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Original Article

Independent association of estimated pulse-wave velocity with all-cause mortality in individuals with type 2 diabetes

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Abstract

Background: Estimated pulse-wave velocity (ePWV), a surrogate measure of arterial stiffness, was shown to independently predict morbidity and mortality from cardiovascular disease and other causes in both the general population and high-risk individuals. However, in people with type 2 diabetes, it is unknown whether ePWV adds prognostic information beyond the parameters used for calculating it.

Aims: To assess the independent association of ePWV with all-cause mortality in individuals with type 2 diabetes.

Design: Prospective cohort study that enrolled 15 773 patients in 19 Italian centres in 2006–08.

Methods: ePWV was calculated from a regression equation using age and mean blood pressure (BP). All-cause mortality was retrieved for 15 656 patients in 2015.

Results: Percentage and rate of deaths, Kaplan–Meier estimates and unadjusted hazard ratios increased from Quartile I to Quartile IV of ePWV. After adjustment for age, sex, BP levels and anti-hypertensive treatment, the strength of association decreased but mortality risk remained significantly higher for Quartiles II (+34%), III (+82%) and IV (+181%) vs. Quartile I and was virtually unchanged when further adjusting for other cardiovascular risk factors and complications/comorbidities. Each $m \cdot s^{-1}$ increase in ePWV was associated with an increased adjusted risk of death in the whole cohort (+53%) and in participants with (+52%) and without (+65%) cardiorenal complications. Moreover, ePWV significantly improved prediction of mortality risk over cardiovascular risk factors and complications/comorbidities, though the net increase was modest.

Conclusions: These findings suggest that ePWV may represent a simple and inexpensive tool for providing prognostic information beyond traditional cardiovascular risk factors.

Trial registration: ClinicalTrials.gov, NCT00715481, https://clinicaltrials.gov/ct2/show/NCT00715481.

Introduction

Arterial stiffness is the consequence of the loss of large artery cushioning function, which has multiple adverse haemodynamic effects, including increased early aortic systolic blood pressure (BP) rise, early (mid-to-late systole) arrival of reflection waves to the proximal aorta and increased pressure and flow pulsatility in the microvasculature.[1] These haemodynamic changes result in isolated systolic hypertension with increased pulse pressure, reduced coronary perfusion pressure and increased left ventricular afterload promoting left ventricular remodelling, dysfunction and failure, even in the absence of coronary artery disease. In addition, target organ damage occurs, especially in organs operating at low arteriolar resistance because of high blood flow requirements, such as the kidneys and brain.[1]

Arterial stiffening is a manifestation of vascular ageing that is accelerated by smoking, diabetes, obesity and dyslipidaemia as

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well as by hypertension and chronic kidney disease (CKD), which are both causes and consequences of the stiffening of arterial wall.[1] In particular, increased arterial stiffness is a common feature in type 2 diabetes,[2] also due to the association with the conditions clustering into the metabolic syndrome[3] and with CKD.[4]

Arterial stiffness may explain a great proportion of the increased morbidity and mortality from cardiovascular disease (CVD) and other causes associated with ageing and several disorders.[1] Stiffness was in fact shown to predict these outcomes beyond traditional risk factors,[5,6] both in the general population[7] and high-risk individuals,[8,9] thus accounting, at least partly, for residual CVD risk and aiding in net reclassification of CVD risk.[10] Moreover, stiffness was found to be independently associated with renal and CVD outcomes in patients with CKD[11,12] and, hence, it has been proposed as a useful prognostic tool in these individuals.[4]

Carotid-femoral pulse-wave velocity (PWV) is the current reference method for measuring large artery stiffness, though alternative methods have been proposed.[1] However, even if the American Heart Association stated that it is reasonable to assess carotid-femoral PWV,[10] the adoption of this measure in clinical practice is limited because of the need for costly and specialized equipment and specific technical expertise. Therefore, a formula using age and mean BP, the two main determinants of arterial stiffness,[13,14] has been developed to calculate estimated PWV (ePWV), which was shown to have similar predictive value as measured carotid-femoral PWV.[15] In fact, several studies have shown a significant association of ePWV with all-cause and cause-specific mortality and CVD events in the general population[15–18] and individuals with hypertension.[15,19,20] Interestingly, this association was independent of traditional risk factors, including age and BP (as systolic BP, both systolic and diastolic BP, pulse pressure or mean BP).[15–20] Two recent prospective cohort studies in participants in the National Health and Nutrition Examination Survey (NHANES) showed that ePWV was associated with all-cause and CVD mortality also in individuals with obesity[21] and diabetes.[22] However, this association was independent of confounders that included history of hypertension, but not age (in the study in diabetic patients) and BP levels (in both studies),[21,22] raising the question whether ePWV may be a useful tool for risk stratification also in these individuals by providing incremental value over the parameters used for calculating it.

To address this issue, we assessed the independent association of ePWV with all-cause mortality in the large cohort of individuals with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study.

Materials and methods

Design

The RIACE Study was an observational, prospective, cohort study on the impact of estimated glomerular filtration rate (eGFR) on morbidity and mortality in individuals with type 2 diabetes.[23]

Patients

The RIACE cohort enrolled 15 773 Caucasian patients consecutively attending 19 hospital-based, tertiary referral outpatients diabetes clinics of the National Health Service throughout Italy in the years 2006–08. Exclusion criteria were dialysis or renal transplantation.

Baseline data

Baseline data were collected using a standardized protocol across participating centres.[23]

Participants underwent a structured interview to collect the following information: age at the time of the interview, smoking status, physical activity (PA) level, known diabetes duration, comorbidities (including chronic obstructive pulmonary disease, chronic liver disease and cancer) and current glucose-, lipid- and BP-lowering treatments.

Body mass index (BMI) was calculated from weight and height and BP was measured with a mercury sphygmomanometer after a 5-min rest. Two consecutive readings were taken 10 min apart by a trained observer with the patients seated with the arm at the heart level and the cuff correctly placed on the arm circumference. Standard adult cuffs were used (9–13 inches), except for severely obese patients, where large cuffs (13–17 inches) were employed. The second readings were used for the analysis.[24] Then, ePWV was calculated from a regression equation using age and mean BP according to the following formula described by Greve *et al.*[15] and derived from the Reference Values for Arterial Stiffness Collaboration:[14] $\text{ePWV}\ (\text{m}\cdot\text{s}^{-1}) = 9.587 - (0.402 \times \text{age}) + [4.560 \times 0.001 \times (\text{age}^2)] - [2.621 \times 0.00001 \times (\text{age}^2) \times \text{mean BP}] + (3.176 \times 0.001 \times \text{age} \times \text{mean BP}) - (1.832 \times 0.01 \times \text{mean BP})$, where age is expressed in years and mean BP is calculated as diastolic BP+0.4×[systolic BP−diastolic BP].

Haemoglobin A_{1c} (HbA_{1c}) was measured by HPLC using DCCT-aligned methods, triglycerides and total and HDL cholesterol were determined in fasting blood samples by standard colorimetric enzymatic methods, and LDL cholesterol concentration was estimated using the Friedewald formula: LDL cholesterol=total cholesterol−HDL cholesterol − (triglycerides/5) (in mg/dl).

The presence of diabetic kidney disease (DKD) was assessed by measuring albuminuria and serum creatinine, as previously detailed.[23] Albumin excretion rate was obtained from 24-h urine collections or calculated from albumin-to-creatinine ratio in early-morning urine samples; albumin concentration was measured by immunonephelometry or immunoturbidimetry. Serum (and urine) creatinine was measured by the modified Jaffe method, traceable to IDMS, and eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[25] Patients were then assigned to one of the following DKD phenotypes: no DKD, albuminuric DKD with preserved eGFR, non-albuminuric DKD or albuminuric DKD with reduced eGFR.[23]

The presence of diabetic retinopathy (DR) was assessed in each centre by an expert ophthalmologist by dilated fundoscopy, as previously detailed.[26] Patients with mild or moderate non-proliferative DR were classified as having non-advanced DR, whereas those with severe non-proliferative DR, proliferative DR or maculopathy were grouped into the advanced, sight threatening DR category.

Previous major acute events, including myocardial infarction, stroke, foot ulcer/gangrene/amputation and cerebrovascular, carotid and lower limb revascularization, were adjudicated based on hospital discharge records by an *ad hoc* committee in each centre.[27]

All-cause mortality

The vital status of study participants on 31 October 2015 was verified by interrogating the Italian Health Card database (http://sistemats1.sanita.finanze.it/wps/portal/), which provides updated and reliable information on current Italian residents.[23]

Statistical analysis

Data are expressed as mean ± SD or median (interquartile range), for continuous variables, and number of cases and percentage, for categorical variables.

Patients were stratified by quartiles of ePWV and comparisons among quartiles were performed by one-way ANOVA or Kruskal–Wallis test, according to the parametric or non-parametric distribution of continuous variables, and Pearson's χ^2 test for categorical variables. Crude mortality rates by ePWV quartiles were described as events per 1000 patient-years from start of follow-up to censoring, with 95% exact Poisson confidence intervals (CIs) by a Poisson regression model. Kaplan–Meier survival probabilities for all-cause mortality were estimated according to ePWV quartiles and differences were analysed using the log-rank statistic. The hazard ratios (HRs) and their 95% CIs according to ePWV (as continuous variable or quartiles) were estimated by Cox proportional hazards regression with backward selection of variables. These analyses were sequentially adjusted for age categories (<55, 55–64, 65–74 and ≥75 years), sex, systolic and diastolic BP (or, alternatively, mean BP or pulse pressure) and anti-hypertensive treatment (Model 1), plus other CVD risk factors, i.e. smoking status, PA level, diabetes duration, HbA_{1c}, BMI, triglycerides, total and HDL cholesterol and anti-hyperglycaemic and lipid-lowering therapy (Model 2) and plus presence of complications (DKD phenotype, DR grade and any CVD event) and any severe comorbidity (Model 3).

Finally, receiver operating characteristic (ROC) curves and the corresponding areas under the curve (AUCs) were calculated for evaluating the marginal improvement provided by ePWV in the prediction of all-cause death over traditional CVD risk factors, complications and comorbidities. For these analyses, the covariates included in Models 1, 2 and 3 were used, without and with addition of ePWV.

All *P*-values were two-sided, and a $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) and, for ROC analysis, MedCalc version 22.014 (MedCalc Software Ltd, Ostend, Belgium).

Results

As shown in Table 1, age, proportion of females, diabetes duration, HDL cholesterol, systolic and diastolic BP, mean BP, pulse pressure, albuminuria and prevalence of anti-hyperglycaemic, anti-hypertensive, anti-platelet and anti-coagulant treatment as well as of complications and comorbidities increased from Quartile I to Quartile IV. The opposite was observed for smoking, PA level, BMI, triglycerides and eGFR.

As previously reported, valid information on vital status was retrieved for 15 656 participants (99.3% of the cohort). Of these individuals, 12 054 (76.99%) were alive, whereas 3602 (23.01%) had deceased (follow-up duration: 7.42 ± 2.05 years, death rate: 31.02 per 1000 person-years).[23]

Percentages and rates of deaths, Kaplan–Meier estimates and unadjusted HRs (Figures 1 and 2A) increased from Quartile I to Quartile IV. After adjustment for age, sex, BP levels and anti-hypertensive treatment, the strength of association decreased, but mortality risk remained significantly higher for Quartiles II (+34%), III (+82%) and IV (+181%) vs. Quartile I (Figure 2B) and was virtually unchanged when further adjusting for the other CVD risk factors (Figure 2C) and for complications/comorbidities (Figure 2D). The other independent variables associated with mortality are reported in Supplementary Table S1. Finally, each $m \cdot s^{-1}$ increase in ePWV was associated with an increased risk of death (adjusted as in Model 3) in the whole cohort [HR 1.529 (95% CI 1.497–1.561), $P < 0.0001$] and in participants with [1.520 (1.484–1.557), $P < 0.0001$] and without [1.648 (1.588–1.711), $P < 0.0001$] CVD and/or DKD at baseline. Results were similar when substituting MBP for systolic and diastolic BP, whereas the association between ePWV and mortality was weaker when including pulse pressure as covariate.

The analysis of ROC curves showed a modest, but statistically significant improvement of mortality risk prediction when ePWV was added to the covariates included in Models 1, 2 and 3 (Figure 3).

Discussion

This analysis of the RIACE cohort of individuals with type 2 diabetes shows that ePWV is associated with all-cause mortality independently of complications, comorbidities and traditional CVD risk factors, including the parameters used for calculating this surrogate measure of arterial stiffness. In addition, ePWV improved prediction of mortality risk over CVD risk factors, complications and comorbidities, though the net difference was modest.

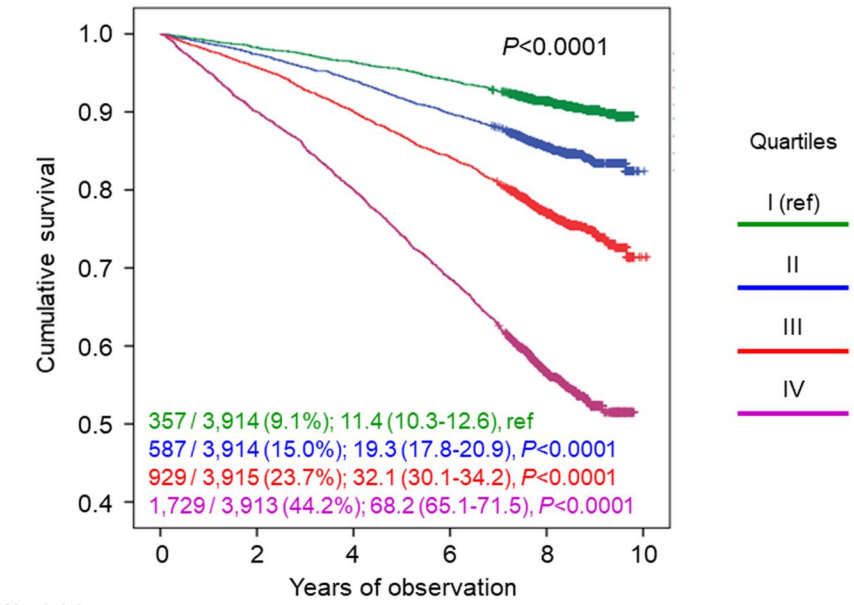
These findings are in keeping with several reports from the general population and hypertensive individuals, where ePWV was also found to improve prediction and risk discrimination beyond traditional scoring systems incorporating both age and systolic BP,[15,19,20] though not consistently.[17]

More importantly, our results add on a previous study in adults with diabetes from the NHANES 1999–2018 cohort,[22] in which the Cox regression model included history of hypertension, but not age and BP levels as covariates. Our finding that the association of ePWV with mortality was independent on age and BP levels indicates that, also in people with type 2 diabetes, ePWV incorporates prognostic information from quadratic terms and interactions between age and BP, which are not accounted for in traditional risk prediction models based on linear associations between age, BP and outcomes.[28] This observation has important implications for routine clinical practice. First, ePWV may serve as a proxy of vascular age in people with type 2 diabetes by capturing both active and passive arterial stiffening, which affects preferentially central over peripheral arteries of these individuals[29] and reflects multiple mechanisms. These mechanisms include endothelial dysfunction and inflammation,[30] elastin and collagen cross-linking mediated by advanced glycation end-products[31] and medial calcification that is worsened by the coexistence of CKD.[32] As such, ePWV may represent a simple and inexpensive tool for risk stratification of diabetic patients and identification of those who deserve a more aggressive treatment.[28] Second, monitoring ePWV may be useful for predicting the effect of treatments on outcomes. In fact, though no specific agent has yet been developed, the lifestyle and pharmacological interventions for risk factor control were shown to be effective also in decreasing arterial stiffness, though not consistently.[4] Indeed, a secondary analysis of the Systolic Blood Pressure Intervention Trial showed that ePWV decreased in the intensive but not in the standard treatment group and the proportion of participants whose PWV decreased in response to treatment was larger in the intensive than in the standard treatment group.[20] More importantly, intensive treatment was superior to standard treatment in improving the primary composite cardiovascular outcome only when associated with a reduction in ePWV and, within the standard treatment group, individuals whose ePWV decreased in response to anti-hypertensive treatment showed a 42% reduced risk of all-cause mortality, effects that were independent of changes in systolic BP.[20]

Table 1. Baseline clinical features of study participants by ePWV quartiles

Variables	I	II	III	IV	P
N (%)	3914	3914	3915	3913	
ePWV, m·s^{-1}	8.37 ± 0.81	10.12 ± 0.37	11.40 ± 0.40	13.33 ± 0.98	
(range)	(4.89–9.45)	(9.46–10.74)	(10.74–12.13)	(12.13–19.74)	
Deaths, n (%)	357 (9.1)	587 (15.0)	929 (23.7)	1729 (44.2)	<0.0001
Age, years	54.3 ± 7.3	63.9 ± 4.7	70.0 ± 4.4	78.2 ± 5.2	<0.0001
Age categories, n (%)					<0.0001
<55 years	1874 (47.9)	135 (3.5)	11 (0.3)	0 (0.0)	
55–64 years	1896 (48.4)	2070 (52.9)	463 (11.8)	31 (0.8)	
65–74 years	144 (3.7)	1687 (43.1)	2992 (76.4)	979 (25.0)	
≥75 years	0 (0.0)	22 (0.6)	449 (11.5)	2903 (74.2)	
Sex, n (%)					<0.0001
Females	1466 (37.5)	1575 (40.2)	1690 (43.2)	2023 (51.7)	
Males	2448 (62.5)	2339 (59.8)	2225 (56.8)	1890 (48.3)	
Smoking, n (%)					<0.0001
Never	1979 (50.6)	2132 (54.5)	2290 (58.5)	2448 (62.6)	
Former	992 (25.3)	1140 (29.1)	1149 (29.3)	1126 (28.8)	
Current	943 (24.1)	642 (16.4)	476 (12.2)	339 (8.7)	
PA level, n (%)					<0.0001
Inactive or moderately inactive	2121 (54.2)	2382 (60.9)	2573 (65.7)	2868 (73.3)	
Moderately active	1675 (42.8)	1462 (37.4)	1309 (33.4)	1030 (26.3)	
Highly active	118 (3.0)	70 (1.8)	33 (0.8)	15 (0.4)	
Diabetes duration, years	6.8 ± 6.0	10.4 ± 7.8	13.8 ± 9.3	18.7 ± 11.2	<0.0001
HbA_{1c}, %	7.58 ± 1.68	7.51 ± 1.46	7.49 ± 1.42	7.60 ± 1.43	0.002
BMI, kg·m^{-2}	29.4 ± 5.7	29.3 ± 5.1	29.0 ± 5.0	28.2 ± 4.7	<0.0001
Triglycerides, mg·dl^{-1}	123.0 (86.9–179.0)	121.0 (88.0–167.0)	116.0 (84.0–164.6)	115.0 (85.0–158.0)	<0.0001
Total cholesterol, mg·dl^{-1}	184.6 ± 39.5	184.5 ± 38.5	183.4 ± 37.1	186.3 ± 37.7	0.012
HDL cholesterol, mg·dl^{-1}	47.7 ± 13.2	49.2 ± 13.1	50.7 ± 13.8	51.6 ± 14.1	<0.0001
LDL cholesterol, mg·dl^{-1}	108.1 ± 33.5	107.5 ± 32.8	106.3 ± 31.9	108.6 ± 32.2	0.013
Dyslipidaemia, n (%)	3154 (80.6)	3255 (83.2)	3225 (82.4)	3222 (82.3)	0.023
Systolic BP, mmHg	125.9 ± 13.2	136.1 ± 14.4	141.9 ± 16.5	148.4 ± 19.2	<0.0001
Diastolic BP, mmHg	75.3 ± 8.8	78.4 ± 9.0	79.7 ± 9.1	81.7 ± 9.6	<0.0001
Mean BP, mmHg	92.2 ± 8.8	97.6 ± 9.1	100.4 ± 9.8	103.9 ± 11.0	<0.0001
Pulse pressure, mmHg	50.5 ± 11.9	57.7 ± 13.6	62.2 ± 15.1	66.8 ± 17.0	<0.0001
Hypertension, n (%)	2503 (63.9)	3357 (85.8)	3537 (90.3)	3699 (94.5)	<0.0001
Anti-hyperglycaemic treatment, n (%)					<0.0001
Lifestyle	656 (16.8)	540 (13.8)	509 (13.0)	408 (10.4)	
Non-insulin	2284 (58.4)	2403 (61.4)	2415 (61.7)	2517 (64.3)	
Insulin	974 (24.9)	971 (24.8)	991 (25.3)	988 (25.2)	
Lipid-lowering treatment, n (%)	1590 (40.6)	1878 (48.0)	1955 (49.9)	1815 (46.4)	<0.0001
Anti-hypertensive treatment, n (%)	2123 (54.2)	2779 (71.0)	2963 (75.7)	3207 (82.0)	<0.0001
Anti-platelet treatment, n (%)	1124 (28.7)	1477 (37.7)	1761 (45.0)	1886 (48.2)	<0.0001
Anti-coagulant treatment, n (%)	76 (1.9)	128 (3.3)	206 (5.3)	259 (6.6)	<0.0001
Albuminuria, mg·day^{-1}	11.2 (5.8–25.0)	12.6 (6.1–30.3)	13.8 (6.9–32.0)	17.3 (8.3–46.7)	<0.0001
Serum creatinine, mg·dl^{-1}	0.84 ± 0.34	0.89 ± 0.39	0.93 ± 0.34	1.01 ± 0.46	<0.0001
eGFR, ml·min^{-1}·1.73m^{-2}	93.7 ± 18.6	83.7 ± 18.1	76.6 ± 18.4	67.1 ± 19.2	<0.0001
DKD phenotype, n (%)					<0.0001
No DKD	2962 (75.7)	2714 (69.3)	2462 (62.9)	1846 (47.2)	
Albuminuric DKD with preserved eGFR	730 (18.7)	797 (20.4)	720 (18.4)	719 (18.4)	
Non-albuminuric DKD	97 (2.5)	217 (5.5)	429 (11.0)	733 (18.7)	
Albuminuric DKD with reduced eGFR	125 (3.2)	186 (4.8)	304 (7.8)	615 (15.7)	
DR grade, n (%)					<0.0001
No	3216 (82.2)	3059 (78.2)	2970 (75.9)	2944 (75.2)	
Non-advanced	392 (10.0)	437 (11.2)	538 (13.7)	580 (14.8)	
Advanced	306 (7.8)	418 (10.7)	407 (10.4)	389 (9.9)	
CVD, n (%)					
Any	615 (15.7)	838 (21.4)	1010 (25.8)	1157 (29.6)	<0.0001
Myocardial infarction	325 (8.3)	403 (10.3)	498 (12.7)	516 (13.2)	<0.0001
Coronary revascularization	315(8.0)	435 (11.1)	428 (10.9)	401 (10.2)	<0.0001
Any coronary event	442 (11.3)	579 (14.8)	669 (17.1)	706 (18.0)	<0.0001
Stroke	55 (1.4)	100 (2.6)	163 (4.2)	195 (5.0)	<0.0001
Carotid revascularization	98 (2.5)	171 (4.4)	253 (6.5)	334 (8.5)	<0.0001
Any cerebrovascular event	149 (3.8)	257 (6.6)	387 (9.9)	499 (12.8)	<0.0001
Ulcer/gangrene/amputation	95 (2.4)	124 (3.2)	136 (3.5)	201 (5.1)	<0.0001
Lower limb revascularization	61 (1.6)	111 (2.8)	135 (3.4)	143 (3.7)	<0.0001
Any peripheral event	140 (3.6)	209 (5.3)	234 (6.0)	300 (7.7)	<0.0001
Comorbidities n (%)					
Any	590 (15.1)	674 (17.2)	745 (19.0)	778 (19.9)	<0.0001
COPD	113 (2.9)	143 (3.7)	168 (4.3)	250 (6.4)	<0.0001
Chronic liver disease	348 (8.9)	355 (9.1)	338 (8.6)	320 (8.2)	0.528
Cancer	181 (4.6)	234 (6.0)	315 (8.0)	301 (7.7)	<0.0001

ePWV, estimated pulse-wave velocity; PA, physical activity; HbA_{1c}, haemoglobin A_{1c}; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; DKD, diabetic kidney disease; DR, diabetic retinopathy; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease.



N. at risk						
All	15,656	14,926	14,010	13,179	8,243	3
Q-I	3,914	3,846	3,774	3,682	2.491	0
Q-II	3,914	3,810	3,680	3,514	2,307	1
Q-III	3,915	3,747	3,525	3,298	2,013	2
Q-IV	3,913	3,523	3,131	2,685	1,432	0

Figure 1. Survival analysis by ePWV quartiles. Kaplan–Meier analysis according to ePWV quartiles. Number and percentage of deaths, death rates as events per 1000 patient-years (95% CI) and number of participants at risk are shown for each quartile. ePWV, estimated pulse-wave velocity; 95% CI, 95% confidence interval.

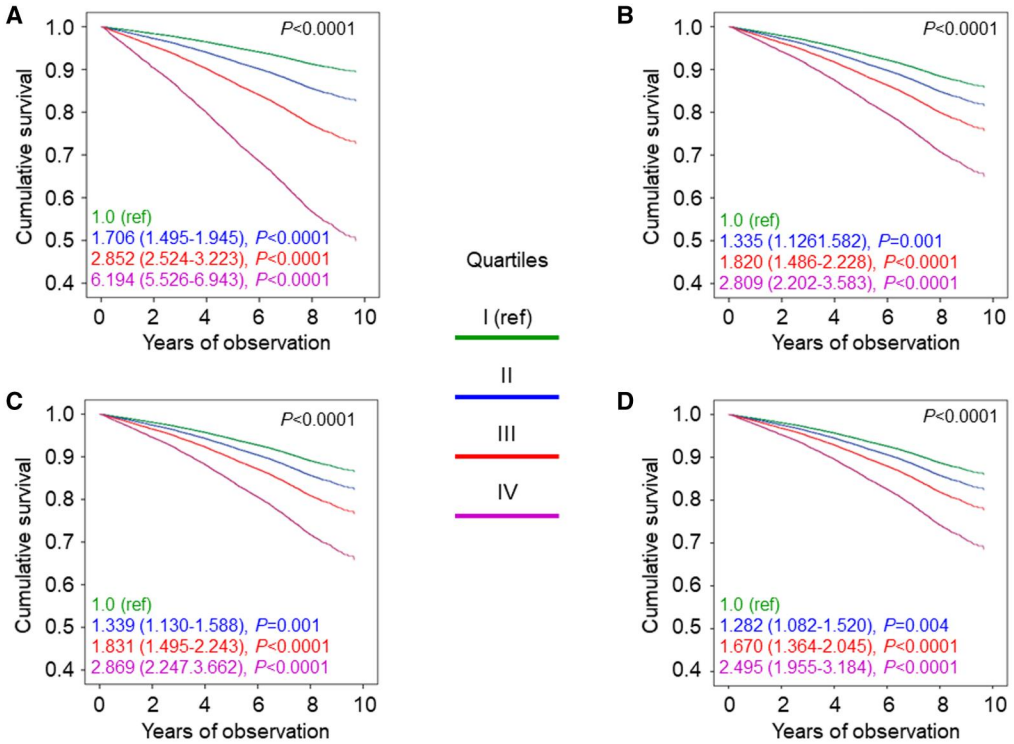


Figure 2. Survival analysis by ePWV quartiles. Cox proportional hazards regression, unadjusted (**A**) and adjusted for sex, age categories, systolic and diastolic BP and anti-hypertensive treatment (**B**, Model 1), plus other CVD risk factors (smoking habits, PA level, BMI, diabetes duration, HbA_{1c}, total and HDL cholesterol, anti-hyperglycaemic and lipid-lowering treatment) (**C**, Model 2), plus complications (DKD phenotype, DR grade and any CVD event) and comorbidities (any, including COPD, chronic liver disease, and cancer) (**D**, Model 3). HRs (95% CI) for mortality are shown for each quartile. ePWV, estimated pulse-wave velocity; BP, blood pressure; PA, physical activity; BMI, body mass index; HbA_{1c}, haemoglobin A_{1c}; DKD, diabetic kidney disease; DR, diabetic retinopathy; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; 95% CI, 95% confidence interval.

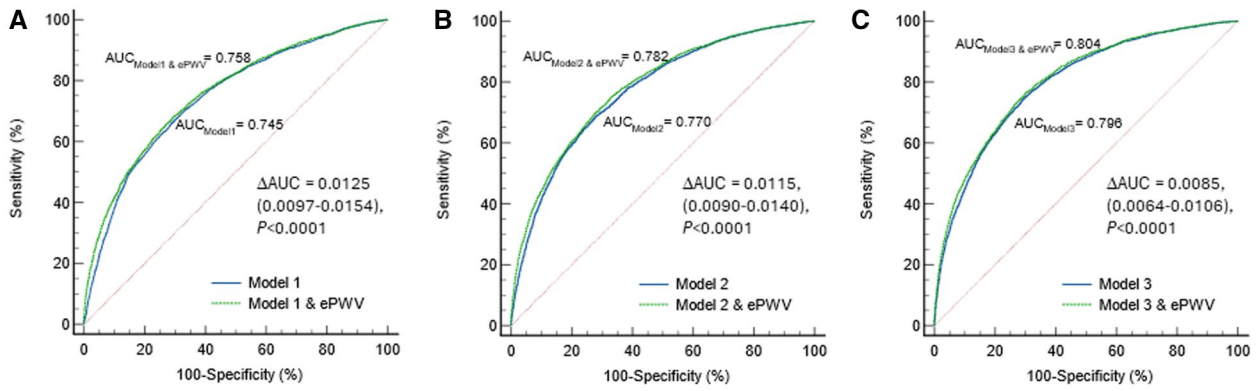


Figure 3. ROC curve analysis. Marginal improvement provided by ePWV in the prediction of all-cause death over sex, age categories, systolic and diastolic BP and anti-hypertensive treatment (**A**, Model 1), plus other CVD risk factors (smoking habits, PA level, BMI, diabetes duration, HbA_{1c}, total and HDL cholesterol, anti-hyperglycaemic and lipid-lowering treatment) (**B**, Model 2), plus complications (DKD phenotype, DR grade and any CVD event) and comorbidities (any, including COPD, chronic liver disease and cancer) (**C**, Model 3). The AUC (95% CI) is shown for each model, with and without ePWV. ROC, receiver operating characteristic; ePWV, estimated pulse-wave velocity; BP, blood pressure; PA, physical activity; BMI, body mass index; HbA_{1c}, haemoglobin A_{1c}; DKD, diabetic kidney disease; DR, diabetic retinopathy; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; AUC, area under the curve; 95% CI, 95% confidence interval.

However, though ePWV represents a valid alternative to measured PWV, it seems to incorporate at least partly different risk information and capture distinct aspects of vascular ageing. In fact, ePWV was shown to predict CVD events following adjustment for carotid-femoral PWV and *vice versa*.[15] Moreover, ePWV itself explained <50% of the variance in carotid-femoral PWV[33] and there was only a moderately strong linear association between ePWV and carotid-femoral PWV.[15,33] Finally, ePWV was associated more strongly than carotid-femoral PWV with established measures of vascular ageing, such as carotid thickness, stiffness and augmentation index.[33] Therefore, even if ePWV may not perform well as a surrogate measure of carotid-femoral PWV, at least at the individual level, it provides different, but equally important prognostic information.

The excess mortality characterizing diabetic vs. non-diabetic individuals is predominantly, though not exclusively, attributable to an increased risk of CVD.[34] Therefore, the independent association of ePWV with all-cause mortality may reflect the relationship between increased arterial stiffness and CVD. However, studies from the general population have shown that ePWV predicts also all-cause mortality[10,22,14] and cause-specific mortality other than CVD.[19,35] This suggests that morbidities causing non-CVD deaths are related to arterial stiffness in a bidirectional manner via CVD and non-CVD mechanisms, possibly including inflammation, oxidative stress and autonomic dysregulation.[35]

Strength of our study includes the large sample size, the completeness of baseline and follow-up data and the assessment of a wide range of clinical parameters, which allowed accounting for several confounding factors. However, there are several limitations. First, the lack of information on the causes of death did not allow detecting differences in CVD vs. non-CVD deaths and the impact of other causes of death that might be associated with increased stiffness. Second, the study findings may not be applicable to the general Italian ambulatory population, but only to the individuals attending outpatients diabetes clinics. Finally, the observational design makes causal interpretation impossible.

Conclusions

These findings suggest that, also in diabetic individuals, calculating ePWV may add prognostic information beyond traditional CVD risk factors and risk prediction models based on them and represent a simple and inexpensive alternative to measuring PWV.

Supplementary material

Supplementary material is available at *QJMED* online.

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Conflict of interest

A.S.: consultant fees from Axxam, Bayer and Novo Nordisk, and lecture fees from Eli Lilly, Novo Nordisk and Sanofi-Aventis; E.O.: consultant fees from Eli Lilly and Novo Nordisk, and lecture fees from Astellas; Martina Vitale: lecture fees from MundiPharma and Novo Nordisk; M.G.: consultant fees from Eli Lilly, and lecture fees from Eli Lilly, Merck Sharp & Dohme and Novo Nordisk; V.R.: lecture fees from Astra-Zeneca, Eli Lilly and Sanofi-Aventis; E.B.: consultant fees from Abbott, Bayer, Becton Dickinson, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly and Novo Nordisk; C.F.: lecture fees from Abbot, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Mundipharma and Theras Lifetech; R.T.: consultant fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi-Aventis, and lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Novo Nordisk; M.V.: lecture fees from Lifescan and Novo Nordisk; A.N.: consultant fees from AstraZeneca, lecture fees from Eli Lilly, Medtronic and Novo Nordisk, and grant support from AlfaSigma, Novo Nordisk,

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Data availability

The datasets used and/or analysed during this study are available from the corresponding author on reasonable request.

Disclaimer

The funders did not play any role in study design; in the collection, analysis and interpretation of data; in the writing of the report; nor in the preparation, review or approval of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the ethics committee of the coordinating centre (Sant'Andrea University Hospital, Rome, Italy, N.4306) and subsequently by the ethics committee of each participating centre. Participants provided an informed consent.

Consent for publication

Not applicable.

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