Digital arterial pressure pulse wave analysis and cardiovascular events in the general population: the Prevention of Renal and Vascular End-stage Disease study

Maarten A. De Jonga, Arie M. Van Roonb, Jens T. Bakkerab, Hendrik T.J. Bijenab, Douwe J. Mulderb, Frank P. Browersc, Wiek H. Van Gilstc, Adriaan A. Voorsc, Ron T. Gansevoorta, Stephan J.L. Bakkerad, and Martin H. De Borsta

Background: Arterial stiffness influences the contour of the digital pressure pulse wave.

Method: Here, we investigated whether the digital pulse propagation index (DPPI), based on the digital pressure pulse wave, DPPI is associated with cardiovascular events, heart failure, and mortality in a large population-based cohort. Between 2001 and 2003, DPPI was measured with a Portapres noninvasive hemodynamic monitoring device (Finapres Medical Systems, Amsterdam, The Netherlands) in participants of the Prevention of Renal and Vascular End-stage Disease study, a community-based cohort. We assessed the main determinants of the DPPI and investigated associations of DPPI with cardiovascular events and mortality.

Results: The study included 5474 individuals. Mean age was 52.3 ± 11.8 years and 50.5% was male. Median baseline DPPI was 5.81 m/s (interquartile range 5.47–6.20). Higher age, mean arterial blood pressure, body height, heart rate, current smoking, and lower HDL cholesterol levels and waist circumference were independent determinants of the DPPI \( r^2 = 0.43 \). After adjustment for heart rate, high log DPPI was associated with all-cause mortality [hazard ratio: 1.67, 95% confidence interval (1.55–1.81) per SD; \( P < 0.001 \)], cardiovascular mortality [hazard ratio 1.95 (1.72–2.22); \( P < 0.001 \)], and incident heart failure with reduced ejection fraction [hazard ratio 1.81 (1.60–2.06); \( P < 0.001 \)]. These associations remained independent upon further adjustment for confounders. Optimal cutoff values for DPPI ranged between 6.1 and 6.3 m/s for all endpoints. After multivariable adjustment, DPPI was no longer associated with coronary artery disease events or cerebrovascular events.

Conclusion: The DPPI is associated with an increased risk of development of new onset heart failure with reduced ejection fraction and all-cause and cardiovascular mortality, but not with coronary artery events or cerebrovascular events.

Keywords: heart failure, mortality, pulse contour analysis, risk factors

Abbreviations: AUC, area under the curve; CAD, coronary artery disease; cfPWV, carotid–femoral pulse wave velocity; CVD, cardiovascular disease; DPPI, digital pulse propagation index; DVP, digital volume pulse; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PPT, pulse propagation time; PREVEND, Prevention of Renal and Vascular End-stage Disease; UAE, urinary albumin excretion per 24 h

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide [1]. Large artery stiffness is a hallmark of vascular aging, and may be a consequence of pathological processes including hypertension. Increased arterial stiffness is associated with cardiovascular risk factors, morbidity [2–4], and mortality [2,4–6]. Hence, the early detection of arterial stiffening may contribute to the identification of high-risk patients, and may thereby improve prevention of CVD [7,8].

Journal of Hypertension 2020, 38:1064–1071
aDivision of Nephrology, bDivision of Vascular Medicine, Department of Internal Medicine, cDepartment of Cardiology, University Medical Center Groningen, Groningen and dTop Institute Food and Nutrition, Wageningen, The Netherlands

Correspondence to Martin H. de Borst, MD, PhD, Division of Nephrology, Department of Internal Medicine, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel: +31 50 361 6161; fax: +31 50 361 9350; e-mail: m.h.de.borst@umcg.nl

Received 10 August 2018 Revised 23 December 2019 Accepted 13 January 2020

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DOI:10.1097/HJH.0000000000002390
Digital pulse wave analysis is a technique that intends to assess arterial stiffness using the peripheral arterial pulse waveform. This waveform can be measured from a finger, using photoplethysmography or a pressure sensor [9–11]. Here, we obtained digital finger pressure pulse data, which can subsequently be used to derive the pulse propagation time (PPT), defined as the time between the systolic and diastolic peak (Fig. 1) [9]. Finally, the digital pulse propagation index (DPPI, expressed in meter per second) can be calculated by dividing the height of each individual by the PPT [9]. DPPI Previous studies have shown that digital volume pulse (DVP) analysis, which is a slightly different method based on photoplethysmography, has a low failure rate and good within-individual repeatability [12,13] and has been correlated with individual cardiovascular risk scores [12–14]. Digital pulse wave measurement is relatively simple, rapid and requires no special training [8–10]. However, it remains unclear whether DPPI is a predictor of cardiovascular outcomes. While pulse contour analysis initially appeared to correspond closely with the gold standard of arterial stiffness measurement, carotid–femoral pulse wave velocity (cfPWV) [10,13], later studies only observed a weak association between these methods [15]. Although cfPWV has been clinically validated, prospective data on associations between DPPI and cardiovascular morbidity and mortality are sparse.

Here, we investigated potential associations between the pulse contour-based DPPI, measured using a pressure sensor (PortaPres), and cardiovascular outcomes in the general population-based Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort.

METHODS

Study population
The study was performed using the data of the PREVEND cohort study, which has been described elsewhere [16].

Assessment of endpoints
Data on hospitalization for nonfatal CVD were obtained from the Dutch national registry of hospital discharge diagnoses. Coronary artery disease (CAD) events and cerebrovascular events were coded according to International Statistical Classification of Diseases and Related Health Problems (ICD)-10. CAD events were defined as myocardial infarction, a diagnosis of ischemic heart disease, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. Cerebrovascular events were defined as intracranial hemorrhages, occlusion and stenosis of cerebral prearterial arteries, or carotid endarterectomy. Both fatal and nonfatal events were scored. New onset heart failure [with either reduced (HFrEF, left ventricular ejection fraction (LVEF) ≤40%) or preserved (HFrEF, LVEF ≥50%) ejection fraction] were identified by an adjudication committee in accordance with the guidelines of the European Society of Cardiology, as published previously [18]. Mortality data were obtained through the municipal register. Cause of death was classified using the primary cause of death as listed on the death certificate using ICD-10. Person-time was calculated from the date of DPPI measurement and the date of death. Surviving patients were censored based on the date of the last attended follow-up visit.
Assessment of covariates
BP was measured on the right arm, in supine position, every minute for 10 min, using an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical, Tampa, Florida, USA). The mean of the last two recordings was used to calculate the mean arterial BP (MAP). Participants collected two 24-h urine samples. UAE was determined by nephelometry (Dade Behring Diagnostic, Marburg, Germany). Urine sodium excretion was measured with a MEGA clinical chemistry analyzer (Merck, Darmstadt, Germany). Plasma HDL and total cholesterol, triglycerides, N-terminal-pro-brain natriuretic peptide (NT-proBNP) and serum glucose and creatinine were measured on a Roche Modular analyzer (Roche Diagnostics, Mannheim, Germany).

Self-administered questionnaires were used to assess demographics, cardiovascular and renal medical history and family history, medication use, ethnicity, smoking status, alcohol consumption, and attained education [16]. Data on medication use was complemented with information from community pharmacies (with complete medication records of >90% of participants) [19]. Smoking status was categorized as never, former, and currently smoking. Type 2 diabetes mellitus was defined as a fasting plasma glucose more than 7.0 mmol/l, a nonfasting plasma glucose more than 11.1 mmol/l, or use of antidiabetic medication. Estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based Chronic Kidney Disease-Epidemiology collaboration (CKD-EPI) equation, which also includes variables for age, sex, and ethnicity. Missing data on covariates (number of cases: cholesterol: 226, NT-ProBNP: 165, eGFR: 164, waist circumference: 22, urine albumin excretion: 124) were handled using multiple imputation.

Statistical analysis
Data are shown as mean and SD or median and interquartile range (IQR) for skewed distributed variables. Categorical variables are shown as total and percentage. The DPPI was log 10-transformed for all analyses. Covariates with skewed distributions were log-transformed when appropriate. Differences in baseline variables across these quartiles were assessed using analysis of variance (ANOVA), Kruskal–Wallis, and Chi-squared tests. Univariable and subsequent multivariable linear regression was used to assess likely determinants of the DPPI.

Cox proportional hazards models were subsequently used to estimate hazard ratios for the outcomes of interest based on the logDPPI. Harrell's C was calculated as a measure of goodness of model fit. The initial model was adjusted for heart rate (HR) (model 1), and subsequent models were additionally adjusted for age, sex, and body height (model 2), MAP, use of antihypertensive drugs, smoking, prior history of CVD and NT-proBNP (model 3), and lastly for waist circumference, HDL cholesterol, triglycerides, presence of diabetes mellitus, eGFR, UAE, and urinary sodium excretion (model 4). Independent associations between logDPPI and outcomes were subsequently investigated again after exclusion of participants with a history of CVD, using the fully adjusted model (model 4). To visualize significant associations between the DPPI and outcomes, restricted cubic splines were generated with knots placed at the 10th, 50th, and 90th percentile. Receiver operating characteristic (ROC) curves were used to identify the optimal cutoff values for DPPI based on Youden’s J statistic (sensitivity + specificity – 1) [20]. Multiplicative interaction terms and effect modification was used to explore the consistency of the association between the DPPI and mortality. The investigated potential effect modifiers were relevant correlates of DPPI, identified by the prior linear regression analysis, as well as clinically relevant covariates. For this purpose, continuous variables were dichotomized based on clinically relevant cutoff values.

Statistical analyses were performed using SPSS version 23.0 (SPSS, Inc, Chicago, Illinois, USA). For all tests, a two-sided P value of less than 0.05 was regarded as statistically significant. Figures were generated using Graphpad version 6 (GraphPad Software, San Diego, California, USA). Restricted cubic spline fitting was performed with R 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
Mean age of the 5487 PREVEND participants in our study was 52.3 ± 11.8 years and 50.6% were male. The majority of the cohort (96.1%) was of white descent. Median baseline DPPI was 5.81 m/s (IQR 5.47–6.20). The distribution of DPPI was skewed to the right. Baseline characteristics of the cohort per quartile of DPPI are presented in Table 1. Participants with high DPPI were older (P < 0.001) and more likely to be male (<0.001). In addition, high DPPI was associated with established cardiovascular risk factors, including mean arterial BP (MAP) and smoking (all P < 0.001).

Associations between potential determinants and logDPPI were further explored using multivariable linear regression analysis (Table 2). Higher age, higher MAP, greater length, higher HR, active smoking, male sex, and lower HDL cholesterol levels were all associated with a higher DPPI. The resulting model explained 43% of the variance in DPPI. In multivariable models adjusted for age sex and height, diastolic blood pressure (DBP) was more strongly associated with MAP (B 0.542) or DBP (B 0.362) than with SBP (B 0.265), and was only weakly associated with pulse pressure (PP) (B 0.078; Supplementary Table 1, http://links.lww.com/HJH/B279).

Digital pulse propagation index and mortality
During a median follow-up of 8.3 (IQR 7.7–8.9) years, 289 (5.3%) participants died, of whom 74 (1.3%) of cardiovascular causes. Participants who died had a higher DPPI than those who did not (5.78 [5.46–6.62] vs. 6.30 m/s [5.83–6.78]; P < 0.001). Cox regression analysis showed a significant association between logDPPI and the risk of both all-cause [hazard ratio 1.67 (1.55–1.81) per SD change, P < 0.001] and cardiovascular mortality [hazard ratio 1.95 (1.72–2.22) per SD change, P < 0.001; Fig. 2]. Both associations remained significant after multivariable adjustment for potential confounders (Table 3). In the fully adjusted model, each SD increase in logDPPI was associated with a 14% greater risk of all-cause mortality and with a 45% greater risk of cardiovascular mortality. The optimal cutoff value for DPPI in relation to all-cause mortality was 6.2 m/s [area under the curve (AUC)ROC: 0.70; sensitivity: 55%; specificity: 79%]. For cardiovascular mortality, the optimal cutoff value was 6.3 m/s (AUCROC: 0.75; sensitivity: 64%; specificity: 80%).
Digital pulse propagation index and cardiovascular events

The association between DPPI and mortality was not materially changed when the model was adjusted for SBP rather than MAP (Supplemental Table 2, http://links.lww.com/HJH/B279). The association between logDPPI and mortality was not materially changed when the model was adjusted for age or sex and body height (CAD events: hazard ratio 1.17 <0.001, respectively) and cerebrovascular events [hazard ratio 1.63 (1.43–1.87), P < 0.001] but lost significance upon further adjustment for covariates.

Association of the digital pulse propagation index with cardiovascular events

During follow-up, 272 (5.0%) participants experienced a CAD event and 99 (1.8%) experienced a cerebrovascular event. Results of Cox regression analysis are shown in Table 4. logDPPI was significantly associated with both CAD [hazard ratio per SD 1.54 (95% confidence interval 1.41–1.67), P < 0.001] and cerebrovascular events [hazard ratio 1.63 (1.45–1.87), P < 0.001] in models adjusted for HR. These associations remained after further adjustment for age, sex and body height [CAD events: hazard ratio 1.17 (1.05–1.32), P = 0.009]; cerebrovascular events: hazard ratio 1.26 (1.06–1.49) per SD, P = 0.04], but lost significance upon further adjustment for covariates.

Association of the digital pulse propagation index with heart failure

In total, 146 participants developed new onset heart failure during follow-up. Of these, 86 (1.6%) participants

Data presented as mean ± SD, or median [IQR] or percentage of the population for normally, skewed, or nominal data, respectively. Differences were tested using analysis of variance (ANOVA), or Kruskal–Wallis tests for continuous data and with χ² tests for categorical data. AHD, antihypertensive drugs; CKD-EPI, Chronic Kidney Disease–Epidemiology collaboration; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPPI, digital pulse propagation index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LLD, lipid lowering drugs; MAP, mean arterial pressure.

### TABLE 1. Baseline characteristics according to quartiles of digital pulse propagation index

| Full cohort | Quartile 1 <5.47 m/s | Quartile 2 5.47–5.81 m/s | Quartile 3 5.81–6.20 m/s | Quartile 4 >6.20 m/s | P value |
|-------------|---------------------|--------------------------|--------------------------|---------------------|---------|
| Participants, n | 5487 | 1371 | 1372 | 1372 | 1372 |
| DPPI (mean over 15 min) | 5.81 [5.47–6.20] | 5.22 [5.11–5.36] | 5.64 [5.56–5.72] | 5.98 [5.89–6.08] | 6.55 [6.34–6.90] |
| Men (%) | 50.6 | 19.8 | 47.9 | 65.2 | 69.8 |
| Age (years) | 52.3 ± 11.8 | 47.1 ± 10.3 | 49.7 ± 11.1 | 52.9 ± 11.3 | 59.4 ± 11.0 |
| Waist circumference (cm) | 91.9 ± 12.6 | 86.3 ± 12.6 | 89.8 ± 11.7 | 93.9 ± 11.5 | 97.4 ± 11.8 |
| Length (m) | 1.73 ± 0.09 | 1.68 ± 0.08 | 1.73 ± 0.09 | 1.76 ± 0.09 | 1.75 ± 0.09 |
| Race (%) | <0.001 |
| White | 96.1 | 94.3 | 95.8 | 97.1 | 97.1 |
| Black | 1.0 | 1.0 | 0.8 | 0.6 | 1.4 |
| Asian | 1.9 | 3.3 | 2.2 | 1.0 | 0.9 |
| Other | 1.1 | 1.4 | 1.2 | 1.3 | 0.6 |
| Family history of CVD (%) | <0.001 |
| History of CVD (%) | 48.4 | 45.0 | 48.4 | 50.7 | 49.3 |
| Pulse pressure (mmHg) | 52.2 [5.47–6.20] | 5.22 [5.11–5.36] | 5.64 [5.56–5.72] | 5.98 [5.89–6.08] | 6.55 [6.34–6.90] |
| SBP (mmHg) | 125.5 ± 18.3 | 115.5 ± 14.8 | 122.7 ± 16.3 | 127.0 ± 16.0 | 136.7 ± 19.2 |
| DBP (mmHg) | 73.4 ± 9.1 | 67.0 ± 7.2 | 71.6 ± 7.5 | 75.1 ± 7.8 | 79.7 ± 9.0 |
| MAP (mmHg) | 92.2 ± 12.3 | 84.4 ± 9.6 | 90.0 ± 10.6 | 93.8 ± 10.3 | 100.6 ± 12.4 |
| Heart rate (bpm) | 68.4 ± 10.9 | 65.0 ± 8.5 | 67.2 ± 9.5 | 69.3 ± 9.8 | 72.3 ± 10.6 |
| Use of AHD (%) | 20.9 | 14.1 | 16.2 | 19.9 | 32.7 |
| Smoking (%) | <0.001 |
| Never | 29.6 | 37.6 | 32.9 | 28.9 | 20.0 |
| Former | 41.8 | 39.2 | 40.7 | 41.7 | 47.2 |
| Current | 27.3 | 21.7 | 26.3 | 29.4 | 32.8 |
| Alcohol use (%) | <0.001 |
| None/or hardly ever | 23.0 | 25.5 | 22.7 | 20.8 | 23.4 |
| 1–4/month | 15.8 | 18.7 | 17.0 | 13.9 | 13.8 |
| 2–7/week | 35.2 | 37.2 | 35.2 | 36.2 | 32.7 |
| 1–3/day | 20.2 | 15.5 | 21.0 | 22.5 | 22.2 |
| >3/day | 5.2 | 2.6 | 4.1 | 6.6 | 7.8 |
| Total cholesterol (mmol/l) | 5.42 ± 1.0 | 5.1 ± 1.0 | 5.39 ± 1.05 | 5.53 ± 1.05 | 5.59 ± 1.04 |
| HDL cholesterol (mmol/l) | 1.22 [1.04–1.43] | 1.33 [1.15–1.54] | 1.25 [1.06–1.47] | 1.17 [1.00–1.38] | 1.14 [0.97–1.35] |
| Triglycerides (mmol/l) | 1.10 [0.81–1.58] | 0.90 [0.67–1.28] | 1.06 [0.77–1.50] | 1.22 [0.90–1.72] | 1.30 [0.93–1.88] |
| Use of LDL (%) | 8.9 | 5.9 | 7.1 | 8.6 | 14.1 |
| History of diabetes mellitus (%) | <0.001 |
| 2.4 | 1.3 | 1.9 | 2.1 | 4.3 |
| Serum glucose (mmol/l) | 4.93 ± 0.92 | 4.72 ± 0.81 | 4.88 ± 0.91 | 4.94 ± 0.76 | 5.17 ± 1.10 |
| Serum creatinine (µmol/l) | 73.7 ± 19.8 | 68.5 ± 13.5 | 72.6 ± 18.98 | 75.1 ± 15.2 | 78.6 ± 27.3 |
| eGFR (CKD-EPI) | 93.3 ± 15.8 | 96.5 ± 14.7 | 95.4 ± 15.3 | 93.7 ± 14.9 | 87.7 ± 74.5 |
| Urinary sodium excretion | 145 ± 54 | 134.3 ± 48.0 | 143.1 ± 51.8 | 151.5 ± 56.0 | 152.6 ± 59.3 |
| Urinary albumin excretion | 8.60 [5.06–15.1] | 7.09 [5.49–10.83] | 8.16 [5.95–13.3] | 9.11 [6.37–14.8] | 11.28 [7.06–26.92] |

Participants, n: 5487; number of participants in each quartile: Quartile 1: 1371, Quartile 2: 1372, Quartile 3: 1372, Quartile 4: 1372. P value: 0.001 for all comparisons.
developed HFrEF while 60 (1.1%) developed HFpEF. LogDPPI was associated with incident HFrEF \([hazard ratio 1.81 (1.60–2.06), P < 0.001; Fig. 2]\) and incident HFpEF \([hazard ratio 1.31 (1.04–1.63), P = 0.019]\). The association between DPPI and new-onset HFrEF remained significant in the fully adjusted model \([hazard ratio 1.32 (1.08–1.60), P = 0.005; Table 5]\), suggesting a 32% greater risk of incident HFrEF per SD increase in logDPPI. The association with HFpEF was lost after further adjustment for covariates. After exclusion of participants with a prior history of CVD, logDPPI remained associated with incident HFrEF \([hazard ratio 1.56 (1.29–1.90), P < 0.001 per SD]\). For HFrEF, the optimal cutoff value for DPPI was 6.1 m/s \((AUC_{ROC} = 0.71; sensitivity: 63%; specificity: 72%)\). Adjustment for SBP instead of MAP did not significantly alter this association (Supplemental Table 2, http://links.lww.com/HJH/B279).

**DISCUSSION**

Large artery stiffness is widely recognized as a risk factor for cardiovascular and all-cause mortality [21]. Here, we demonstrate that the DPPI, derived from the peripheral PP waveform, is associated with a higher mortality risk in the general population. The association between DPPI and mortality was independent of traditional cardiovascular risk factors. In the fully adjusted model, one SD higher logDPPI was associated with a 15% higher risk of mortality, while the risk of cardiovascular mortality was 43% higher for an SD higher logDPPI. In addition, we demonstrate an association between the DPPI and incident HFrEF, with a 31% greater risk of incident HFrEF per SD of logDPPI after adjustment for confounders. These independent associations all remained significant after exclusion of participants with a known history of CVD. Optimal cutoff values for DPPI were relatively consistent for all end points, ranging between 6.1 and 6.3 m/s, which corresponds to the cutoff between the third and fourth quartile of our study population.

Pulse contour analysis has previously been shown to be reproducible with minimal intraobserver variation [22,23].

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**TABLE 2. Univariable and multivariable determinants of log-transformed digital pulse propagation index**

|                     | Univariable | Multivariable |
|---------------------|-------------|---------------|
|                     | \(\beta\)   | \(P\) value  | \(\beta\)   | \(P\) value  |
| Age                 | 0.386       | <0.001       | 0.327       | <0.001       |
| Mean arterial blood pressure | 0.482       | <0.001       | 0.292       | <0.001       |
| Body height         | 0.228       | <0.001       | 0.290       | <0.001       |
| Heart rate          | 0.241       | <0.001       | 0.233       | <0.001       |
| Current smoking     | 0.098       | <0.001       | 0.121       | <0.001       |
| Male sex            | 0.327       | <0.001       | 0.068       | <0.001       |
| Waist circumference | 0.314       | <0.001       | 0.050       | <0.001       |
| HDL cholesterol     | -0.213      | <0.001       | -0.037      | 0.005        |
| Triglycerides       | 0.240       | <0.001       |             |              |
| 24-h urinary albumin excretion | 0.225       | <0.001       |             |              |
| Use of antihypertensive drugs | 0.179       | <0.001       |             |              |
| eGFR (CKD-EPI)      | -0.157      | <0.001       |             |              |
| Total cholesterol   | 0.137       | <0.001       |             |              |
| 24-h urinary sodium excretion | 0.118       | <0.001       |             |              |
| History of cardiovascular disease | 0.112       | <0.001       |             |              |
| Use of lipid-lowering drugs | 0.107       | <0.001       |             |              |
| NT-proBNP           | 0.107       | <0.001       |             |              |
| History of diabetes | 0.063       | <0.001       |             |              |

Model 1: univariable analysis; model 2: multivariable model after stepwise backward elimination \(r^2 = 0.43\). CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal-pro brain natriuretic peptide.
Previous cross-sectional studies have shown that the method may have added benefit in the stratification of CVD risk [12–14,22]. Our results extend these findings by showing that differences in DPPI relate to the long-term risk of mortality after adjustment for other risk factors, thus providing prospective epidemiological validation for this method.

In this cohort, higher DPPI was notably associated with the presence of traditional cardiovascular risk factors at baseline. In concordance with the pathophysiology of arterial stiffening, age, HR, and MAP were strong determinants of DPPI in a multivariable linear regression model [2,24]. Of note, greater body height was also independently associated with higher DPPI. Sex, waist circumference, smoking status, plasma HDL cholesterol and triglycerides, history of diabetes, eGFR, urinary albumin excretion and urinary sodium excretion were independently associated with DPPI. However, contributions of these factors were comparatively little to the regression model. In line with findings from the Framingham Heart Study, we found no independent association between arterial stiffness and either eGFR or albuminuria [25]. In total, the final linear regression model explained 43% of the variance in DPPI.

### Table 3. Associations of digital pulse propagation index with all-cause and cardiovascular mortality

| Low DPPI (Q1 + Q2) | Intermediate DPPI (Q3) | High DPPI (Q4) | LogDPPI continuous |
|---------------------|------------------------|----------------|---------------------|
| HR (95% CI)         | HR (95% CI)            | HR (95% CI)    | HR (95% CI) per SD  |
| 1.0 (ref)           | 1.87 (1.57–2.24)       | 5.52 (4.13–7.38)| <0.001              |
| 1.0 (ref)           | 1.04 (0.75–1.7)        | 1.72 (1.24–2.39)| <0.001              |
| 1.0 (ref)           | 1.10 (0.77–1.59)       | 1.63 (1.17–2.28)| 0.002               |
| 1.0 (ref)           | 1.09 (0.77–1.61)       | 1.65 (1.18–2.30)| 0.002               |

**Cardiovascular mortality, n = 74**

| Low DPPI (Q1 + Q2) | Intermediate DPPI (Q3) | High DPPI (Q4) | LogDPPI continuous |
|---------------------|------------------------|----------------|---------------------|
| HR (95% CI)         | HR (95% CI)            | HR (95% CI)    | HR (95% CI) per SD  |
| 1.0 (ref)           | 1.85 (1.25–2.75)       | 8.31 (4.55–15.16)| <0.001              |
| 1.0 (ref)           | 1.11 (0.74–1.66)       | 2.59 (1.36–4.95)| 0.001               |
| 1.0 (ref)           | 1.51 (0.67–3.37)       | 2.66 (1.37–5.16)| 0.002               |
| 1.0 (ref)           | 1.57 (0.70–3.54)       | 2.60 (1.33–5.08)| 0.004               |

### Table 4. Associations of digital pulse propagation index with fatal and nonfatal cardiovascular events

| Low DPPI (Q1 + Q2) | Intermediate DPPI (Q3) | High DPPI (Q4) | LogDPPI continuous |
|---------------------|------------------------|----------------|---------------------|
| HR (95% CI)         | HR (95% CI)            | HR (95% CI)    | HR (95% CI) per SD  |
| 1.0 (ref)           | 2.03 (1.71–2.41)       | 4.43 (3.28–5.96)| <0.001              |
| 1.0 (ref)           | 1.29 (0.97–1.74)       | 1.93 (1.37–2.72)| <0.001              |
| 1.0 (ref)           | 1.32 (0.92–1.91)       | 1.54 (1.06–2.25)| 0.03                |
| 1.0 (ref)           | 1.28 (0.88–1.85)       | 1.50 (1.03–2.18)| 0.04                |

**CAD events, n = 227**

| Low DPPI (Q1 + Q2) | Intermediate DPPI (Q3) | High DPPI (Q4) | LogDPPI continuous |
|---------------------|------------------------|----------------|---------------------|
| HR (95% CI)         | HR (95% CI)            | HR (95% CI)    | HR (95% CI) per SD  |
| 1.0 (ref)           | 3.01 (2.29–3.96)       | 4.62 (2.76–7.74)| <0.001              |
| 1.0 (ref)           | 1.99 (1.49–2.66)       | 1.90 (1.07–3.36)| 0.05                |
| 1.0 (ref)           | 2.11 (1.14–3.54)       | 1.54 (0.86–2.76)| 0.25                |
| 1.0 (ref)           | 2.09 (1.18–3.69)       | 1.57 (0.87–2.83)| 0.24                |

**Cerebrovascular events, n = 99**

| Low DPPI (Q1 + Q2) | Intermediate DPPI (Q3) | High DPPI (Q4) | LogDPPI continuous |
|---------------------|------------------------|----------------|---------------------|
| HR (95% CI)         | HR (95% CI)            | HR (95% CI)    | HR (95% CI) per SD  |
| 1.0 (ref)           | 2.31 (1.51–3.01)       | 7.32 (4.15–12.94)| <0.001              |
| 1.0 (ref)           | 1.27 (0.89–1.81)       | 2.64 (1.43–4.87)| 0.001               |
| 1.0 (ref)           | 1.33 (0.67–2.69)       | 2.16 (1.14–4.09)| 0.013               |
| 1.0 (ref)           | 1.34 (0.66–2.72)       | 2.26 (1.18–4.33)| 0.009               |

**Model 1: association for log-transformed DPPI adjusted for heart rate DPPI; model 2: model 1 + adjustment for age, sex, and body height; model 3: model 2 + adjustment for MAP, use of antihypertensive drugs, smoking, prior history of cardiovascular disease, and NT-proBNP; model 4: model 3 + adjustment for waist circumference, HDL cholesterol, triglycerides, history of diabetes, eGFR, urinary albumin excretion and urinary sodium excretion. CAD, coronary artery disease; CI, confidence interval; DPPI, digital pulse propagation index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MAP, mean arterial pressure.**
Our results show that the DPPI is independently associated with mortality, and suggest that this association is driven by cardiovascular mortality. The DPPI was also strongly associated with HFpEF. However, the associations with cerebrovascular events and HFrEF were lost upon multivariable adjustment. When analyzed as a continuous variable, CAD was also not associated with DPPI after adjustment for confounders. However, we did observe a significantly higher hazard ratio for CAD for participants in the highest quartile of our cohort. The lack of a strong association with CAD is in line with a previous study showing that the DPPI is not associated with CAD identified by coronary angiography [13]. These observations may result from the fact that the DPPI is related to peripheral rather than aortic stiffness, unlike cPWV [13]. Similarly, cerebrovascular events are more strongly associated with aortic stiffness than with peripheral arterial stiffness [26]. The significant association between cardiovascular mortality and DPPI but not (in continuous analysis) with coronary artery events or cerebrovascular events may suggest that the excess mortality risk in participants with high DPPI is mainly driven by deaths due to heart failure, although this could not be definitively clarified by our current data.

Several mechanisms have previously been proposed to explain the associations between arterial stiffness and mortality. For example, higher DPPI may be indicative of genetic and structural predisposition to cardiovascular risk [27]. In addition, associations have been reported between DPPI and markers of higher bone resorption and lower bone formation in patients with CKD stage 1–4, suggesting a link between the DPPI and vascular calcification [28]. Lastly, arterial stiffness may be linked to systemic inflammation [29–31]. Quantification of these and other processes impacting arterial ageing is likely to aid in the prediction of cardiovascular risk, as well as in the epidemiological and mechanistic study of CVD. Our study has a number of limitations. First, our study is observational in nature and therefore no conclusions can be drawn on causality. Second, by design, the study cohort includes a larger proportion of individuals with microalbuminuria than the general population [16]. Accordingly, we have adjusted our analyses for albuminuria. Third, our cohort consists primarily of whites due to the geographical area of recruitment; future studies on the role of the DPPI in nonwhite populations are warranted. Fourth, our study made use of a single 15-min arterial stiffness measurement at baseline even though arterial stiffening is a dynamic process, the rate of which may vary over time. In the absence of repeated measurements, this variability is unaccounted for, which may lead to underestimation of the strength of associations due to regression dilution bias. Fifth, the method used to derive arterial stiffness from the digital pressure pulse is indirect. As such, the DPPI may not reflect true large artery stiffness due to confounding by properties of peripheral vessels. Sixth, cause of death in this cohort was classified using the primary cause of death as reported on patients’ death certificate. However, the reported cause of death may not properly reflect the true cause of death for all patients. On the contrary, informed consent for this study did not allow for a full review of medical records to further clarify cause of death. Lastly, the use of patient height to calculate an index expressed in meters per second is relatively imprecise, and might contribute to imprecision in the DPPI. This is reflected by the finding that height remained a determinant of the DPPI in linear regression analysis. However, inclusion of height in our survival analysis did not materially alter our results. Lastly, in this study, pulse contour analysis was performed using the digital arterial pressure waveform. This methodology is different from DVP, which has been used in several previous studies [10,11]. Although these different waveforms may be relatable to each other through a generalized transfer function, they are not identical and may convey different information. To our knowledge, arterial pressure-based waveform analysis has not been correlated with cPWV, the current standard to quantify arterial stiffness.

In conclusion, higher DPPI corresponded closely with the presence of known causal risk factors for CVD in this large, well characterized general population-based cohort. Moreover, DPPI was independently associated with incident systolic heart failure, all-cause and cardiovascular mortality after adjustment for these risk factors. However, DPPI was not independently associated with risk of CAD events or cerebrovascular events. Further validation studies should confirm whether this accessible marker of arterial stiffness has value in risk stratification for these end points, and should define the position of DPPI in comparison with other available methods to determine vascular stiffness.

ACKNOWLEDGEMENTS

Conflicts of interest
There are no conflicts of interest.

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