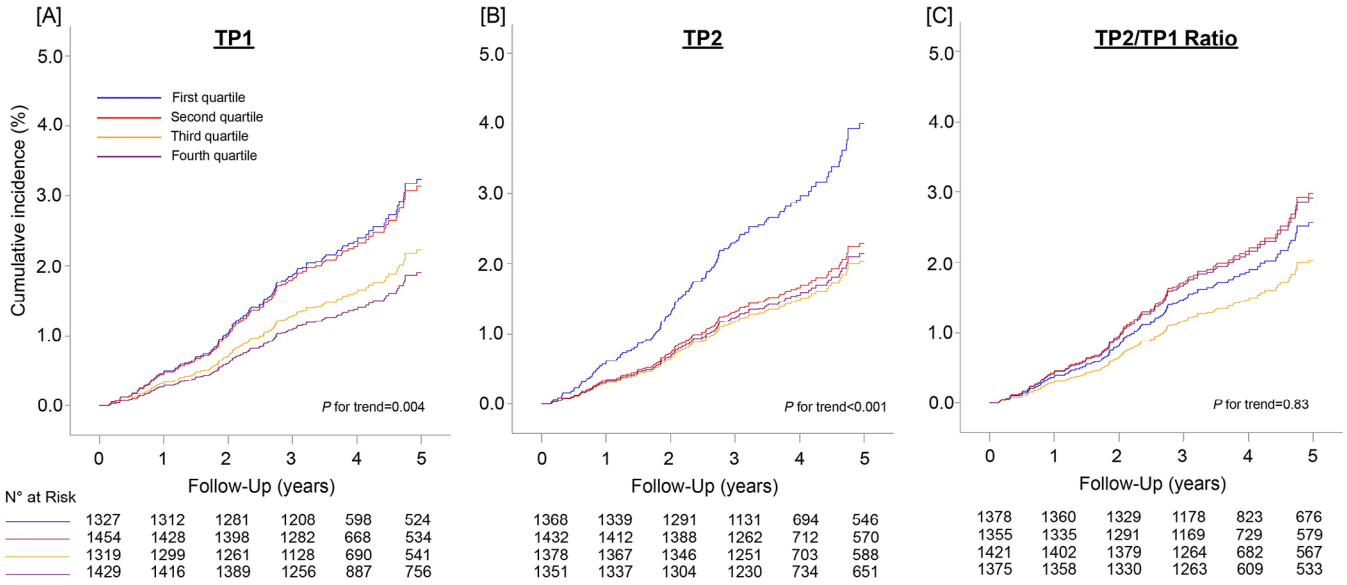


**FIGURE 2** | Cumulative incidence of total mortality by quartiles of TP1, TP2, and the TP2/TP1 ratio.
TP1 and TP2 were standardized to the average in the whole study population (mean or ratio) of sex, age, and heart rate. Cumulative incidence was derived by proportional hazard regression with adjustment for cohort as random effect.

Table S3). For TP2, death rates also decreased with longer TP2 intervals ($p < 0.001$; Table S3); trends were similar for cardiovascular and cardiac endpoints but did not reach significance ($p \geq 0.10$). For the TP1/TP2 ratio, the association was not significant for total mortality ($p = 0.83$), but the cardiovascular and cardiac event rates increased with higher category of the ratio ($p \leq 0.036$; Table S3). The cumulative incidence of total mortality (Figure 2) and of cardiovascular and cardiac events (Figure 3) confirmed the findings presented in Table S3.

### 3.3 | Relative Risk in Multivariable-Adjusted Analyses

Standardized hazard ratios (HRs) expressing the risk associated with a 1-SD increment in the explanatory variable were computed with cumulative adjustments applied for cohort (random effect), body mass index, smoking and drinking, serum cholesterol, antihypertensive drug treatment, history of cardiovascular disease, diabetes mellitus, and systolic and diastolic pressure (Table 2). The proportional hazard assumptions were met in all models. With full adjustment applied, the HR relating cardiac endpoints to TP1 was 0.81 (95% CI: 0.68–0.97; $p = 0.021$), but total mortality and cardiovascular endpoints were unrelated to TP1 ($p \geq 0.17$). Furthermore, the fully adjusted HRs relating total mortality and cardiovascular endpoints to TP2 were 0.82 (95% CI: 0.72–0.94; $p = 0.004$) and 0.87 (95% CI: 0.77–0.98; $p = 0.021$), respectively. The cardiac endpoint was not associated with TP2 (HR: 0.92; 95% CI: 0.78–1.07; $p = 0.28$). Total mortality and the cardiovascular and cardiac endpoints were unrelated to TP2/TP1 ratio ($p \geq 0.12$).

For total mortality and cardiovascular endpoints, the net reclassification improvement (NRI) was significant ($p \leq 0.010$) for adding TP2 to the base model including conventional risk factors and systolic and diastolic blood pressure. For cardiac events, TP1 did not add to the model refinement (Table 3).

### 3.4 | Sensitivity Analysis

The correlation coefficients of PWV with TP1 and TP2 were −0.121 ($p < 0.001$) and 0.005 ($p = 0.76$), respectively. With additional adjustment for PWV in 3366 instead of 5529 persons, the HRs for the cardiac endpoint in relation to TP1 and PWV were 0.78 (95% CI: 0.62–0.98; $p = 0.036$) and 1.10 (95% CI: 1.01–1.21; $p = 0.039$), respectively. In models additionally adjusted for PWV, the HRs for total mortality and cardiovascular endpoints in relation to TP2 were directionally similar compared to the whole cohort, but given the smaller sample size lost formal significance: 0.86 (95% CI: 0.62–1.19; $p = 0.36$) and 0.86 (95% CI: 0.66–1.12; $p = 0.27$). However, in the subgroup, the multivariable-adjusted HRs relating total mortality and the cardiovascular endpoints to PWV were 1.09 (95% CI: 1.00–1.19; $p = 0.050$) and 1.10 (95% CI: 1.02–1.19; $p = 0.014$).

### 3.5 | Subgroup Analyses

In fully adjusted models, the HR relating total mortality to TP2 was smaller in 2998 women than 2531 men (0.67 [95% CI: 0.54–0.83] vs. 0.95 [95%CI: 0.50–1.12]; interaction $p$: 0.026) and in 1925 older (≥ 60 years) compared to 3604 younger (< 60 years) participants (0.80 [95% CI: 0.69–0.94] vs. 0.88 [95%CI: 0.67–1.17]; interaction $p < 0.001$). Findings were similar for cardiac endpoints in relation to TP1 (data not shown).

The HRs relating mortality to TP2 were directionally similar in 1883 participants treated for hypertension compared with 3646 untreated individuals: 0.82 (95% CI: 0.68–0.99; $p = 0.048$) versus 0.81 (95% CI: 0.67–0.98; $p = 0.029$). This was also the case for the

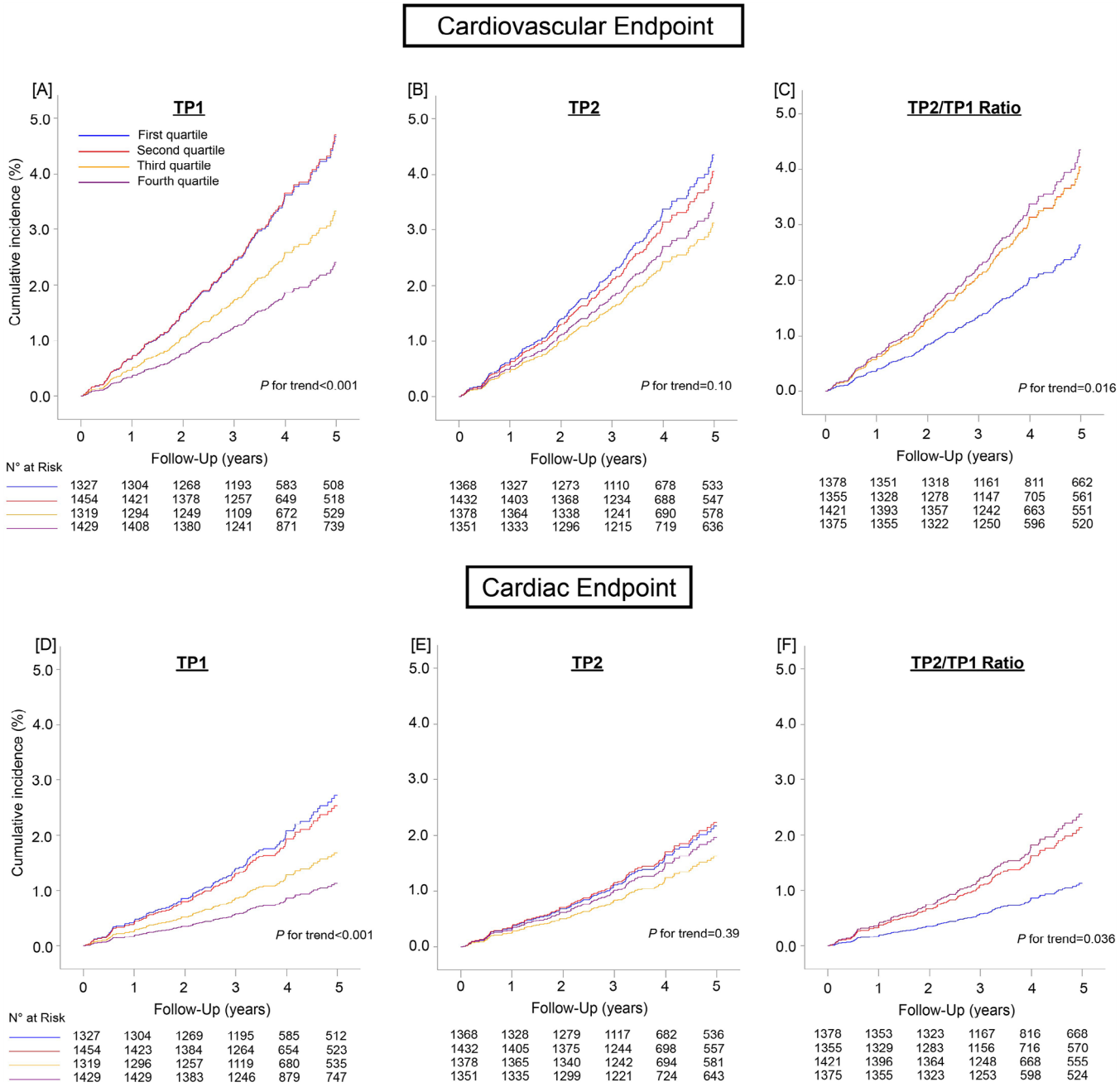


**FIGURE 3** | Cumulative incidence of cardiovascular and cardiac endpoints by quartiles of TP1, TP2, and the TP2/TP1 ratio. TP1 and TP2 were standardized to the average in the whole study population (mean or ratio) of sex, age, and heart rate. Cumulative incidence was derived by proportional hazard regression with adjustment for cohort as random effect.

association of cardiovascular endpoints with TP2: 0.87 (95% CI: 0.74–1.03; $p = 0.097$) versus 0.83 (95% CI: 0.69–1.01; $p = 0.063$) and for cardiac endpoints in relation to TP1: 0.92 (95% CI: 0.74–1.13; $p = 0.42$) versus 0.69 (95% CI: 0.50–0.93; $p = 0.017$) in treated and untreated individuals, respectively. The interaction $p$ values for treatment status were $\geq 0.41$.

## 4 | Discussion

Previous studies in patients with coronary heart disease [7, 8, 10] or end-stage renal failure [11] reported that shorter TP1 was a forerunner of adverse health outcomes, whereas in a population study [3] the adjusted association of total and cardiovascular mortality was not significant. Our current study advances the field, because it was multi-ethnic, including cohorts from six European countries, China, Uruguay, and Argentina [13] and by assessing the association of adverse health outcomes not only with TP1 but also with TP2 and the TP2/TP1 ratio. The key finding was that in multivariable-adjusted models shorter TP2 predicted death and a cardiovascular endpoint. In keeping with findings in the Framingham Heart Study [18], the associations with TP2 were mainly driven by women and participants aged 60 years or more. Additionally, shorter TP1 was also associated with a higher risk of a cardiac endpoint. Over and beyond established risk factors, including systolic and diastolic blood pressure, for mortality and

**TABLE 2** | HRs expressing the risk per 1-SD increment in TP1, TP2, and the TP2/TP1 ratio.

| Endpoint timing parameter | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Total mortality | | | | | | |
| TP1, ms | 0.97 (0.85–1.12) | 0.68 | 1.00 (0.87–1.14) | 0.98 | 0.98 (0.86–1.12) | 0.79 |
| TP2, ms | 0.84 (0.73–0.96) | 0.011 | 0.81 (0.71–0.93) | 0.002 | 0.82 (0.72–0.94) | 0.004 |
| TP2/TP1 ratio | 0.96 (0.83–1.10) | 0.53 | 0.91 (0.79–1.05) | 0.20 | 0.93 (0.81–1.06) | 0.27 |
| Cardiovascular endpoint | | | | | | |
| TP1, ms | 0.86 (0.75–0.99) | 0.037 | 0.91 (0.80–1.04) | 0.17 | 0.91 (0.80–1.04) | 0.17 |
| TP2, ms | 0.94 (0.83–1.06) | 0.31 | 0.86 (0.76–0.98) | 0.021 | 0.87 (0.77–0.98) | 0.021 |
| TP2/TP1 ratio | 1.11 (0.97–1.26) | 0.12 | 1.02 (0.89–1.16) | 0.83 | 1.02 (0.89–1.16) | 0.82 |
| Cardiac endpoint | | | | | | |
| TP1, ms | 0.76 (0.64–0.91) | 0.003 | 0.80 (0.67–0.96) | 0.017 | 0.81 (0.68–0.97) | 0.021 |
| TP2, ms | 0.98 (0.84–1.15) | 0.81 | 0.91 (0.77–1.06) | 0.22 | 0.92 (0.78–1.07) | 0.28 |
| TP2/TP1 ratio | 2.16 (1.46–3.21) | < 0.001 | 1.14 (0.97–1.35) | 0.11 | 1.14 (0.97–1.34) | 0.12 |

*Note:* Model 1 was adjusted for cohort (random effect), sex, age, heart rate, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug treatment, history of cardiovascular disease, and diabetes mellitus. Model 2 additionally accounted for brachial systolic blood pressure. Model 3 also accounted for brachial diastolic blood pressure. Hazard ratios given with 95% CI express the risk associated with a 1-SD increment in TP1, TP2, or the TP2/TP1 ratio.
Abbreviation: HRs, hazard ratios.

**TABLE 3** | IDI and NRI for the 5-year risk of an endpoint.

| Endpoint timing parameter | IDI | | | NRI | | |
|---|---|---|---|---|---|---|
| | IDI (%) | 95% CI (%) | *P* | NRI (%) | 95% CI (%) | *P* |
| Total mortality | | | | | | |
| TP2, ms | 19.35 | −3.66 to 29.73 | 0.072 | 0.48 | 0.09–1.35 | 0.010 |
| Cardiovascular endpoint | | | | | | |
| TP2, ms | 15.29 | −1.99 to 23.71 | 0.068 | 0.45 | 0.08–1.33 | 0.008 |
| Cardiac endpoint | | | | | | |
| TP1, ms | 10.17 | −5.83 to 19.86 | 0.16 | 0.09 | −0.04–0.51 | 0.18 |

*Note:* The base model included cohort (random effect), sex, age, heart rate, body mass index, smoking and drinking, serum cholesterol, antihypertensive drug treatment, history of cardiovascular disease, diabetes mellitus, and brachial systolic and diastolic blood pressure. The IDI is the difference between the discrimination slopes of the base model and the base model extended by timing parameters. The discrimination slope is the difference in predicted probabilities (%) between participants without and with an endpoint. The NRI is the sum of the percentages of participants reclassified correctly in individuals without and with an endpoint. IDI and NRI estimates are given with 95% CI.
Abbreviations: ID, integrated discrimination; IDI, integrated discrimination improvement; NRI, net reclassification index.

the cardiovascular endpoint, TP2 refined the classification of participants with and without an endpoint, but this was not the case for TP1 in relation to the cardiac endpoint. The TP2/TP1 ratio did not contribute to risk stratification. In multivariable models additionally adjusted for PWV in a subgroup of 3366 of 5529 study participants (60.9%), the associations of the endpoints under study with TP1 and TP2 were directionally similar, albeit only significant for the cardiac endpoint in relation to TP1, given the smaller sample size.

The current observation that shorter TP2 predicts mortality and cardiovascular endpoints is in keeping with long-established hemodynamic mechanisms occurring in conjunction with the stiffening of the central elastic arteries [1, 19–21]. The pulse wave generated by left ventricular ejection propagates through the conduit vessels but is partially reflected at innumerable sites of impedance mismatch throughout the arterial tree, including points of change in wall diameter, change in material properties of the arterial wall, and branching points [19]. There is no discrete peripheral site in the arterial system at which reflection occurs [1]. However, the multiple reflected waves are integrated into a single combined reflected wave, which sums with the forward ejected wave and thus forms the final pattern of the aortic pulse wave [1]. Stiffer aortas conduct backward waves at greater velocity

and therefore promote an earlier arrival of the reflected waves in the cardiac cycle for any given distance to reflection sites. In young, healthy adults, wave reflections arrive at the aorta predominantly during diastole, augmenting diastolic pressure and promoting coronary blood flow [19–21]. When the central elastic arteries stiffen, as occurs with aging or in hypertensive patients, reflections arrive at the aorta in mid-to-late systole, producing systolic pressure augmentation and enlarging left ventricular afterload [21]. The inverse association of total mortality with TP2 therefore reflects the deleterious effects of arterial stiffening in general, while the inverse associations of cardiovascular and cardiac endpoints with TP2 and TP1, respectively, additionally reveal the unfavorable interplay between systolic augmentation, left ventricular function [21], and coronary blood flow [19].

### 4.1 | Clinical Implications

Studies dealing with the age-related changes in the composition of the aortic wall and clinical trials focusing on central arterial pressure directly point to the clinical implication of our current findings. Aortic stiffness, as captured in the current study by TP1 and TP2, integrates the lifetime injury to the arterial wall. Elastin and collagen are the major constituents of the extracellular matrix in the media of the central elastic arteries. Elastin provides reversible extensibility during systole, while collagen generates tensile strength. As people age, the elastin fibers become fragmented and the mechanical load is transferred to collagen fibers, which are up to 1000 times stiffer than elastin [22]. This process already starts in young adulthood, but the deposition of elastin by vascular smooth muscle cells only occurs during fetal development and in early infancy, and is switched off thereafter [23]. This implies that elastin fiber damage is basically irreversible [23]. The age-related changes in the aortic wall reflect the pulsatile stress with each heartbeat, approximately 40 million per year for a heart rate of 70 beats per minute. Although aging is irreversible, the process of elastin fragmentation is accelerated by the height of systolic blood pressure and heart rate, while dyslipidemia and diabetes, adversely affect the composition of the extracellular matrix and the integrity of the endothelial lining promoting fibrosis and inflammation [24]. Because of the irreversibility of these processes, prevention of aortic stiffening by effectively addressing risk factors, in particular hypertension [25], is an adagio that should be high on the agenda of all clinicians. Complacency and therapeutic inertia still remain the major stumble blocks in cardiovascular prevention, in particular in women, in whom the cardiovascular risk is often underestimated [26–28].

In the SPARTE trial [29], hypertensive patients were randomized to a therapeutic strategy targeting the normalization of PWV, measured every 6 months ($n = 264$) or to a therapeutic strategy only implementing the European Hypertension Guidelines [30] ($n = 272$). After a median follow-up of 48.3 months, there was no significant between-group difference in the primary outcome, a composite cardiovascular endpoint (HR: 0.74; 95% CI: 0.40–1.38). However, the secondary endpoints were met by showing that treatment for hypertension guided by PWV reduced office and ambulatory blood pressure and aortic stiffening more than with application of hypertension guidelines. SPARTE and a subgroup analysis of the Systolic Pressure Intervention Trial [31] clearly demonstrated that any parameter reflecting aortic stiffness mirrors the cumulative load of risk factors over a person's lifetime. This explains why on top of common risk factors, including blood pressure, the integrated discrimination improvement (IDI) was not significant for any timing parameter and why the NR index associating mortality and the cardiovascular endpoint with TP2 was small, albeit significant.

### 4.2 | Study Limitations

Although the IDCARS database is a powerful resource, our study must be interpreted within the context of its potential limitations. First, the reconstruction of the aortic pulse wave from the radial pulse wave using the SphygmoCor technology requires the application of a generalized transfer function, which has been validated [2], but has also been criticized [32]. For example, the SPC-301 micromanometer interfaced with the SphygmoCor device uses a single pressure sensor for applanation tonometry, but some validation studies of the generalized transfer function have utilized a servo-controlled automated tonometric system based on an arrayed sensor to avoid issues related to a manually operated single sensor [33, 34]. Second, the demographic characteristics, the period of recruitment, and the assessment of endpoint 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, which is a strong point compared with meta-analyses of summary statistics [35]. Finally, Blacks show a steeper relation of adverse health effects with both central and brachial systolic BP, for instance, illustrated for left ventricular hypertrophy in a Sub-Saharan cohort [36]. Thus, the current observations cannot be extrapolated to people with Black ancestry.

### 4.3 | Perspectives

Shorter TP2 was associated with a higher risk of mortality and cardiovascular complications and shorter TP1 with a higher risk of a cardiac endpoint. Our study therefore adds to the growing evidence supporting the assessment of the central pulse wave for risk stratification in clinical centers where the technology is readily available [1, 19-21]. On the other hand, parameters associated with aortic stiffness reflect the lifelong exposure to the load of reversible common risk factors. In women and men alike, early intervention with these risk factors is the only way to prevent the loss of life years both in number and in quality of life. This key message remains actual in high-income countries, but it is even more relevant in low- and middle-income countries, where the prevalence of non-communicable diseases is drastically increasing as a consequence of the demographic transition and worsening of lifestyle [37].

#### Author Contributions

Jan A. Staessen initiated and coordinates the IDCARS project. Yi-Bang Cheng, Yan Li, and Jan A. Staessen conceived the current study, did the statistical analyses, and wrote the first draft of the manuscript. De-Wei An, Lucas S. Aparicio, Qi-Fang Huang, Chang-Sheng Sheng, Teemu

J. Niiranen, Fang-Fei Wei, José Boggia, Katarzyna Stolarz-Skrzypek, Natasza Gilis-Malinowska, Valérie Tikhonoff, Wiktoria Wojciechowska, Edoardo Casiglia, Krzysztof Narkiewicz, Wen-Yi Yang, Jan Filipovský, Kalina Kawecka-Jaszcz, and Ji-Guang Wang supervised data collection in the nine participating centers. Tim S. Nawrot supervised the work of De-Wei An during his 2-year scholarship at the University of Leuven in Belgium. All authors read and commented on successive drafts of the manuscript. Yi-Bang Cheng, Yan Li, and Jan A. Staessen vouch for the integrity of the data and took the final decision to submit the manuscript for publication.


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### Ethics Statement

The IDCARS population studies received ethical approval from the competent Institutional Review Boards in their country of origin. Ethical clearance for the secondary use of anonymized data were waived.

### Consent

Participants provided written informed consent.

### Conflicts of Interest

Teemu J. Niiranen received payment or honoraria for lectures and presentations from AstraZeneca and Servier. Krzysztof Narkiewicz received honoraria for lectures from Adamed, Berlin-Chemie/Menarini, Egis, Eli Lilly, Gedeon Richter, Gilead, Janssen Pharma, Krka, Novo Nordisk, Polpharma, Recordati, Sandoz, Servier, and Zentiva. Yan Li reports having received research grants from A&D (A&D Company Ltd., China), Bayer, Omron (OMRON Healthcare Inc., China), Salubris, and Shyndec. None of these payments has any bearing on the conduct of the IDCARS project. The companies listed were not involved in the statistical analysis, the writing of the manuscript, or the decision to submit this article.

### Data Availability Statement

All relevant data are within the paper. Informed consent given by study participants did not include data sharing with third parties. Anonymized data can be made available to investigators for targeted non-commercial research based on a motivated request to be submitted to J.A. Staessen and pending ethical clearance by each of the nine participating centers.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.

## APPENDIX

### The International Database of Central Arterial Properties for Risk Stratification (IDCARS) Investigators:

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