Does Estimated Pulse Wave Velocity Add Prognostic Information?

MORGAM Prospective Cohort Project

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Abstract—The Reference Values for Arterial Stiffness Collaboration has derived an equation using age and mean blood pressure to estimated pulse wave velocity (ePWV), which predicted cardiovascular events independently of Systematic COoronary Risk Evaluation (SCORE) and Framingham Risk Score. The study aim was to investigate the independent association between ePWV and clinical outcomes in 107 599 apparently healthy subjects (53% men) aged 19 to 97 years from the MORGAM Project who were included between 1982 and 2002 in 38 cohorts from 11 countries. Using multiple Cox-regression analyses, the predictive value of ePWV was calculated adjusting for country of inclusion and either SCORE, Framingham Risk Score, or traditional cardiovascular risk factors (age, sex, smoking, systolic blood pressure, body mass index [BMI], total and high-density lipoprotein cholesterol). Cardiovascular mortality consisted of fatal stroke, fatal myocardial infarction, or coronary death, and the composite cardiovascular end point consisted of stroke, myocardial infarction, or coronary death. Model discrimination was assessed using Harrell's *C*-statistic. Adjusting for country and logSCORE or Framingham Risk Score, ePWV was associated with all-cause mortality (hazard ratio, 1.23 [95% CI 1.20–1.25] per m/s or 1.32 [1.29–1.34]), cardiovascular mortality (1.26 [1.21–1.32] or 1.35 [1.31–1.40]), and composite cardiovascular end point (1.19 [1.16–1.22] or 1.23 [1.20–1.25]; all $P<0.001$). However, after adjusting for traditional cardiovascular risk factors, ePWV was only associated with all-cause mortality (1.15 [1.08–1.22], $P<0.001$) and not with cardiovascular mortality (0.97 [0.91–1.03]) nor composite cardiovascular end point (1.10 [0.97–1.26]). The areas under the last 3 receiver operator characteristic curves remained unchanged

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*A list of all GISSI study participants is given in the Appendix in the Data Supplement.

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when adding ePWV. Elevated ePWV was associated with subsequent mortality and cardiovascular morbidity independently of systematic coronary risk evaluation and Framingham Risk Score but not independently of traditional cardiovascular risk factors. (*Hypertension*. 2020;75:1420-1428. DOI: 10.1161/HYPERTENSIONAHA.119.14088.)
• Data Supplement

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Early age-related changes in the cardiovascular system, often referred to as early vascular ageing (EVA), are associated with subsequent overt cardiovascular disease.[1,2] The cardinal change in EVA is increased arterial stiffness often measured as increased pulse wave velocity (PWV).[3] Similar to other measures of target organ damage, EVA is hypothesized to be a marker of an individual subject's sensitivity to the harmful effects of the cardiovascular risk factors present and its presence or absence may thereby improve individual cardiovascular risk assessment.[1,4,5]

Carotid-femoral PWV (cfPWV) is considered the gold standard for assessing PWV. Studies have shown that it predicts cardiovascular events independently of traditional cardiovascular risk factors[6–9] and may even add significantly to risk prediction in models using traditional risk factors.[10] However, this finding is not universal.[11] cfPWV is somewhat difficult and expensive to measure and therefore not generally available. In contrast, pulse pressure is easy to measure but does not add much prognostic information to systolic blood pressure (BP).[12]

We have previously demonstrated that both systolic BP and pulse pressure are associated with major cardiovascular events, independently of both diastolic BP and mean BP, and that this relationship is influenced by aging,[13,14] indicating an additive prognostic importance of intrinsic vascular changes that could represent EVA. Additionally, we have recently[15] shown that in healthy participants from the 10-year follow-up of the Danish part of the Multi-national Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project and in a Parisian cohort of patients with essential hypertension without known cardiovascular disease, an estimated pulse wave velocity (ePWV) can be calculated from age and mean BP using the equation generated from the Reference Values for Arterial Stiffness Collaboration[3] that had similar predictive value as cfPWV. Furthermore, ePWV predicted a combined cardiovascular end point independently of Systemic COronary Risk Evaluation (SCORE), Framingham risk score (FRS), and cfPWV. The fact that the predictive value of ePWV remained significant after adjustment for SCORE and FRS suggested that these traditional risk score models underestimated important prognostic interactions between age and BP.

Using the large population-based cohort of the MONICA, Risk, Genetics, Archiving and Monograph (MORGAM) Project, we aimed to investigate whether ePWV takes into account prognostically important interactions between mean BP and age that are not incorporated in SCORE or FRS, or captured by individual traditional cardiovascular risk factors.

Methods

We used data from large population cohort studies from many countries. The data are not available in a public repository. Access to the data is restricted by the ethical approvals and the legislation of the European Union and the countries of each study. Approval by the Principal Investigator of each cohort study and the MORGAM/BiomarCaRE Steering Group will be required for release of the data. The MORGAM Manual at https://www.thl.fi/publications/morgam/manual/contents.htm gives more information on access to the data.

Cohorts

The present study used baseline (1982–2002) and 10-year follow-up harmonized data on subsequent all-cause mortality (ACM) as well as fatal and nonfatal myocardial infarction or stroke, from 38 population-based cohorts in 11 European countries from the MORGAM Project[16] (Table S1 in the Data Supplement). The cohorts in the MORGAM Project had either been part of the World Health Organization's MONICA Project or had used the same standardized MONICA survey procedures for data collection as described in the MORGAM manual.[17]

A total of 17 552 participants were excluded due to missing values related to the following baseline variables: (1) history of cardiovascular disease (n=781), diabetes mellitus (DM; n=1753), and use of antihypertensive drugs (n=4224), and (2) the cardiovascular risk factors used in the traditional risk score models (n=9528); as well as missing values related to any of the end points (n=1266). Next, we excluded 16 440 patients with a history of prevalent cardiovascular disease, DM (the equation for ePWV from The Reference Values for Arterial Stiffness Collaboration was calculated in subjects without prevalent cardiovascular disease or DM), or those who were using antihypertensive drugs at baseline, leaving a total of 107 599 apparently healthy participants aged 19 to 97 years available for the current analysis.

Baseline variables

History of cardiovascular disease consisted of stroke (ischemic or hemorrhagic), or coronary heart disease, which included myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention. For Warsaw and Brianza cohort 3, coronary heart disease also included angina pectoris when the data did not permit its separation from myocardial infarction. The use of antihypertensive drugs, daily smoking, and DM were self-reported. Weight (in kilograms) and height (in meters) were measured. BMI was subsequently calculated. Blood pressure was measured twice in the right arm in the sitting position using a standard or random zero mercury sphygmomanometer after 5 minutes of rest[12] except in 4 cohorts where BP was measured only once using an automated device (FRA-LIL, FRA-STR, FRA-TOU, and UNK-BEL). The means of the first and second systolic BP and diastolic BP were used when possible. Total cholesterol and HDL (high-density lipoprotein) cholesterol were measured in serum samples by local laboratories.[18] A more detailed description and quality assessment of MORGAM baseline data has been published.[19]

Outcomes

The end points included ACM, cardiovascular mortality consisting of fatal stroke or death from coronary heart disease, and a composite end point (CEP) consisting of fatal or nonfatal stroke, death from coronary heart disease, or nonfatal myocardial infarction. Observations continued until an end point was reached or the end of the 10-year follow-up period (1992–2012 depending on the cohort—see Table S1 in the Data Supplement). Events were identified by national or regional health information systems. Most MORGAM centers used the World Health Organization's MONICA or other similar diagnostic criteria[18] to validate the events occurring during follow-up. Details of the data collection procedures and quality assessments of MORGAM end points have been described previously.[19–21]

Calculation of ePWV

The Reference Values for Arterial Stiffness Collaboration has previously published an equation describing how cfPWV was related to

age and MBP in groups with different a priori cardiovascular risk, taking nonlinearity and interactions into account.[3] Similar to a prior study,[15] we used the equation derived from the Reference Population of Collaboration Cohort: $7.84-0.33\times age+3.8\times10^{-3}\times age^2-1.97\times10^{-5}\times age^2\times Mean\ BP+2.5\times10^{-3}\times(age\times mean\ BP)-1.9\times10^{-3}\times mean\ BP$ to calculate ePWV. Mean BP was calculated as diastolic BP+0.4 (systolic BP−diastolic BP). As EVA is often defined as cfPWV ≥upper quartile in a normal population,[1,4] we classified participants as having high ePWV (≥9.4 m/second) or low ePWV (<9.4 m/s) based on the upper quartile of ePWV of 9.4 m/s in our apparently healthy population.

Risk Score Models

SCORE was used to estimate the 10-year risk of a broader cardiovascular mortality (CVM). We classified participants as having low (broader CVM <1%), moderate (1%≤ broader CVM <5%), high (5%≤ broader CVM <10%), or very high (broader CVM ≥10%) cardiovascular risk based on age, sex, systolic BP, total cholesterol, and daily smoking.[22] The SCORE equation has been adapted to the incidence of CVM in high-/low-risk countries, and we used the country specific classification of high-/low-risk countries as defined in the period of the follow-up of the cohorts.[23]

FRS was used to estimate the risk of a broader CEP consisting of cardiovascular death and nonfatal cardiovascular events, such as myocardial infarction, ischemic heart disease, peripheral artery disease, stroke, or transient ischemic attack, based on the same traditional risk factors as SCORE but also adding HDL cholesterol and the presence or absence of DM. However, subjects with DM were not included in the apparently healthy population in this paper. Participants were classified as having low (<10%), low-intermediate (10%≤ and <15%), intermediate-high (15%≤ and <20%), or high (≥20%) risk of the broader CEP.[23]

Statistical Analyses

All statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY). Categorical variables were presented as number (percentage), and continuous variables were summarized by median (lower quartile to upper quartile). Hazard ratios and 95% CIs for the association of baseline ePWV with the risk of mortality (ACM and CVM) and CEP were estimated using multivariable adjusted Cox regression models, with time from baseline as the time variable. In the primary analysis, we examined the independent association of ePWV with each of the 3 end points after adjustment for country and the following individual cardiovascular risk factors in the model: age, sex, smoking, systolic BP, BMI, total cholesterol, and HDL cholesterol. Secondarily, we examined whether ePWV added significant prognostic information to a model including country and either SCORE or FRS, both as continuous variables. Model discrimination was assessed with the use of Harrell's *C*-statistic.[25]

Table 1. General Characteristics Stratified by SCORE and ePWV

	Low SCORE		Moderate SCORE		High SCORE		Very high SCORE	
ePWV, m/s	Low	High	Low	High	Low	High	Low	High
Variables								
Number of participants	65 137	2107	15 122	17 767	434	5702	7	1323
Men (%)	28 008 (43)	506 (24)	12 702 (84)	9594 (54)	434 (100)	4562 (80)	7 (100)	1191 (90)
Smokers (%)	22 147 (34)	232 (11)	6502 (43)	284 316	417 (96)	4562 (43)	7 (100)	979 (74)
Age, y	36 (23–52)	48 (37–55)	52 (41–61)	59 (47–73)	56 (50–62)	64 (52–82)	59 (56–61)	66 (55–81)
BMI, kg/m²	25 (19–34)	28 (21–40)	26 (20–33)	27 (20–37)	26 (20–32)	27 (21–36)	25 (22–28)	26 (19–35)
Systolic BP, mm Hg	124 (100–153)	155 (130–190)	124 (100–153)	151 (118–184)	124 (100–145)	155 (122–199)	118 (104–131)	169 (133–210)
Diastolic BP, mm Hg	76 (57–97)	97 (82–118)	78 (60–95)	88 (68–110)	75 (59–90)	89 (69–115)	73 (59–77)	93 (71–121)
Pulse pressure, mm Hg	48 (29–73)	57 (35–87)	46 (28–70)	58 (34–91)	49 (29–73)	66 (39–103)	46 (32–54)	76 (48–108)
Mean BP, mm Hg	96 (76–117)	120 (105–143)	96 (79–114)	111 (91–137)	95 (79–105)	116 (94–145)	91 (77–99)	124 (100–152)
Total cholesterol, mmol/L	5.4 (3.6–7.8)	6.0 (4.1–8.7)	6.1 (4.1–8.5)	6.2 (4.1–8.8)	6.6 (4.1–8.7)	6.4 (4.3–9.1)	7.2 (6.5–7)	6.7 (4.5–9.5)
HDL-C, mmol/L	1.45 (0.83–2.3)	1.48 (0.83–2.3)	1.35 (0.65–2.2)	1.42 (0.80–2.4)	1.28 (0.72–2.0)	1.40 (0.82–1.37)	1.15 (0.78–2.4)	1.42 (0.77–2.5)
SCORE	0 (0.0–0.0)	0 (0.0–0.0)	1.54 (1.0–4.0)	2.2 (1.0–4.0)	5.6 (5.0–8.0)	6.3 (5.0–9.0)	10.4 (10.0–11.0)	13.1 (10.1–23)
FRS	3.6 (1.0–11.2)	8.5 (3.9–15.9)	12.3 (3.9–29)	15.7 (6.3–30)	25 (13.2–30)	26 (15.6–30)	28 22–30	29 22–30
ePWV, m/s	7.1 (5.8–8.9)	9.7 (9.2–11.1)	8.4 (7.0–9.2)	10.4 (9.3–12.8)	8.7 (7.6–9.2)	11.6 (9.4–15.6)	8.8 (8.3–9.1)	12.5 (10.1–15.9)
All-cause mortality (%)	861 (1.3)	71 (3.4)	838 (5.5)	1534 (8.6)	6515	125 422	114	45 835
CVM (%)	93 (0.1)	13 (0.6)	155 (1)	322 (2)	19 (4)	293 (5)	1 (14)	119 (9)
CEP (%)	618 (0.9)	80 (4)	866 (6)	1472 (8)	59 (14)	959 (17)	11 (4)	330 (25)

Values are presented as numbers (percentages) or median (lower quartile–upper quartile). CVM includes fatal stroke or death from coronary heart disease and composite cardiovascular end point includes fatal or nonfatal stroke, death from coronary heart disease, or nonfatal myocardial infarction. Low ePWV refers to <9.4 m/s and high ePWV refers to ≥9.4 m/s. SCORE categories: low (broader CVM <1%), moderate (1%< broader CVM <5%), high (5%< broader CVM <10%), or high (broader CVM >10%) CV risk based on age, sex, SBP, total cholesterol, and daily smoking. FRS categories: low (<10%), low-intermediate (10%< and <15%), intermediate-high (15%< and <20%), or high (>20%) cardiovascular risk based on age, sex, SBP, total cholesterol, daily smoking, and diabetes mellitus. BMI indicates body mass index; BP, blood pressure; CEP, composite cardiovascular end point; CVM, cardiovascular mortality; ePWV, estimated pulse wave velocity; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; and SCORE, systematic coronary risk evaluation.

All explanatory variables met the proportional hazards assumption of the Cox regression model, as assessed by Schoenfeld residuals. For SCORE and FRS, we used the numerical risk estimates as covariates in the Cox models. Due to the nonlinearity of SCORE, the risk estimates were logarithmically transformed.

The magnitude of reclassification was tested using SCORE and FRS risk categories and net reclassification improvement for ePWV ≥9.4 m/s (upper quartile; net reclassification improvement=[up-reclassified persons with events/total number of persons with events)−(down-reclassified persons with events/total number of persons with event)+(down-reclassified persons without events/total number of persons without events)−(up-reclassified persons without events/total number of persons without events].[26] As only reclassification between moderate and high SCORE risk changes the indication for pharmacological primary prevention,[27] we have, based on previous experience,[15,28] focused on upgrading participants with moderate SCORE risk and ePWV ≥9.4 m/s to high SCORE risk without allowing down-grading of participants with high SCORE risk and ePWV<9.4 m/s to moderate SCORE risk because disqualifying this subgroup from primary prevention seemed unethical to us. However, as a sensitivity analysis, we also examined reclassification allowing downgrading. Pharmacological primary prevention is not recommended in subjects with low intermediate FRS but may be considered in subjects with high intermediate FRS. Therefore, we decided that participants with high intermediate FRS and ePWV ≥9.4 m/s were upgraded to high FRS and participants with high intermediate FRS and ePWV<9.4 m/s were downgraded to low intermediate FRS dissolving the high intermediate FRS group completely.

For all analyses, a 2-tailed $P<0.05$ was considered statistically significant.

Results

General Characteristics

The study population comprised 107 599 apparently healthy subjects aged 19 to 97 years (53% men; Table S1). The levels of traditional risk factors were higher with higher SCORE category (Table 1) and FRS category (Table 2). During 10 years of follow-up, 4.7% died (0.9% from cardiovascular causes), and 4.1% experienced a CEP (Table S1 in the Data Supplement). The incidence rates of each of the 3 end points were higher in higher SCORE or FRS categories (Figures 1 and 2, respectively). For subjects with a low or moderate SCORE and independently of FRS category, those with a high ePWV had a significantly higher incidence of all 3 end points compared with subjects who had a low ePWV within the same risk category.

Table 2. General Characteristics Stratified by FRS and ePWV

	Low FRS		Low Intermediate FRS		High Intermediate FRS		High FRS	
ePWV, m/s	Low	High	Low	High	Low	High	Low	High
Variables								
Number of participants	51 149	326	18 434	4178	8909	12 083	2208	10 312
Men (%)	179 0235	24 (7.4)	13 088 (71)	104 525	7929 (89)	6283 (52)	2186 (99)	9487 (92)
Smokers (%)	138 1027	196 (0.6)	755 841	155 (3.7)	5256 (59)	1535 (12.7)	2053 (93)	4846 (47)
Age, y	35 (22–53)	54 (33–69)	45 (26–59)	56 (42–70)	49 (36–60)	58 (46–73)	52 (41–61)	63 (50–81)
BMI, kg/m^2	24 (19–33)	27 (19–39)	26 (20–35)	27 (20–38)	26 (20–34)	28 (20–38)	27 (20–34)	27 (20–36)
Systolic BP, mm Hg	122 (99–149)	136 (106–184)	129 (103–157)	142 (114–181)	129 (104–156)	149 (120–189)	130 (106–154)	155 (123–198)
Diastolic BP, mm Hg	75 (56–94)	89 (67–121)	80 (62–99)	89 (68–111)	80 (62–99)	89 (69–112)	79 (62–96)	90 (69–114)
Pulse pressure, mm Hg	47 (29–71)	47 (26–78)	49 (30–74)	53 (32–82)	49 (30–74)	59 (35–93)	51 (33–76)	65 (38–101)
Mean BP, mm Hg	93 (76–114)	108 (84–145)	99 (84–119)	110 (88–136)	100 (81–119)	113 (93–139)	99 (81–117)	116 (94–144)
Total cholesterol, mmol/L	5.2 (3.5–7.3)	5.1 (3.6–7.0)	6.0 (4.1–8.3)	5.8 (4.0–8.2)	6.3 (4.2–8.8)	6.2 (4.1–8.8)	6.6 (4.3–8.9)	6.5 (4.3–9.1)
HDL-C, mmol/L	1.5 (0.9–2.3)	1.7 (1.2–2.4)	1.4 (0.8–2.2)	1.6 (1.0–2.4)	1.2 (0.7–2.0)	1.5 (0.9–2.4)	1.1 (0.7–1.7)	1.3 (0.7–2.3)
SCORE	0.02 (0.0–0.0)	0.15 (0.0–2.0)	0.40 (0.0–2.0)	0.9 (0.0–3.0)	1.3 (0.0–4.0)	2.3 (0.0–6.0)	2.8 (1.0–6.0)	5.9 (1.0–15.0)
FRS	2.4 (1.0–4.7)	4.2 (2.9–4.7)	7.1 (5.3–9.4)	7.7 (5.3–9.4)	13.7 (10.0–18.5)	14.4 (10.0–18.5)	25 (22–30)	27 (22–30)
ePWV, m/s	6.9 (5.7–8.6)	9.6 (9.2–10.5)	7.9 (6.5–9.1)	9.9 (9.2–11.4)	8.3 (6.9–9.2)	10.5 (9.3–12.8)	8.6 (7.5–9.2)	11.3 (9.3–15.3)
All-cause mortality (%)	5591	227	4993	2045	5016	9978	2069	209 420
CVM (%)	41 (0.1)	41	72 (0.4)	331	1021	1932	532	5175
CEP (%)	242 (0.5)	113	4382	1463	5696	8777	29 513	180 717

Values are presented as numbers (percentages) or median (lower quartile–upper quartile). CVM includes fatal stroke or death from coronary heart disease and composite cardiovascular end point includes fatal or nonfatal stroke, death from coronary heart disease, or nonfatal myocardial infarction. Low ePWV refers to <9.4 m/s and high ePWV refers to ≥9.4 m/s. SCORE categories: low (broader CVM <1%), moderate (1%< broader CVM <5%), high (5%< broader CVM <10%), or very high (broader CVM >10%) CV risk based on age, sex, SBP, total cholesterol, and daily smoking. FRS categories: low (<10%), low-intermediate (10%< and <15%), intermediate-high (15%< and <20%), or high (>20%) cardiovascular risk based on age, sex, SBP, total cholesterol, daily smoking, and diabetes mellitus. BMI indicates body mass index; BP, blood pressure; CEP, composite cardiovascular end point; CVM, cardiovascular mortality; ePWV, estimated pulse wave velocity; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; and SCORE, systematic coronary risk evaluation.

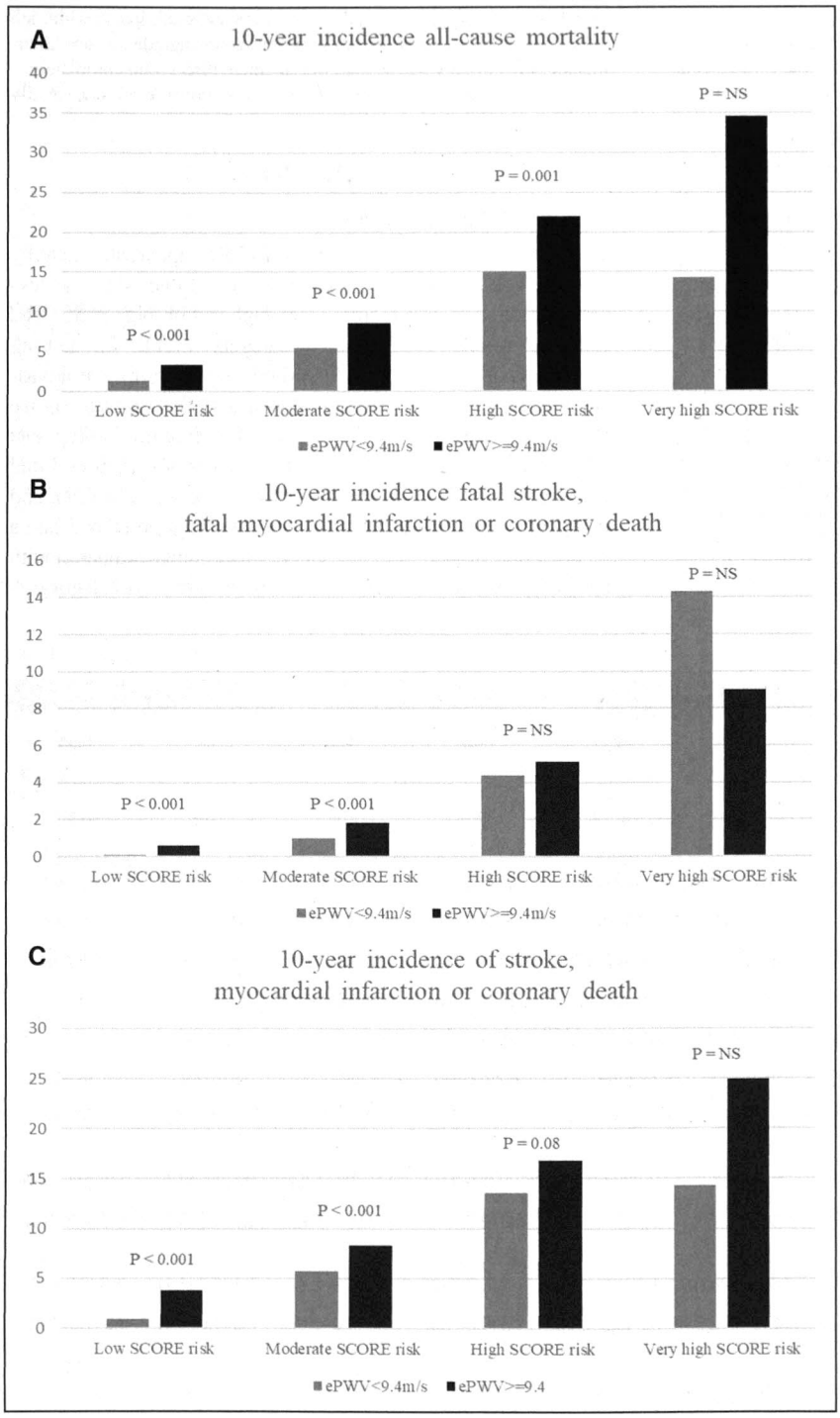

Figure 1. Ten-year incidence rates by estimated pulse wave velocity (ePWV; <9.4 m/s=low and ≥9.4 m/s= high) and systematic coronary risk evaluation (SCORE) category for (**A**) all-cause mortality, (**B**) fatal stroke or death from coronary heart disease (cardiovascular mortality), and (**C**) fatal or nonfatal stroke, death from coronary heart disease, or nonfatal myocardial infarction (composite end point). Low SCORE risk (estimated 10-year risk of cardiovascular mortality [CVM] <1%), moderate (1%≤ CVM <5%), high (5%≤ CVM <10%), or very high (CVM ≥10%).

Association Between ePWV and Outcomes

In Cox-regression analyses adjusting for country, ePWV was significantly associated with all 3 outcomes (P<0.001 for all; Table 3). However, when adjusting for country, age, sex, smoking status, systolic BP, total cholesterol, and HDL cholesterol, ePWV was only associated with ACM (hazard ratio, 1.14 [95% CI, 1.08–1.21]; P<0.001) and CVM (1.17 [1.04–1.32]; P<0.05). When further adjusted for BMI, only the association between ePWV and ACM remained significant (1.15 [1.08–1.22]; P<0.001).

Adjusted for country and logSCORE or FRS, ePWV was associated with ACM (1.23 [1.20–1.25] and 1.32 [1.29–1.34]), CVM (1.26 [1.21–1.32] and 1.35 [1.31–1.40]), and CEP (1.19 [1.16–1.22] and 1.23 [1.20–1.25]), respectively, all P<0.001. In all models, the HRs were higher in women than in men with significant interactions between ePWV and sex for CMV (P=0.001 and P=0.01) and CEP (both P<0.001).

When adjusting for country, ePWV ≥9.4 m/s was associated with all outcomes (HR between 1.14 and 1.25; all P<0.05) independently of logSCORE and FRS, respectively (data not shown). The association between ePWV ≥9.4 m/s and outcomes remained significant in half of the countries (HR between 0.70 and 3.43) when

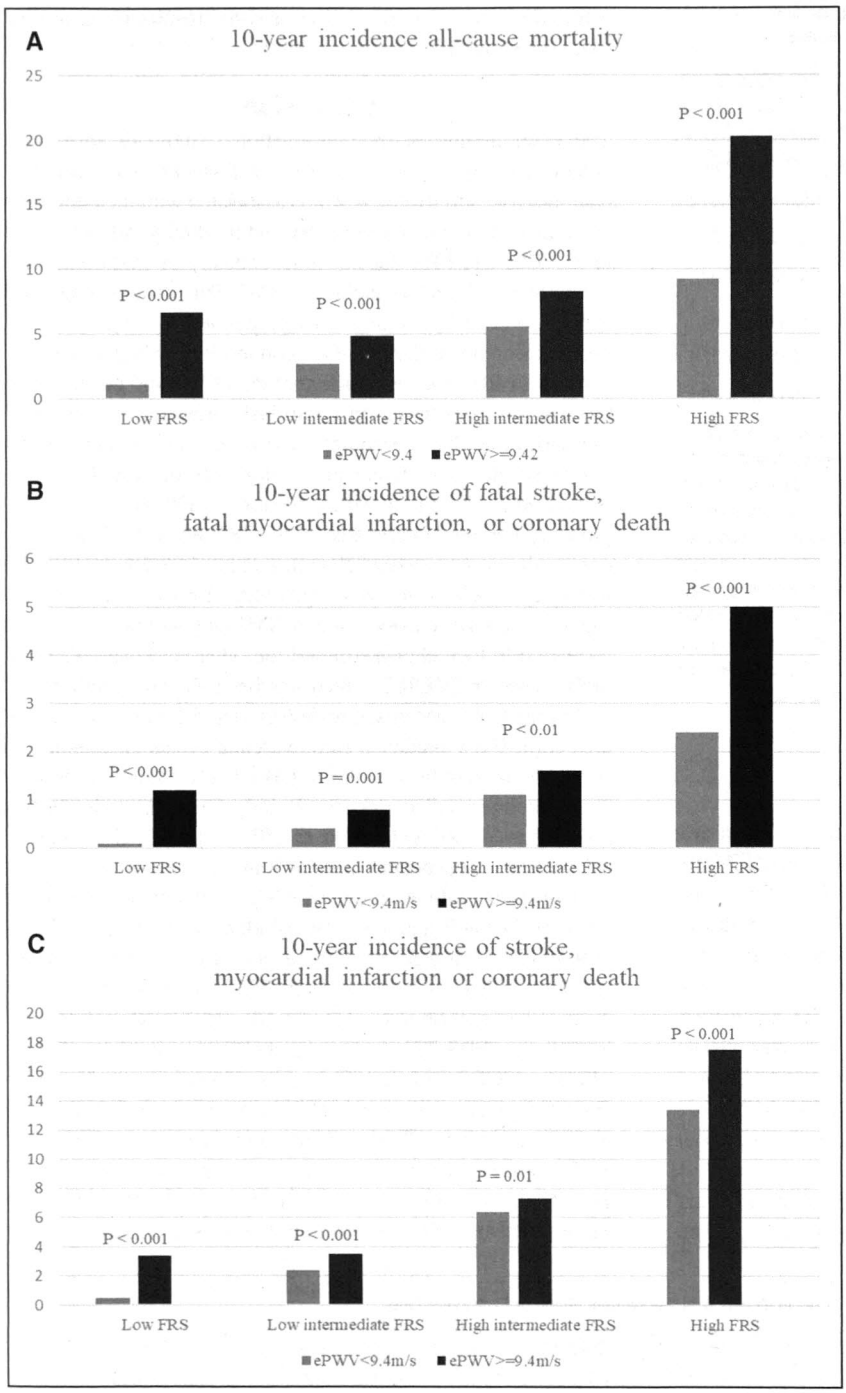

Figure 2. Ten-year incidence rates per by estimated pulse wave velocity (ePWV; <9.4 m/s=low and ≥9.4 m/s=high) and Framingham risk score (FRS) category for (**A**) all-cause mortality, (**B**) fatal stroke or death from coronary heart disease (cardiovascular mortality), and (**C**) fatal or nonfatal stroke, death from coronary heart disease or nonfatal myocardial infarction (composite end point). Low FRS (estimated 10-year risk of the broader composite cardiovascular end point <10%), low-intermediate (10%≤ and <15%), intermediate-high (15%≤ and <20%) or high (≥20%).

adjusting for FRS and significant only in 2 countries (HR between 0.49 and 2.02) when adjusting for logSCORE (data not shown). The association between ePWV ≥9.4 m/s and outcomes remained significant in half of the countries (HR between 0.70 and 3.43) when adjusting for FRS and significant only in 2 countries (HR between 0.49 and 2.02) when adjusting for logSCORE (data not shown).

Area Under the Curve for Models With and Without ePWV

When creating new country-specific risk functions based on the Cox models with all significant traditional cardiovascular risk factors, the area under the receiver operator characteristic curve was 0.871 for ACM, 0.831 for CVM, and 0.827 for CEP, and ePWV did not add significantly to these new risk functions (Table 4). However, adding ePWV to the Cox models with logSCORE or FRS did increase the areas under the receiver operator characteristics curves significantly (Table 4).

Risk Reclassification Analyses

In subjects with a moderate SCORE, ePWV ≥9.4 m/s was associated with greater risks of ACM (8.6% versus 5.5%), CVM (1.8% versus 1.0%), and CEP (8.3% versus 5.7%), all $P<0.001$ (Table S2 in the Data Supplement). In subjects with a moderate

Table 3. Associations Between ePWV and All-Cause Mortality and Cardiovascular End Points Using Adjusted Cox Regression Models

Cox Regression Models Adjustment	All-Cause Mortality	CVM	CEP
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Unadjusted	1.59 (1.57–1.60)‡	1.72 (1.68–1.76)‡	1.59 (1.57–1.61)‡
Model 1	1.60 (1.58–1.62)‡	1.72 (1.68–1.76)‡	1.61 (1.59–1.63)‡
Model 2	1.14 (1.08–1.21)‡	1.17 (1.04–1.32)*	0.97 (0.91–1.03)
Model 3	1.15 (1.08–1.22)‡	0.97 (0.91–1.03)	1.10 (0.97–1.26)
Model 4	1.23 (1.20–1.25)‡	1.26 (1.21–1.32)‡	1.19 (1.16–1.22)‡
Model 5	1.32 (1.29–1.34)‡	1.35 (1.31–1.40)‡	1.23 (1.20–1.25)‡

HR is per m/s increase in ePWV. CVM includes fatal stroke or death from coronary heart disease; composite cardiovascular end point includes fatal or nonfatal stroke, death from coronary heart disease or nonfatal myocardial infarction. Model 1: adjusted for country. Model 2: adjusted for age, sex, smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and country. Model 3: adjusted for age, sex, smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body mass index, and country. Model 4: adjusted for Systematic coronary risk evaluation (SCORE) and country. Model 5: adjusted for Framingham risk score (FRS) and country. CEP indicates composite cardiovascular end point; CVM, cardiovascular mortality; ePWV, estimated pulse wave velocity; and HR, hazard ratio.

*$P<0.05$.

†$P<0.01$.

‡$P<0.001$.

SCORE and with ePWV ≥9.4 m/s as the reclassification measure, 17 767 subjects with 1534 ACM, 332 CVM, and 1472 CEP were reclassified to a high risk, giving NRIs of 14.4%, 15.4%, and 17.8% (all $P<0.001$), respectively. If we also allowed for downward reclassification of subjects with high SCORE with ePWV <9.4 m/s, NRIs were 13.4%, 17.4%, and 16.8% (all $P<0.001$). Reclassifying subjects with high intermediate FRS and ePWV ≥9.4 m/s to high FRS and ePWV <9.4 m/s to low intermediate FRS, upgraded 12 083 subjects with 997 ACM, 193 CVM, and 877 CEP and downgraded 8909 subjects with 501 ACM, 102 CVM, and 569 CEP, giving NRIs of 7.1%, 6.1%, and 4.2% (all $P<0.001$), respectively.

The analyses were repeated using the original SCORE and FRS age interval of 35 to 75 years, a relevant age group when estimating early vascular aging, and the results were similar (data not shown).

Discussion

The main finding of this observational study, in apparently healthy participants across Europe without known cardiovascular disease, was that ePWV was associated with incident mortality and cardiovascular mortality and morbidity independently of SCORE and FRS but not independently of traditional cardiovascular risk factors including BMI. This demonstrates that SCORE and FRS, like any other predefined risk equations, do not perform optimally in other cohorts,[23] enabling other risk markers to add prognostic information. ePWV did not improve the risk functions based on traditional cardiovascular risk factors indicating that the complicated impact of age and BP on arterial stiffness and thereby also on major cardiovascular events is covered by the traditional cardiovascular risk factors and has probably not been overlooked in SCORE nor FRS. Therefore, our results do not support changing either SCORE or FRS by including ePWV in the risk equations. However, our data do suggest that HDL cholesterol and BMI may add prognostic information to total cholesterol and the other cardiovascular risk factors used in SCORE, which has been shown by others.[29,30] According to the systematic review by Ben-Shlomo et al[10] measured aortic PWV predicted cardiovascular events independently of traditional risk factors and improved risk prediction in subjects with intermediate risk significantly. This might also be the case in the MORGAM cohort as cfPWV predicted cardiovascular events independently of ePWV in our previous work.[15]

Consistent with our previous work,[15] we replicated the finding of a SCORE and FRS independent association between ePWV and major cardiovascular events with significant reclassification indices, suggesting that ePWV may be used to improve risk stratification in case of moderate SCORE risk or high intermediate FRS. This suggests that ePWV could be used as an add-on to SCORE in clinical practice. However, this should be done with great caution as the additive prognostic information of high versus low ePWV varied substantially between the different European countries, suggesting a strong cohort dependency. Therefore, we think it is premature to use ePWV to improve cardiovascular risk prediction in individuals in clinical practice

Table 4. Area Under the Receiver Operator Characteristic Curve in Models With and Without ePWV for Each Event Type

Cox Regression Models Adjustment	C-Index*					
	All-Cause Mortality		CVM		CEP	
ePWV added	No	Yes	No	Yes	No	Yes
Model 1	0.845 (0.833–0.858)	0.857† (0.846–0.868)	0.801 (0.794–0.808)	0.820† (0.814–0.826)	0.793 (0.786–0.800)	0.810† (0.803–0.816)
Model 2	0.852 (0.841–0.863)	0.861† (0.851–0.872)	0.833 (0.828–0.839)	0.837† (0.831–0.842)	0.800 (0.793–0.806)	0.810† (0.804–0.816)
Model 3	0.871 (0.861–0.881)	0.871 (0.862–0.881)	0.831 (0.823–0.838)	0.831 (0.823–0.838)	0.827 (0.822–0.833)	0.827 (0.821–0.833)

CVM includes fatal stroke or death from coronary heart disease; composite cardiovascular end point includes fatal or nonfatal stroke, death from coronary heart disease or nonfatal myocardial infarction. Model 1: including systematic coronary risk evaluation (SCORE) and country. Model 2: including Framingham risk score (FRS) and country. Model 3: including age, sex, smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body mass index, and country. CEP indicates composite cardiovascular end point; CVM, cardiovascular mortality; ePWV, estimated pulse wave velocity; FRS, Framingham risk score; and SCORE, systematic coronary risk evaluation.

*Gronnesby and Borgan likelihood-ratio statistic.

†$P<0.001$.

until we know more about the cohort(s) in which ePWV carries prognostic information beyond SCORE and FRS.

Interestingly, ePWV was predictive of ACM even after adjusting for all the traditional cardiovascular risk factors suggesting that ePWV is more than a marker of just cardiovascular risk. This is supported by previous studies evaluating the prognostic importance of cfPWV.[6–10] Possible mechanisms for an age-independent association between ePWV and ACM could be higher risk of orthostatic hypotension, syncope, and fall traumas and/or dysfunctional hemodynamic reactions to infections, bleedings, or traumas.

The strength of the present investigation was the large sample size of 107 599 European individuals, with a 10-year follow-up with a large number of events. Other strengths were the inclusion of a wide age range, an almost equal proportion of men and women, and the standardized baseline and end point assessment available from the well-characterized MORGAM cohorts, with individual validation of the diagnosis in the majority of fatal and nonfatal events.

Some limitations should also be considered. First, BP measurements were only performed at baseline. In addition, the cohort participants may have begun antihypertensive medication or quit smoking during the observational period, both of which affect the risk estimates. Repeat measurements of BP would have taken into account longer-term trajectories, and thus, indicated the real association between the usual level of BP and mortality risk (regression dilution bias).[31] Nonetheless, a single BP reading is still strongly predictive of future CV events.[32] Second, SCORE and FRS were not calibrated to the individual cohort, and therefore, it is highly likely that the actual risk limits are different. Third, the 10-year follow-up period occurred at different timepoints in different cohorts; therefore, SCORE may have overestimated or underestimated risk during parts of the follow-up period although we used the high or low risk SCORE most appropriate for each country taking into account the time of the follow-up period. Fourth, to ensure homogeneity of the end points across cohorts and countries, the definitions of CVM and CEP used in the present study differed from the ones used by SCORE and FRS. Fifth, to avoid excluding important age groups, we used SCORE and FRS in subjects outside the original age interval, but the results were similar when restricting the analyses to subjects aged 35 to 75 years. Consequently, our primary analyses were based on adjustments for individual cardiovascular risk factors and not SCORE or FRS. Sixth, we did not compare the predictive value of ePWV to that of pulse pressure because we have previously found that pulse pressure predicted major cardiovascular events independently of mean BP, but not independently of systolic BP.[13,14] Seventh, our findings may not apply to non-Europeans, individuals with prevalent cardiovascular disease, or those treated with antihypertensive medication. Finally, the baseline of the included studies was between 1982 and 2002 and may not be fully representative of today's society. In addition to the introduction of many prognostically relevant treatments since the early 1980s, the diagnosis of myocardial infarction has improved substantially after the introduction of troponins around the millennium, and coronary heart disease mortality has decreased considerably in all countries.

Perspectives

In conclusion, elevated ePWV was associated with subsequent mortality and cardiovascular morbidity independently of SCORE and FRS but not independently of traditional cardiovascular risk factors. As ePWV did not predict cardiovascular morbidity or mortality independently of the traditional cardiovascular risk factors, our data do not support making a new SCORE or new FRS with ePWV. The varying prognostic importance of ePWV between the different countries suggests that more information is needed before the clinician may consider using ePWV for individual subjects in addition to SCORE or FRS risk assessment.

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References

1. Nilsson PM, Boutouyrie P, Cunha P, Kotsis V, Narkiewicz K, Parati G, Rietzschel E, Scuteri A, Laurent S. Early vascular ageing in translation: from laboratory investigations to clinical applications in cardiovascular prevention. *J Hypertens.* 2013;31:1517–1526. doi: 10.1097/HJH.0b013e328361e4bd
2. Nilsson PM, Lurbe E, Laurent S. The early life origins of vascular ageing and cardiovascular risk: the EVA syndrome. *J Hypertens.* 2008;26:1049–1057. doi: 10.1097/HJH.0b013e3282f82c3e
3. Reference Values for Arterial Stiffness Collaboration. Determinants of pulse wave velocity in healthy people in the presence of cardiovascular risk factors: 'establishing normal and reference values.' *Eur Heart J.* 2010;31:2338–2350. doi: 10.1093/eurheartj/ehq165
4. Nilsson Wadström B, Fatehali AH, Engström G, Nilsson PM. A vascular aging index as independent predictor of cardiovascular events and total mortality in an elderly urban population. *Angiology.* 2019;70:929–937. doi: 10.1177/0003319719857270
5. Ohkuma T, Ninomiya T, Tomiyama H, Kario K, Hoshide S, Kita Y, Inoguchi T, Maeda Y, Kohara K, Tabara Y, et al; Collaborative Group for J-BAVEL (Japan Brachial-Ankle Pulse Wave Velocity Individual Participant Data Meta-Analysis of Prospective Studies)*. Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: an individual participant data meta-analysis. *Hypertension.* 2017;69:1045–1052. doi: 10.1161/HYPERTENSIONAHA.117.09097
6. Greve SV, Blicher MK, Blyme A, Sehestedt T, Hansen TW, Rassmusen S, Vishram JK, Ibsen H, Torp-Pedersen C, Olsen MH. Association between albuminuria, atherosclerotic plaques, elevated pulse wave velocity, age, risk category and prognosis in apparently healthy individuals. *J Hypertens.* 2014;32:1034–1041; discussion 1041. doi: 10.1097/HJH.0000000000000147
7. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension.* 2001;37:1236–1241. doi: 10.1161/01.hyp.37.5.1236

8. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2010;55:1318–1327. doi: 10.1016/j.jacc.2009.10.061
9. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension.* 2002;39:10–15. doi: 10.1161/hy0102.099031
10. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol.* 2014;63:636–646. doi: 10.1016/j.jacc.2013.09.063
11. Verwoert GC, Elias-Smale SE, Rizopoulos D, Koller MT, Steyerberg EW, Hofman A, Kavousi M, Sijbrands EJ, Hoeks AP, Reneman RS, et al. Does aortic stiffness improve the prediction of coronary heart disease in elderly? The Rotterdam Study. *J Hum Hypertens.* 2012;26:28–34. doi: 10.1038/jhh.2010.124
12. Glasser SP, Halberg DL, Sands CD, Mosher A, Muntner PM, Howard G. Is pulse pressure an independent risk factor for incident stroke, reasons for geographic and racial differences in stroke. *Am J Hypertens.* 2015;28:987–994. doi: 10.1093/ajh/hpu265
13. Vishram JK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, Broda G, Palmieri L, Giampaoli S, Donfrancesco C, et al; MORGAM Project. Impact of age on the importance of systolic and diastolic blood pressures for stroke risk: the MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project. *Hypertension.* 2012;60:1117–1123. doi: 10.1161/HYPERTENSIONAHA.112.201400
14. Vishram JK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, Broda G, Palmieri L, Giampaoli S, Donfrancesco C, et al; MORGAM Project. Do other cardiovascular risk factors influence the impact of age on the association between blood pressure and mortality? The MORGAM Project. *J Hypertens.* 2014;32:1025–1032; discussion 1033. doi: 10.1097/HJH.0000000000000133
15. Greve SV, Blicher MK, Kruger R, Sehestedt T, Gram-Kampmann E, Rasmussen S, Vishram JK, Boutouyrie P, Laurent S, Olsen MH. Estimated carotid-femoral pulse wave velocity has similar predictive value as measured carotid-femoral pulse wave velocity. *J Hypertens.* 2016;34:1279–1289. doi: 10.1097/HJH.0000000000000935
16. Evans A, Salomaa V, Kulathinal S, Asplund K, Cambien F, Ferrario M, Perola M, Peltonen L, Shields D, Tunstall-Pedoe H, et al; MORGAM Project. MORGAM (an international pooling of cardiovascular cohorts). *Int J Epidemiol.* 2005;34:21–27. doi: 10.1093/ije/dyh327
17. MORGAM Manual (2001). MORGAM Project e-publications [Internet]. URN:NBN:fi-fe20041529. http://www.thl.fi/publications/morgam/manual/contents.htm. Accessed April 6, 2019.
18. Tuntall-Pedoe H, ed. *Monica Monograph and Multimedia Sourcebook.* Geneva: World Health Organization; 2003.
19. Niemelä M, Kulathinal S, Kuulasmaa K. MORGAM Project (2007) Description and quality assessment of MORGAM data. MORGAM Project e-publications [Internet]. URN:NBN:fi-fe20071495. http://www.thl.fi/publications/morgam/qa/contents.htm. Accessed April 6, 2019.
20. Kulathinal S, Niemelä M, Niiranen T, Saarela O, Palosaari T, Tapanainen H, Kuulasmaa K; Contributors from Participating Centres, for the MORGAM Project. Description of MORGAM Cohorts. MORGAM Project e-publications [Internet]. URN:NBN:fi-fe20051214. Available at: http://www.thl.fi/publications/morgam/cohorts/index.html
21. Asplund K, Karvanen J, Giampaoli S, Jousilahti P, Niemelä M, Broda G, Cesana G, Dallongeville J, Ducimetriere P, Evans A, et al; MORGAM Project. Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project. *Stroke.* 2009;40:2319–2326. doi: 10.1161/STROKEAHA.109.547869
22. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J.* 2003;24:987–1003. doi: 10.1016/s0195-668x(03)00114-3
23. Karjalainen T, Adiels M, Björck L, Cooney MT, Graham I, Perk J, Rosengren A, Söderberg S, Eliasson M. An evaluation of the performance of SCORE Sweden 2015 in estimating cardiovascular risk: The Northern Sweden MONICA Study 1999-2014. *Eur J Prev Cardiol.* 2017;24:103–110. doi: 10.1177/2047487316673142
24. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation.* 2008;117:743–753. doi: 10.1161/CIRCULATIONAHA.107.699579
25. d'Agostino Sr RB, Nam BH. Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Balakrishnan N, Rao CR, eds. *Handbook of Statistics, Vol 23: Advances in Survival Analysis.* Elsevier BV: Amsterdam, the Netherlands. 2004;1–25.
26. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med.* 2008;27:157–172; discussion 207. doi: 10.1002/sim.2929
27. Sehestedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Pedersen C, Torp-Petersen C, Hildebrandt P, Olsen MH. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. *Eur Heart J.* 2010;31:883–891. doi: 10.1093/eurheartj/ehp546
28. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med.* 2011;30:11–21. doi: 10.1002/sim.4085
29. Willeit P, Kaptoge S, Welsh P, Butterworth AS, Chowdhury R, Spackman SA, Pennells L, Gao P, Burgess S, Freitag DF; Natriuretic Peptides Studies Collaboration, et al. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. *Lancet Diabetes Endocrinol.* 2016;4:840–849. doi: 10.1016/S2213-8587(16)30196-6
30. Perini W, Snijder MB, Peters RJ, Kunst AE, van Valkengoed IG. Estimation of cardiovascular risk based on total cholesterol versus total cholesterol/high-density lipoprotein within different ethnic groups: The *HELIUS* study. *Eur J Prev Cardiol.* 2019;26:1888–1896. doi: 10.1177/2047487319853354
31. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990;335:765–774. doi: 10.1016/0140-6736(90)90878-9
32. Miura K, Soyama Y, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, Yoshita K, Kagamimori S, Nakagawa H. Comparison of four blood pressure indexes for the prediction of 10-year stroke risk in middle-aged and older Asians. *Hypertension.* 2004;44:715–720. doi: 10.1161/01.HYP.0000145108.23948.7b

Novelty and Significance

What Is New?

- Pulse wave velocity estimated from age and mean blood pressure was associated with subsequent mortality and cardiovascular morbidity independently of systemic coronary risk evaluation and Framingham risk score but not independently of traditional cardiovascular risk factors, and the prognostic importance varied substantially between the different countries.

What Is Relevant?

- More information is needed before the clinician may consider using estimated pulse wave velocity for individual subjects in addition to systemic coronary risk evaluation or Framingham risk score risk assessment.

Summary

Elevated estimated pulse wave velocity was associated with subsequent mortality and cardiovascular morbidity independently of systemic coronary risk evaluation and Framingham risk score, but not independently of traditional cardiovascular risk factors.