

QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness

A Systematic Review and Meta-Analysis

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- Objectives** The purpose of this study was to calculate robust quantitative estimates of the predictive value of aortic pulse wave velocity (PWV) for future cardiovascular (CV) events and all-cause mortality by meta-analyses of longitudinal studies.
- Background** Arterial stiffness is increasingly recognized as a surrogate end point for CV disease.
- Methods** We performed a meta-analysis of 17 longitudinal studies that evaluated aortic PWV and followed up 15,877 subjects for a mean of 7.7 years.
- Results** The pooled relative risk (RR) of clinical events increased in a stepwise, linear-like fashion from the first to the third tertile of aortic PWV. The pooled RRs of total CV events, CV mortality, and all-cause mortality were 2.26 (95% confidence interval: 1.89 to 2.70, 14 studies), 2.02 (95% confidence interval: 1.68 to 2.42, 10 studies), and 1.90 (95% confidence interval: 1.61 to 2.24, 11 studies), respectively, for high versus low aortic PWV subjects. For total CV events and CV mortality, the RR was significantly higher in high baseline risk groups (coronary artery disease, renal disease, hypertension) compared with low-risk subjects (general population). An increase in aortic PWV by 1 m/s corresponded to an age-, sex-, and risk factor-adjusted risk increase of 14%, 15%, and 15% in total CV events, CV mortality, and all-cause mortality, respectively. An increase in aortic PWV by 1 SD was associated with respective increases of 47%, 47%, and 42%.
- Conclusions** Aortic stiffness expressed as aortic PWV is a strong predictor of future CV events and all-cause mortality. The predictive ability of arterial stiffness is higher in subjects with a higher baseline CV risk. (J Am Coll Cardiol 2010;55:1318-27) © 2010 by the American College of Cardiology Foundation

Arterial stiffness is increasingly recognized as a surrogate end point for cardiovascular (CV) disease (1). Apart from invasive methods, it can also be measured with noninvasive, reproducible, and relatively inexpensive techniques, and, thus, it is suitable for large-scale studies. Arterial stiffness is associated with presence of CV risk factors and atherosclerotic disease (1-7). Importantly, a number of studies examined the ability of arterial stiffness to predict the risk of future fatal and nonfatal CV events (myocardial infarction, stroke, revascularization, stroke, aortic syndromes) and total mortality (8-32). Arterial elastic properties are increasingly used for risk stratification purposes in several populations, and recently, the European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension suggested the measurement of aortic pulse wave velocity

(PWV), which is considered the gold standard method for assessing aortic stiffness, as a tool for assessment of subclinical target organ damage (33).

Although there is a general impression that arterial stiffness has an important predictive role based on the results of individual studies (8-32), no overall quantitative estimate of this role exists. Furthermore, the studies that investigated the predictive role of arterial stiffness involved different populations. Moreover, the sizes of the populations studied were highly diverse and thus gave rise to dissimilar risk estimates. In addition, because most published studies yielded positive results, publication bias may have been involved. Finally, an important issue is whether the predictive ability of arterial stiffness extends beyond CV events. Accordingly, we conducted the present systematic review and meta-analysis with the aim to provide an overview of relevant studies and calculate robust quantitative estimates of the predictive value of arterial stiffness as expressed by aortic PWV for different outcomes such as total CV events, CV mortality, and all-cause mortality. Second, we investigated whether publication bias could have

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affected the true predictive ability of arterial stiffness. Third, we evaluated whether arterial stiffness portends a different predictive ability in populations with different characteristics and estimated baseline CV risk.

Methods

Outcomes. The outcomes of interest were: 1) total CV events (CV deaths and nonfatal CV events [myocardial infarction, stroke, revascularization, aortic syndromes]); 2) CV mortality; and 3) total (all-cause) mortality.

Study eligibility. Studies were deemed eligible if they: 1) were full-length publications in peer-reviewed journals; 2) evaluated aortic PWV; 3) reported a combined CV outcome or CV mortality or total mortality. No restriction criteria were imposed with regard to the type of the population studied (healthy subjects, general population, or populations with risk factors or disease), the size of the population, or the duration of follow-up. All but one (25) of the longitudinal studies included in the meta-analysis were prospective studies.

Literature search. Studies evaluating relationships of arterial stiffness indexes with the risk of future clinical events were drawn from a systematic review of the English literature in the PubMed and Cochrane databases until February 2010. The search terms were “stiffness,” “arterial stiffness,” “arterial elasticity,” or “pulse wave velocity,” and “prediction,” “risk,” “death,” “mortality,” “outcome,” or “events.” Data sources were also identified through manually searching the references of articles.

Extraction of data. The literature search, selection of studies, and extraction of data was done independently by 2 reviewers (C.V., K.A.). Disagreements were resolved by consensus. For each study, we recorded a risk estimate for aortic PWV. Numeric data appearing in the articles were used. In a few studies not reporting these data, we calculated risk estimates from the survival curves.

Statistical analysis. The risk estimates of each study were reported as a hazard ratio, relative risk (RR), odds ratio, or dichotomous frequency data. We treated hazard ratios as RRs. Because no uniform cutoff values are available for aortic PWV, patients were allocated to high stiffness group or low stiffness group according to cutoffs provided by each study (median, upper tertile, optimal cutoff derived by receiver-operator characteristic curve analysis or by an individually specified level of increase) (Table 1). When available, we used the adjusted risk estimates from multivariate models. To evaluate the shape (e.g., linear) of the association of aortic PWV with the risk of clinical events over the whole range of aortic PWV distribution, we calculated pooled RRs by tertiles of aortic PWV (8,13,19,23,25,28). The pooled RRs across the tertiles were compared using the nonparametric Friedman test.

We performed meta-analyses of studies measuring aortic PWV to obtain the pooled RRs separately for: 1) total CV events; 2) CV mortality; and 3) all-cause mortality. The proportion of inconsistency across studies not explained by chance was quantified with the I^2 statistic. Heterogeneity between subgroups was calculated with Cochran's Q test (34). When

significant heterogeneity existed among studies, the random effects model was used to obtain the pooled RRs. We also calculated adjusted RRs per absolute PWV difference (1 m/s and 1 SD) in addition to the calculation of RR of high versus low stiffness groups in each study. Finally, we performed a sensitivity analysis to evaluate whether the strength of risk estimates differs between high-risk groups (subjects with coronary artery disease, renal disease, hypertension, and diabetes) and low-risk groups (general population). Risk estimates between subgroups were compared with a test of interaction (35). The RRs and confidence intervals (CIs) of individual studies were illustrated with forest plots.

To estimate the contribution of continuous study moderators to the overall heterogeneity, we ran a meta-regression analysis with restricted maximum likelihood estimates. The presence of publication bias was investigated graphically by funnel plots of precision, and its implications for our results were assessed by the Duval and Tweedie trim-and-fill method (36) and the classic fail-safe N method. All analyses were performed with Comprehensive Meta Analysis Version 2 (Biostat, Englewood, New Jersey) (37).

Results

Qualitative summary. Our search identified 126 publications, which were narrowed by preliminary review to 40 potentially relevant original articles. Further, articles were excluded because of cross-sectional study design ($n = 5$), measurement of local aortic stiffness ($n = 4$), and report of end points other than CV events or death ($n = 11$). Twenty studies measuring aortic PWV were deemed eligible for our meta-analysis (8–15,19–21,23–28,30–32) (Table 1). Three of those studies (12,13,32) provided risk estimates from a part of the population included in other studies (9,21) and were excluded from the main meta-analysis (high vs. low stiffness). However, one of these studies (13) was included in the evaluation of the shape (e.g., linear) of the association of aortic PWV with risk (see section on the shape of the association between aortic PWV and clinical events) because, of the 3 studies (9,12,13), only this particular one (13) provided risk according to tertiles. Another article was also excluded because it presented results for PWV index (measured PWV minus theoretical PWV) (15) from the same cohort as that in another article (8). Finally, our meta-analysis included 17 original articles assessing relationships of aortic PWV with CV events, CV mortality, and all-cause mortality. One study (31) presented separate data in men and women, so a total of 18 cohorts were included in the meta-analysis. In total, the included studies analyzed 15,877 subjects (the population of 1 study [13] was not added). Several populations such as patients with hypertension, diabetes, end-stage renal disease (ESRD), and coronary artery disease and subjects from the general population or

Abbreviations and Acronyms

CI	= confidence interval
CV	= cardiovascular
ESRD	= end-stage renal disease
PWV	= pulse wave velocity
RR	= relative risk

Table 1 Overview of Studies on the Association Between Aortic PWV and Clinical End Points

First Author, Year (Ref. #)	Population (Sample Size)	Age (yrs)	% Men	Follow-Up Duration (yrs)	Events	Modality	Distance
Anderson et al., 2009 (28)	Nondiabetic general population (n = 174)	60 ± 10	51.1	19.6	58 deaths	Doppler flow	Sternoclavicular notch to AA bifurcation
Blacher et al., 1999 (8)	ESRD (n = 241)	51.5 ± 16.3	61.0	6.0	73 deaths, 48 CV deaths	Doppler flow	Aortic arch to FA
Boutouyrie et al., 2002 (13)*	Hypertension (n = 1,045)	51 ± 12	65.0	5.7	53 coronary events, 97 CV events,	Pressure transducer (Complior)	CCA to FA
Choi et al., 2007 (25)†	Chest pain patients (n = 497)	57.7 ± 10.1	47.7	2.6	1 death, no CV deaths, 120 CV events	Fluid-filled system (right Judkins catheter)	Left subclavian artery to FA
Cruickshank et al., 2002 (14)	Diabetes (n = 394)	60 ± 10	60.0	10.7	179 deaths	Doppler flow	Sternoclavicular notch to AA bifurcation
Laurent et al., 2001 (9)*	Hypertension (n = 1,980)	50 ± 13	65.5	9.3	107 deaths, 46 CV deaths	Pressure transducer (Complior)	CCA to FA
Mattace-Raso et al., 2006 (23)	Community-based adults (n = 2,835)	71.7 ± 6.7	39.0	4.0–9.0	352 deaths, 156 CV events	Pressure transducer (Complior)	CCA to FA
Meaume et al., 2001 (10)	Subjects >70 yrs (n = 141)	87.1 ± 6.6	27.0	2.5	27 CV deaths	Pressure transducer (Complior)	CCA to FA
Mitchell et al., 2010 (30)	General population (n = 2,232)	63 ± 12	42	7.8	151 CV events	Arterial tonometry	Sternal notch to FA minus sternal notch to CCA
Pannier et al., 2005 (19)	ESRD (n = 305)	53.1 ± 16.2	62.0	5.8	96 CV deaths	Pressure transducer (Complior)	CCA to FA
Shoji et al., 2001 (11)	ESRD (n = 265)	55.4 ± 10.5	41.0	5.3	81 deaths, 36 CV deaths	PWV meter (PWV –200)	Second intercostal sternal edge to FA
Shokawa et al., 2005 (20)	Ethnic minority (n = 492)	63.7 ± 8.8	44.7	10.0	43 deaths, 14 CV deaths	Pressure transducer (MCG400)	CCA to FA
Sutton-Tyrrell et al., 2005 (21)	Community-based old adults (n = 2,488)	73.7 ± 2.9	48.0	4.6	265 deaths, 111 CV deaths, 616 CV events	Doppler flow	CCA to FA
Terai et al., 2008 (27)	Hypertension (n = 676)	62 ± 12	55.0	4.8	22 deaths, 88 CV events	Pressure transducer (FCP-4731 device)	CCA to FA minus sternal notch to CCA
Wang et al., 2010 (31)	General population (n = 1,272)	52 ± 13	53	15	225 deaths, 64 CV deaths	Doppler flow	Not reported
Willum-Hansen et al., 2006 (24)	General population (n = 1,678)	40–70	52.0	9.4	62 CV deaths, 154 CV events	Piezoelectric pressure transducers (Hellige GmbH)	CCA to FA
Zoungas et al., 2007 (26)	ESRD (n = 207)	55 ± 13	67.6	3.6	17 CV deaths, 65 CV events	Pressure transducer (Millar Mikro-tip, SPT-301)	Sternal notch to FA minus sternal notch to CCA

*Studies have a part of their population in common; the Laurent et al. (9) study (which is larger) was used for the analysis of high versus low stiffness and the Boutouyrie et al. (13) study (which provides tertiles) was used in the analysis for linear association between aortic PWV and clinical events. †Retrospective study.

AA = abdominal aorta; ABI = ankle brachial index; BMI = body mass index; BP = blood pressure; CCA = common carotid artery; CI = confidence interval; CoV = coefficient of variation; CrCl = creatinine clearance; CRP = C-reactive protein; CV = cardiovascular; CVD = cardiovascular disease; ESRD = end-stage renal disease; FA = femoral artery; Hb = hemoglobin; HR = heart rate; Ht = hematocrit; ICC = intraclass correlation coefficient; IMT = intima-media thickness; LVH = left ventricular hypertrophy; PP = pulse pressure; PWV = pulse wave velocity; RC = repeatability coefficient; ROC = receiver-operator characteristic; TC = total cholesterol.

ethnic minorities are included. Details of the individual studies are shown in Table 1. All studies were published since 1999, and the mean/median follow-up ranged from 2.5 years (10) to 19.6 years (28). The sample sizes ranged from 141 (10) to 2,835 (23) individuals.

Fourteen of the included studies assessed CV events including CV mortality (8–11,19–21,23–27,30,31). In most of those studies (n = 11), CV mortality was separately assessed. In 1 of those 11 studies (25), there were no CV

deaths during the follow-up, so this study was not introduced in the respective analysis. All-cause mortality was evaluated in 11 studies (8,9,11,14,20,21,23,25,27,28,31). Age, sex, and other risk factors for CV disease were controlled for in most of the studies (Table 1).

Shape of the association between aortic PWV and clinical events. Nine studies provided data on the risk according to strata of aortic PWV and allowed estimation of the shape of the association between aortic PWV and the risk of clinical

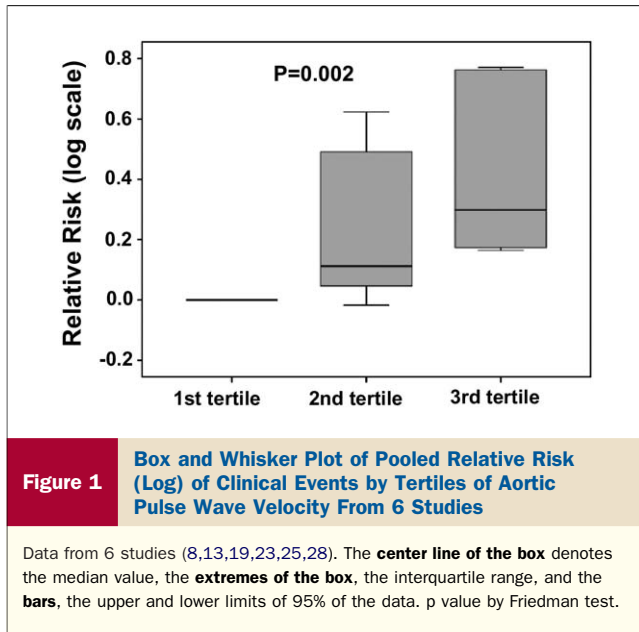
Table 1 Continued

Reproducibility	Aortic PWV in m/s (Mean ± SD)	Aortic PWV Cutoff (High vs. Low)	Aortic PWV Modeled in	Adjusted for
PWV at baseline minus PWV at 1 month: −0.02 (95% CI: −0.06 to 0.03)	10.2 ± 2.1	>10.6 m/s (upper tertile)	Continuous, tertiles	Age, sex
intraobserver variability 5.8 ± 1%	11.1 ± 3.1	>12.0 m/s (upper tertile)	Continuous; tertiles	Age, diastolic BP, sex, smoking, HR, Hb, albumin, LVH, parathormone level, antihypertensive drugs, time to dialysis
Not reported	11.5 ± 3.5	>12.3 m/s (upper tertile)	Continuous; tertiles	Framingham risk score
Not reported	Not reported	>12.5 m/s (upper tertile)	Tertiles	Age, sex, diabetes, smoking, hypertension, HR, PP, dyslipidemia
PWV at baseline minus PWV at 1 month: −0.02 (95% CI: −0.06 to 0.03)	11.6 ± 3.8	3.8-m/s increase	Continuous	Age, systolic BP, sex, diabetes duration, antihypertensive treatment
Intraobserver RC 0.935 interobserver RC 0.890	11.5 ± 3.4	5-m/s increase	Continuous	Age, previous CVD, diabetes, HR, systolic BP, PP, sex, smoking, hypercholesterolemia
Not reported	13.3 ± 2.9	>14.6 m/s in men; >14.2 m/s in women (age-specific upper tertile)	Tertiles	Age, sex, mean BP, PP, HR, ABI, carotid IMT
Reproducibility 8 ± 1%	14.2 ± 3.1	>17.7 m/s (upper decile)	Continuous; upper decile	Systolic and mean BP, previous CVD, CrCl, autonomy in movement, glucose, CRP, antihypert drugs, nitrates
Interobserver correlation coefficient 0.972	9.3 (7.8–11.8) median (interquartile range)	>9.3 m/s (median)	Continuous (inverse transform aortic PWV); quartiles	Age, sex, systolic BP, TC, high-density lipoprotein cholesterol, smoking, diabetes
Not reported	11.1 ± 3.1	Upper tertile	Continuous; tertiles	Age, PP, history of CVD, diabetes, smoking
CoV <5%	8.6 ± 2.2	>8.2 m/s (median)	Continuous; median	Age, sex, smoking, CRP, Ht, BMI, diabetes, dialysis duration, creatinine, systolic and diastolic BP, total protein
Not reported	9.7 ± 1.9	>9.9 m/s (optimal cutoff by ROC curve)	Continuous; cutoff	Age, sex, systolic BP, diabetes, hypercholesterolemia
Between sonographers ICC 0.88 Between readers ICC 0.84	9.0 ± 3.9	>8.4 m/s in men; >7.9 m/s in women (age-specific median)	Continuous; quartiles	Age, sex, race, systolic BP, CV disease, creatinine, TC, HR, ABI<0.9
Intraobserver CV 2.8 ± 1.2%	9.0 ± 0.6	>8.8 m/s (median)	Quartiles	Age, sex, smoking, diabetes, hyperlipidemia, systolic and diastolic BP, creatinine
Not reported	9.5 ± 2.3 (men) 9.5 ± 2.5 (women)	2.3 m/s increase (men); 2.5 m/s increase (women)	Continuous	Unadjusted
Intraobserver RC 9%	11.3 ± 3.4	>13.1 m/s (upper quintile)	Continuous; quintiles	Age, sex, BMI, mean BP, smoking, alcohol intake
ICC 0.95	SD 3.5	>9.9 m/s (cutoff)	Continuous; cutoff	Age, sex, systolic and diastolic BP, diabetes, CVD history, TC, smoking, carotid IMT

events. A total of 6 studies (8,13,19,23,25,28) reported risk according to tertiles, 3 studies reported risk according to quartiles (21,27,30), and 1 study reported risk according to quintiles (24) (Table 1). Analysis of the 6 studies reporting tertiles showed that the pooled RRs increase in a stepwise, linear-like fashion from the first to the third tertile (Fig. 1). **Meta-analysis.** We performed separate meta-analyses for each outcome (total CV events, CV mortality, and all-cause mortality). Pooled RRs for high versus low aortic PWV

were calculated. Furthermore, because our data indicated a linear graded association of aortic PWV with clinical events (Fig. 1), we also calculated pooled RRs for increases in aortic PWV per 1 m/s and 1 SD.

TOTAL CV EVENTS. The magnitude of risk in individuals who had high aortic PWV was significantly higher compared with the risk of individuals with low aortic PWV. The pooled RRs for high aortic PWV were 2.26 (95% CI: 1.89



to 2.70) for total CV events (Fig. 2A). The RR of total CV events for an increase in aortic PWV by 1 m/s was 1.14 (95% CI: 1.09 to 1.20), corresponding to a risk increase of 14% (Fig. 3A). Furthermore, an increase in aortic PWV by 1 SD was associated with an RR of 1.47 (95% CI: 1.31 to 1.64), corresponding to a risk increase of 47% (Fig. 4A).

Because we observed significant heterogeneity between the included studies, we conducted between-study subgroup analyses to investigate its sources. The RR for high aortic PWV was higher in high-risk populations compared with

low-risk populations (RR: 2.44; 95% CI: 2.01 to 2.97 vs. RR: 1.68, 95% CI: 1.45 to 1.96, respectively; $p = 0.003$) (Fig. 5A). The difference of RR per 1-m/s increase and per 1-SD increase was not statistically significant (Fig. 5A). Furthermore, in a population-specific analysis, we found that the RR for high aortic PWV showed a significant increase in ESRD groups and in hypertension groups compared with general population groups (RR: 2.81, 95% CI: 1.97 to 4.02 in ESRD groups vs. RR: 2.46, 95% CI: 1.93 to 3.13 in hypertension groups vs. RR: 1.68, 95% CI: 1.45 to 1.96 in general population groups; $p = 0.01$ for ESRD vs. general population groups and $p = 0.009$ for hypertension groups vs. general population groups).

CV MORTALITY. The pooled RRs of CV mortality were higher for high aortic PWV compared with low aortic PWV subjects (RR: 2.02, 95% CI: 1.68 to 2.42) (Fig. 2B). The RRs of CV mortality for an increase in aortic PWV by 1 m/s and 1 SD were 1.15 (95% CI: 1.09 to 1.21) and 1.47 (95% CI: 1.29 to 1.66) (Figs. 3B and 4B), corresponding to a risk increase of 15% and 47%, respectively. The RR for high aortic PWV was higher in high-risk populations compared with low-risk populations (RR: 2.48; 95% CI: 1.94 to 3.18 vs. RR: 1.68, 95% CI: 1.41 to 2.01, respectively; $p = 0.013$) (Fig. 5B).

ALL-CAUSE MORTALITY. The pooled RRs of all-cause mortality were higher for high aortic PWV compared with low-stiffness subjects (RR: 1.90, 95% CI: 1.61 to 2.24) (Fig. 2C). Overall, the RRs of all-cause mortality for an increase in aortic PWV by 1 m/s and 1 SD were 1.15 (95% CI: 1.09 to 1.21) and 1.42 (95% CI: 1.29 to 1.58) (Figs. 3C and 4C),

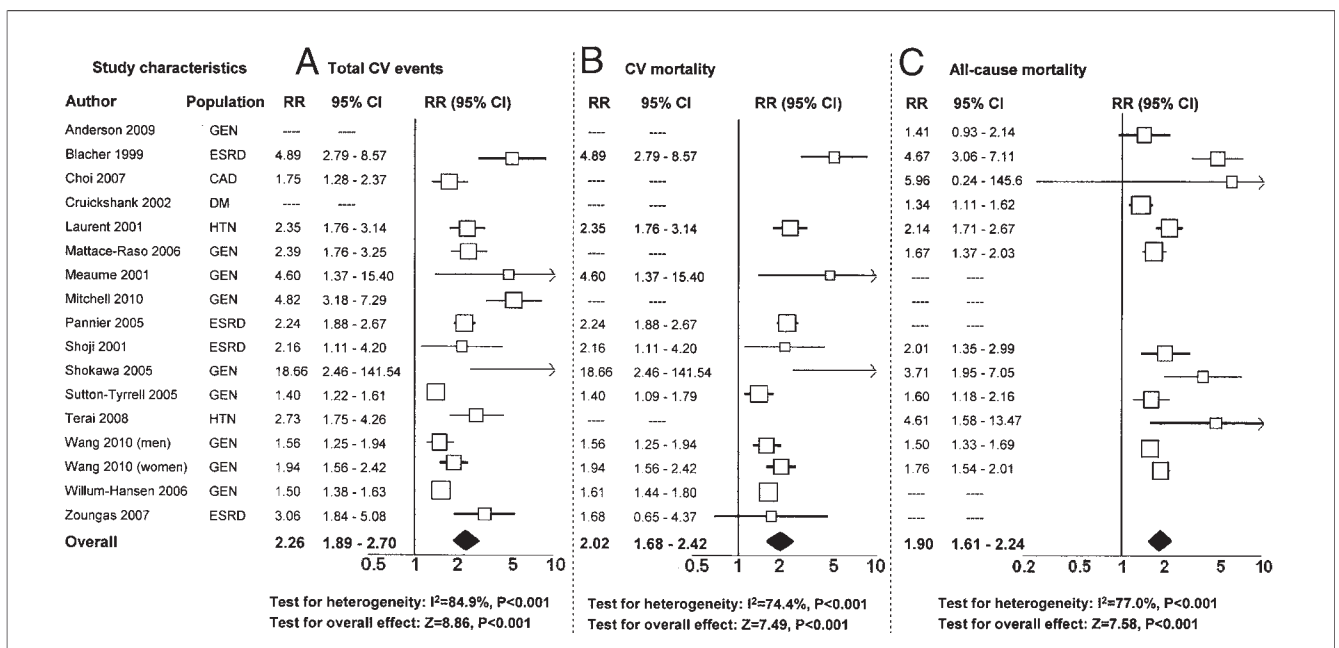


Figure 2 RR and 95% CI for High Aortic PWV and Clinical Events

Relative risk (RR) and 95% confidence interval (CI) for high aortic pulse wave velocity (PWV) and total cardiovascular (CV) events (A), CV mortality (B), and all-cause mortality (C). Studies are listed alphabetically. Boxes represent the RR and lines represent the 95% CI for individual studies. The diamonds and their width represent the pooled RRs and the 95% CI, respectively. CAD = coronary artery disease; DM = diabetes mellitus; ESRD = end-stage renal disease; GEN = general population; HTN = hypertension.

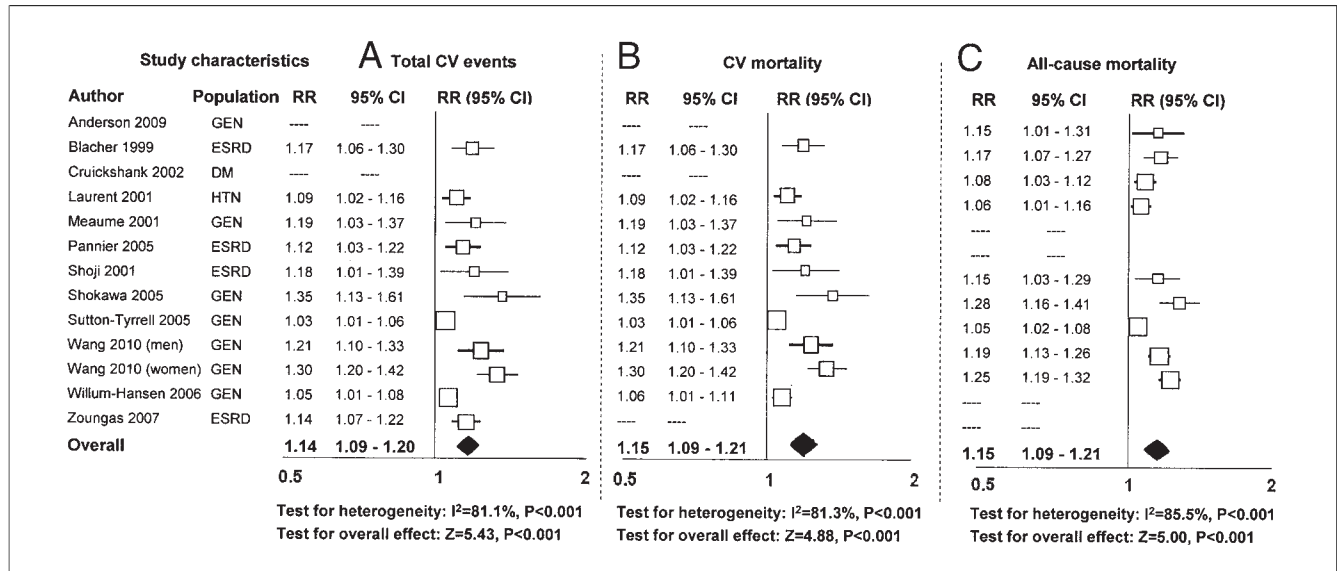


Figure 3 RR and 95% CI for a 1-m/s Increase in Aortic PWV and Clinical Events

RR and 95% CI for a 1-m/s increase in aortic PWV and total CV events (A), CV mortality (B), and all-cause mortality (C). Studies are listed alphabetically. Symbols and abbreviations as in Figure 2.

corresponding to a risk increase of 15% and 42%, respectively. The RR for high aortic PWV was nonsignificantly increased in high-risk groups compared with low-risk groups (RR: 2.43, 95% CI: 1.58 to 3.73 vs. RR: 1.66, 95% CI: 1.46 to 1.88; $p = 0.098$) (Fig. 5C), and especially in ESRD patients (RR: 3.05, 95% CI: 1.34 to 6.98).

Meta-regression analysis. We performed a meta-regression analysis to estimate the impact of continuous study moderators such as age, duration of follow-up, and baseline aortic PWV on

the overall heterogeneity. Age at enrollment was the strongest predictor of the magnitude of the log RR for outcomes in subjects with high aortic PWV, but there were differences according to the group of patients studied. In particular, age was inversely related to the predictive role of high aortic PWV for CV mortality only in ESRD patients (8,11,19,26) (Fig. 6), indicating that aortic PWV is a stronger determinant of prognosis in younger ESRD patients. In contrast, there was no relationship of age and the predictive role of aortic PWV

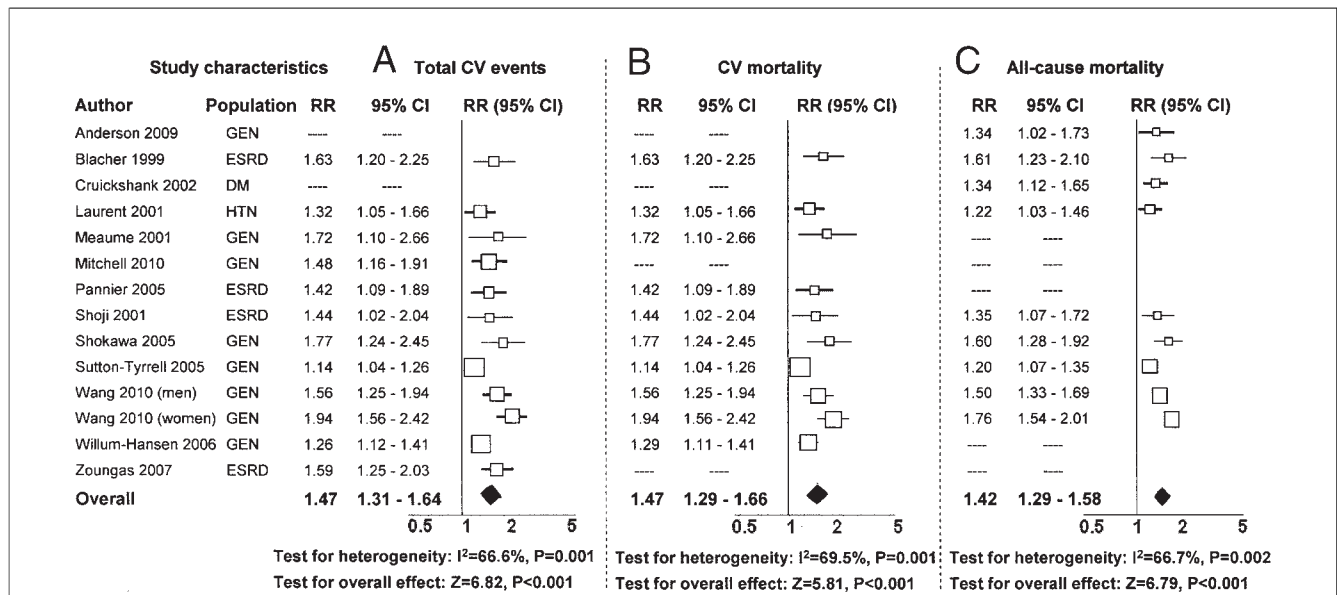


Figure 4 RR and 95% CI for a 1-SD Increase in Aortic PWV and Clinical Events

RR and 95% CI for a 1-SD increase in aortic PWV and total CV events (A), CV mortality (B), and all-cause mortality (C). Studies are listed alphabetically. Symbols and abbreviations as in Figure 2.

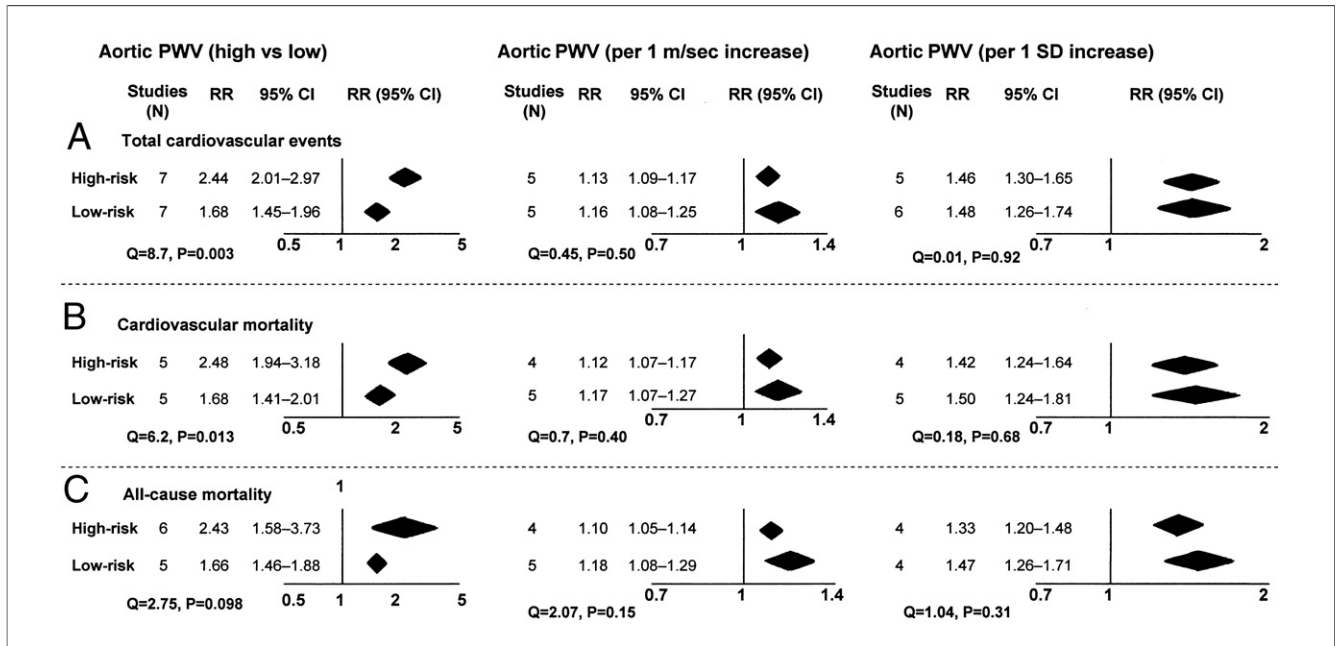


Figure 5 Pooled RR and 95% CI for Aortic PWV and Clinical Events, According to Baseline Risk

Pooled RR and 95% CI for aortic PWV and total CV events (A), CV mortality (B), and total mortality (C), according to baseline risk and disease state. The low-risk group includes studies in general population. All the other populations (see Methods) are included in the high-risk group. Data are provided for high versus low aortic pulse wave velocity (PWV) (left column), increase in aortic PWV by 1 m/s (middle column), and increase in aortic PWV by 1 SD (right column).

in hypertensive patients and in the general population subjects, indicating that stiffness retains its predictive ability independently of age in those groups. There were no consistent strong relationships between the predictive capacity of high aortic PWV and the duration of follow-up or the value of aortic PWV at enrollment.

Publication bias. STUDIES RELATING AORTIC PWV WITH COMPOSITE CV OUTCOMES (14 STUDIES, 15 COHORTS). The funnel plot was asymmetrical at the bottom (Fig. 7A, top), suggesting an absence of small studies with small or negative risk estimates in our meta-analysis, either because of publication bias or because of a true inexistence of negative studies (absence of publication bias). The trim-and-fill method im-

puted missing studies and recalculated our pooled risk estimate (Fig. 7A, bottom). The imputed RR was 1.71 (95% CI: 1.42 to 2.05), which is lower than our original risk estimate but is still a significant one. Importantly, the result of the fail-safe N test of our pooled analysis is 1,542, which is reassuring. The fail-safe N test computes the number of missing studies (with a mean effect of zero) that would need to be added to the analysis to yield a statistically nonsignificant overall effect, and it is very unlikely that there are more than 102 (1,542/15 = 102.8) unpublished or undiscovered studies for every 1 study that we found. These findings suggest that the apparent publication bias is insufficient to affect our results or interpretations in a meaningful way.

STUDIES RELATING AORTIC PWV WITH ALL-CAUSE MORTALITY (11 STUDIES, 12 COHORTS). Similarly, the funnel plot was asymmetric at the bottom (Fig. 7B, top). The trim-and-fill method showed an imputed RR of 1.65 (95% CI: 1.36 to 1.99) (Fig. 7B, bottom), which remains significant. The result of the fail-safe N test of our pooled analysis is 719, which is reassuring because it is very unlikely that there are more than 59 (719/12 = 59.9) unpublished or undiscovered studies for every 1 study that we found.

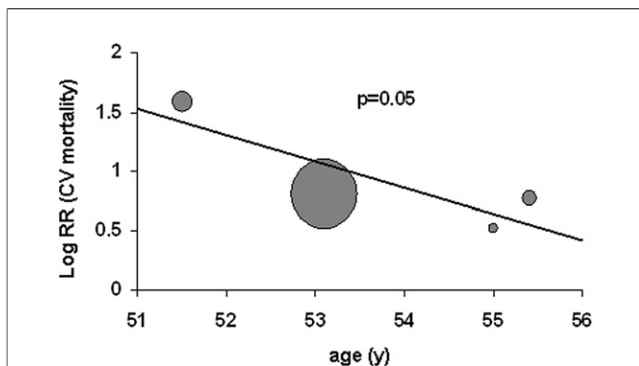


Figure 6 RR of CV Mortality in Patients With High Aortic PWV and ESRD as a Function of Age

Data from 4 studies (8,11,19,26). The size of the data markers relates to the weight of each study. Abbreviations as in Figure 2.

Discussion

In this systematic review and meta-analysis, we pooled the aortic PWV data for 15,877 subjects from 17 available published studies who were followed up for a mean of 7.7 years. Within each patient group, the risk of CV events, CV mortality, and all-cause mortality in subjects

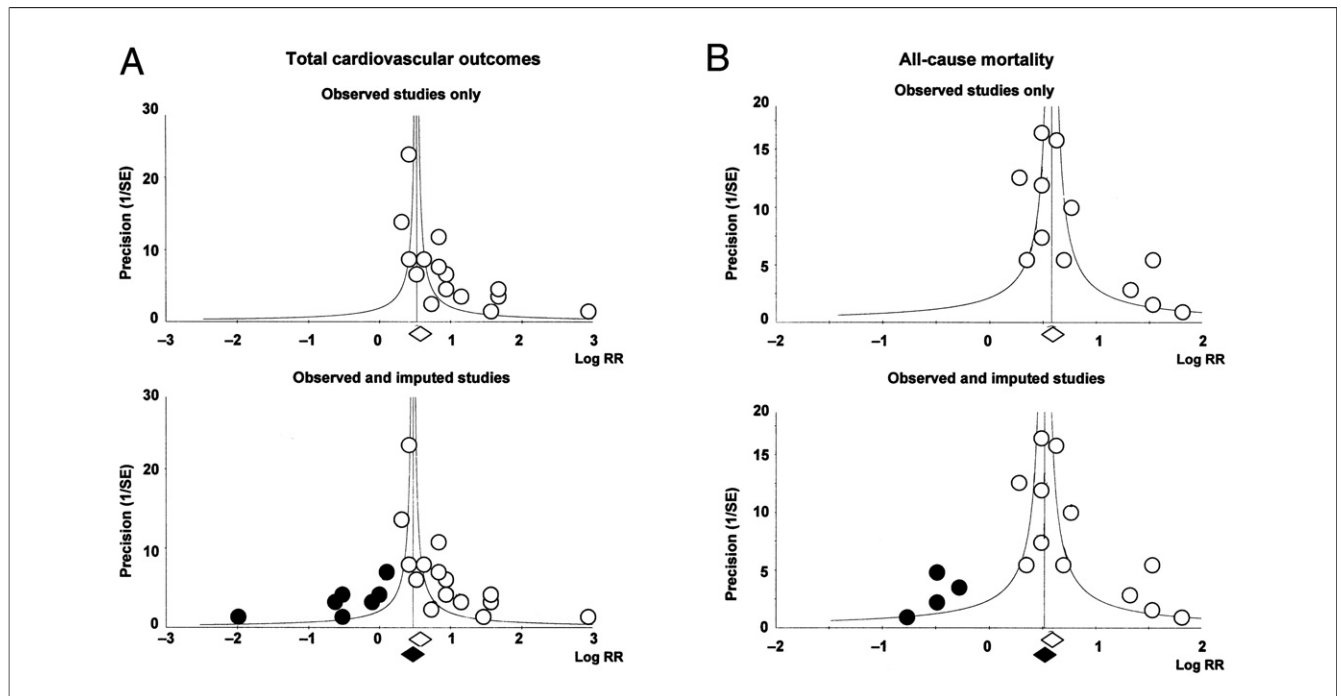


Figure 7 Publication Bias for Total CV Outcomes and All-Cause Mortality and Its Potential Impact

(A) Total CV outcomes; (B) all-cause mortality. The open circles in the top and bottom plots represent individual studies relating aortic pulse wave velocity with events, and the open diamonds are the RR and 95% CI for the meta-analysis. The solid circles in the bottom plots represent imputed studies, and the solid diamonds are the RR and 95% CI for the meta-analysis after adjusting for publication bias. Abbreviations as in Figure 2.

with increased aortic PWV, which is considered as the gold standard index of aortic stiffness, is almost twice as high compared with the risk of subjects with lower aortic PWV. Importantly, the predictive value of increased arterial stiffness is larger in patients with higher risk disease states, such as renal disease. Although for each patient group exact values may differ slightly, for an increase in aortic PWV of 1 m/s or of 1 SD, the risk increases by more than 10% or 40%, respectively.

Although some narrative reviews supporting the predictive role of arterial stiffness have been published to date (including the European guidelines for arterial hypertension that suggested aortic PWV as a tool for assessment of subclinical target organ damage) (1,2,4–7,33), the present study is the first meta-analysis to provide robust pooled estimates of this role. An important strength of our study is the exhaustive search strategy that likely enabled us to capture most, if not all, relevant studies. Furthermore, as a meta-analysis, the present study overcomes the potentially biased inclusion and weighing of results that may appear in reviews when interpreting the available evidence. Furthermore, we dealt with potential publication bias. The fact that there are not many published studies with negative results may be due to a true “universal” predictive role of aortic PWV or may reflect publication bias. Even if the latter is the case, our analysis (using 2 approaches, the trim-and-fill and fail-safe N methods) indicates that any publication bias may have accounted only for a slight overestimation of a true predictive role of aortic PWV for clinical outcomes.

The predictive value of arterial stiffness is based on its pathophysiological importance for arterial and overall CV performance (1–5). Large artery stiffening increases left ventricular afterload (1,3) and is associated with left ventricular hypertrophy (38) and impaired coronary perfusion (3,39,40). Thus, the coronary perfusion/myocardial demand equilibrium is unbalanced. Furthermore, stiffening of large arteries is involved in the pathogenesis of hypertension (1–5). Our analysis demonstrated that aortic PWV has predictive value independent of classic CV risk factors and other potential confounders. This indicates that arterial stiffness may integrate not only the effect of the genetic background (41) but also of the cumulative damage of CV risk factors on the arterial wall over a long period of time, whereas the individual risk factors can fluctuate over time and their values, recorded at the time of risk assessment, may not reflect their true impact on the arterial wall. Aortic PWV may represent a surrogate end point, which may in fact indicate in which patients the traditional CV risk factors translate into real risk.

Our findings are potentially applicable to clinical practice. First, they justify inclusion of arterial stiffness by European guidelines for arterial hypertension and suggest extension to other disease states or population groups. Our analysis showed that the risk associated with increased arterial stiffness is similar to the risk of established risk predictors commonly used in clinical practice, such as left ventricular hypertrophy (42,43). Furthermore, an important finding of our analysis is that arterial stiffness is a powerful predictor of all-cause mortality in addition to CV outcomes. Interestingly, CV mortality ac-

counted only for 50% to 55% of cases of all-cause mortality in the included studies (Table 1). Although pathophysiological explanations are not readily identifiable, this could reflect the existence of common pathogenetic mechanisms, such as aging, inflammation, and oxidative stress, over a wide range of conditions. Improvement of arterial stiffness per se is beneficial in terms of prognosis in high-risk groups (44), and our results highlight the role of arterial stiffness as a potential treatment target in broader patient groups. Further dissection of our principal finding provided interesting information. Because the populations of the enrolled studies differed with respect to baseline CV risk, population size, age distribution, and length of follow-up, we investigated the role of these factors by separate meta-analyses and by meta-regression analysis. Our analysis indicates that aortic PWV has a better ability to predict adverse outcomes in subjects with higher baseline CV risk (patients with coronary artery disease, renal disease, hypertension, or diabetes) than in subjects with presumably lower risk (general population). Although there was no difference in risk prediction/estimates in relation to age in hypertensive patients or in general population subjects, there was a better predictive ability of stiffness for clinical events in younger ESRD patients. Explanations for the latter may include a “selection” phenomenon, with ESRD survivors who reach an older age being less vulnerable to the harmful effects of arterial stiffening. It should be noted, however, that because the statistical power of our meta-regression analyses in most groups of patients was limited due to the small number of available studies, the present data may underestimate the discriminative ability of stiffness in some populations, and clearly there is need for further studies.

Our study provides interesting caveats with regard to the heterogeneity of methods used across studies measuring aortic PWV. For example, there is no universal consensus on which distance should be introduced in the PWV equation for calculations. Although some studies subtract the carotid-sternal distance from the carotid-femoral distance or the sternal-femoral distance to account for the opposite direction of flow (26,27,30), Table 1 shows that most studies use the whole distance between the 2 sites of measurement, thus leading to an overestimation of true wave velocity measured directly with invasive methods (45). Although all approaches are approximations without important impact in intervention studies with repeated measurements, when comparing populations or pooling data from different studies, differences in the methods used to assess the path length may be important (1). Less than one-half of the studies that we included adjusted for heart rate (Table 1), which determines both CV outcomes and PWV. Many studies adjusted for body mass index or weight (Table 1) because these metrics relate to both PWV and CV events. However, adjusting for waist circumference would provide perhaps more insights because this would also control for a potential overestimation of the carotid-femoral path across an enlarged abdomen in obese individuals. Accordingly, a consensus is necessary on these issues so that future studies use uniform techniques and analytical approaches. This will facilitate between-studies comparison and definition of cutoff values in different populations and will further promote the implementation of aortic PWV in everyday clinical practice. Furthermore, as aortic PWV is

the best documented and most widely used marker of arterial stiffness to date, standardization of its measurement will also facilitate comparability and validation of other emerging stiffness indexes.

Study limitations. In this analysis, we used aggregate data as reported in published articles (or calculated from other data provided in the articles) rather than data for individual patients. Accordingly, we did not deal with potential methodological problems of the original studies. Furthermore, the ability of aortic PWV to discriminate, calibrate, and reclassify risk could not be assessed. Only 2 of the included studies (23,30) provided robust estimates of the discriminatory power of aortic PWV beyond classic risk factors or measures of subclinical atherosclerosis. Second, to define high and low stiffness, we used the cutoff values used by each study because there are no established cutoffs for stiffness measurements. This may have theoretically introduced a bias factor. Reference values and cutoff points are important elements for clinical integration of arterial stiffness, and apart from published data (46–48), further studies are under way (49). Although the robustness of our principal finding (that aortic PWV is an important risk predictor) is significantly reinforced by the clear relationship of aortic PWV as a continuous variable (1-m/s or 1-SD increase) with all 3 outcomes, independent of all important confounders, we cannot with certainty rule out the role of residual confounding. Furthermore, our meta-regression findings may be limited by the small number of available studies. Finally, although CV mortality and all-cause mortality were uniformly defined, the definition of total CV events differed among the studies included in analysis.

Conclusions

Aortic PWV is a strong predictor of future CV events and all-cause mortality. The predictive ability of arterial stiffness is higher in subjects with a higher baseline CV risk. These findings support implementation of aortic PWV into clinical practice and stress the need to establish reference values.

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