Hypertension

ORIGINAL ARTICLE

End Point–Based Threshold for the Ambulatory Arterial Stiffness Index

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BACKGROUND: The ambulatory arterial stiffness index (AASI) is increasingly used in clinical research and practice. This individual-participant meta-analysis aims to consolidate the prognostic accuracy of AASI in the general population and to derive an end point–based AASI risk threshold.

METHODS: In 12 558 individuals enrolled in 14 population studies (48.8% women; mean age, 59.3 years), AASI was derived by regressing 24-hour diastolic on systolic blood pressure (mm Hg/mm Hg). Using Cox regression, the risk-carrying AASI threshold was established by examining stepwise increasing AASI levels and by determining the AASI level, yielding a 10-year risk similar to an office systolic pressure of 140 mm Hg.

RESULTS: Over 10.7 years (median), 3027 all-cause deaths and 2183 cardiovascular end points occurred. In all participants, multivariable-adjusted hazard ratios expressing the all-cause deaths and cardiovascular end point risk per 1-SD AASI increment were 1.08 (95% CI, 1.04–1.13) and 1.13 (95% CI, 1.07–1.18). In a randomly defined subset of 8189 individuals, the risk-carrying AASI thresholds converged to 0.50 with hazard ratios (≥0.50 versus <0.50) of 1.14 (95% CI, 1.04–1.26) for all-cause deaths and 1.13 (95% CI, 1.01–1.26) for cardiovascular end point. In the replication sample (n=4369), these hazard ratios were 1.13 (95% CI, 1.01–1.26) and 1.19 (95% CI, 1.04–1.35). AASI continuous or per threshold significantly improved model performance. Analyses of secondary end points and subgroups stratified by sex, age, hypertension status and treatment, history of cardiovascular disease, and nocturnal dipping were confirmatory.

CONCLUSIONS: Over and beyond traditional risk factors, AASI improves risk stratification. Exceeding the risk-carrying 0.50 AASI threshold necessitates increased vigilance in managing risk factors before irreversible cardiovascular complications occur. ***(Hypertension.* 2025;83:00–00. DOI: 10.1161/HYPERTENSIONAHA.125.25442.)** • **Supplement Material**.

Key Words: blood pressure ■ cardiovascular diseases ■ morbidity ■ mortality ■ vascular stiffness

Over the human lifespan, aging and age-related risk factors lead to stiffening of the central elastic arteries.[1,2] Aortic pulse wave velocity (PWV) is the gold standard for the noninvasive assessment of central arterial stiffness[3] and integrates a large panel of traditional risk factors into a single comprehensive measurement.[1–4] On top of risk factors, PWV is an independent predictor of mortality and cardiovascular complications in

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.125.25442.
For Sources of Funding and Disclosures, see page XXX.

Hypertension is available at www.ahajournals.org/journal/hyp

ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

Over 200 articles support the ambulatory arterial stiffness index (AASI) as a predictor of adverse health outcomes. However, the proposed AASI risk thresholds cannot be generalized because, generated in selected patients, they are researcher-defined. This individual-participant meta-analysis of 14 randomly selected population cohorts (n=12 588) aimed to consolidate the prognostic accuracy of AASI and to derive an end point–based risk threshold. End points were analyzed by comprehensively adjusted Cox models.

What Is Relevant?

Over 10.7 years of follow-up, mortality (n=3027) and cardiovascular complications (n=2183) increased by 8% and 13% per 1-SD AASI increments.
Across AASI quartiles, hazard ratios significantly increased from 0.98 to 1.13 for mortality and from 0.92 to 1.15 for the cardiovascular end points.
In the randomly defined derivation data set (n=8189), the risk-carrying AASI thresholds converged to 0.50 and were reproduced in the replication data set (n=4369).
AASI continuously and per 0.50 threshold refined models and risk prediction.
Analyses of secondary end points and subgroups were confirmatory.

Clinical/Pathophysiological Implications?

AASI improves risk stratification in an unbiased study sample, representative of the general population. Given the ethnic and regional diversity of the current study population, generalizability is high. Exceeding the risk-carrying 0.50 AASI threshold necessitates vigilance in managing risk factors underlying arterial stiffening for the timely prevention of cardiovascular complications.

Nonstandard Abbreviations and Acronyms

AASI	ambulatory arterial stiffness index
BP	blood pressure
HDL	high-density lipoprotein
HR	hazard ratio
IDACO	International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome
IDI	integrated discrimination improvement
MAP	mean arterial pressure
NRI	net reclassification improvement
PWV	aortic pulse wave velocity
R_MAP	residual of mean arterial pressure regressed on ambulatory arterial stiffness index
SPARTE	Strategy for Preventing Cardiovascular and Renal Events Based on Arterial Stiffness

patients with hypertension, diabetes, or chronic kidney disease and in the general population.[1–4]

In 2006, studies in China[5] and Europe[5,6] simultaneously introduced the ambulatory arterial stiffness index (AASI) as a noninvasive measure of arterial stiffness. The underlying concept, already proposed in 1914,[7] was that loss of arterial elasticity influences the height of diastolic blood pressure (BP) and its relation to systolic BP. AASI was computed from individual 24-hour ambulatory BP recordings as 1 minus the regression slope of diastolic on systolic BP; higher AASI reflects greater arterial stiffness. In multivariable-adjusted analyses of 11 291 Irish patients, followed for 5.3 years, AASI predicted cardiovascular mortality.[6] A PubMed search without language limitations identified 228 articles published from 2006 to March 2025 with the ambulatory arterial stiffness index in the title or abstract. A systematic review detected 13 relevant outcome studies published up to July 31, 2023, including 28 855 adult patients, followed up from 2.2 to 15.2 years.[8] The relative risk ratios ranged from 1.07 to 1.57 and were significant for total mortality, major cardiovascular complications, and stroke.[8] However, the AASI thresholds used for risk stratification were researcher-defined and derived in highly selected patients.[8] To enhance the clinical applicability of AASI, the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO)[9,10] was analyzed to firmly establish, in an individual-person meta-analysis of 14 population studies, the association of adverse health outcomes with AASI and to determine and replicate an end point–based AASI threshold.

METHODS

Data Availability

All available data are shown within this article and the Supplemental Material. Anonymized individual data are available from the corresponding author upon request, on condition that an analysis plan is submitted along with the request

and that the principal investigators of all IDACO cohorts and the local institutional review boards approve data sharing. Informed consent given by study participants did not include data sharing with third parties. Anonymized data can be made available to investigators for targeted noncommercial research based on a motivated request to be submitted to J.A.S. and pending ethical clearance by each of the 14 participating centers.

Study Cohorts

All included studies adhered to the principles of the Declaration of Helsinki[11] and received ethics approval from the competent institutional review boards in their country of origin. Ethics clearance for the secondary use of anonymized data was waived. Participants gave written informed consent. Previous publications describe the IDACO database in detail.[9,10] Population studies qualified for inclusion if information on office and ambulatory BP and cardiovascular risk factors was available at baseline and if follow-up included both fatal and nonfatal outcomes. Of the 17 003 people included in the database, 4445 were excluded because they were aged <30 years and healthy without arterial stiffness[12] (n=2016), because their ambulatory BP recording included fewer than 8 daytime and 4 nighttime readings (n=2069), or because the correlation between the 24-hour systolic and diastolic ambulatory BP was not significant so that AASI could not be reliably derived (n=360). Thus, the number of individuals statistically analyzed was 12 558. The Supplemental Methods (pages S2 and S3 in the Supplemental Material) and Table S1 provide detailed information on the population sampling methods, timelines, and country of recruitment.

BP and Arterial Properties

Nurses or physicians measured office BP with a standard mercury sphygmomanometer or with validated auscultatory or oscillometric devices.[13–21] Hypertension was a 24-hour ambulatory BP of ≥130-mm Hg systolic or ≥80-mm Hg diastolic or the use of antihypertensive drugs.[22] For ambulatory BP monitoring (Table S2), portable monitors were programmed to obtain BP readings at 30-minute intervals during the whole day or at intervals of 15 to 30 minutes during daytime and ranging from 20 to 60 minutes during nighttime. Using time-weighted robust regression, AASI was computed from individual 24-hour ambulatory BP recordings as 1 minus the regression slope of diastolic on systolic BP (Figure S1; Video).[6,23] Subtracting the regression slope from unity ensures that AASI and other measures of arterial stiffness have the same sign in relation to various determinants of arterial function.[24] The regression model included an intercept because diastolic BP remains above zero even at minimal diastolic blood flow.[25]

A substudy of 888 individuals, nested within IDACO, was allowed to explore the concordance between PWV and AASI. Aortic PWV was measured by sequential electrocardiographically gated recordings of the arterial pressure waveform at the carotid and femoral arteries.[4] Pulse wave travel distance was the distance from the suprasternal notch to the femoral sampling site minus the distance from the suprasternal notch to the carotid sampling site. Pulse transit time was the average of 10 consecutive heartbeats. PWV is the ratio of the travel distance in meters to transit time in seconds.

Ascertainment of End Points

Vital status and the incidence of fatal and nonfatal end points were obtained from the appropriate sources in each country. All end points were prespecified and coded according to the *International Classification of Diseases*. The Supplemental Methods (page S4 in the Supplemental Material) lists the *International Classification of Diseases* codes for each end point.

The coprimary end points were total mortality and a composite cardiovascular end point consisting of cardiovascular mortality combined with nonfatal cardiac end points, heart failure, and stroke. Secondary end points included cardiovascular mortality, cardiac events (death from ischemic heart disease, sudden death, nonfatal myocardial infarction, coronary revascularization, and heart failure), and stroke, not including transient ischemic attack. In all outcome analyses, only the first event within each category was considered.

Statistical Analysis

The Supplemental Methods (pages S5–8 in the Supplemental Material) include an in-depth description of the statistical methods. Absolute risk was assessed from the cohort-sex-age–specific (<50, 50–69, and ≥70 years) incidence rates of end points standardized by the direct method[26] and relative risk from hazard ratios (HRs) obtained by proportional hazard regression. The basic adjustment of the HRs accounted for cohort (random effect), sex, age, body mass index, and mean arterial pressure (MAP). However, given the significant correlation between AASI and MAP, the covariable introduced in the Cox models to represent the BP level was the residual of MAP regressed on AASI (R_MAP) (Figure S2). Extended adjustment additionally accounted for heart rate, smoking (0, 1) and drinking (0, 1), the total-to-HDL (high-density lipoprotein) serum cholesterol ratio, antihypertensive drug treatment, diabetes, and history of cardiovascular disease. To compare the relative risk across quartiles of AASI, the deviation-from-mean-coding was applied.[27] This approach avoids defining an arbitrary reference group and generates 95% CIs for all strata in the analysis. In Cox models including AASI as a continuously distributed variable, HRs expressed the relative risk per 1-SD increment. The number of imputed covariables is listed by cohort in Table S3 and represents only 0.62% of the total data space (minus race, sex, and BP). The proportional hazards assumption was checked by the Kolmogorov-type supremum test.

After stratification for sex, age (<50, 50–69, and ≥70 years), and cohort (Table S1), a random function was applied to subdivide the total IDACO study population (n=12 558) into a discovery (n=8189) and replication (n=4369) data set. The default significance throughout the current study was a 2-tailed α-level of ≤0.05 with the z-value to compute 2-sided CIs set at 1.96. However, given the prior probability in the discovery data set, in the replication analysis, the α-level was 1-tailed with the z-value set at 1.65.

To determine an operational threshold for AASI in the discovery data set, a 2-pronged strategy was applied using Cox regression.[4,28] First, multivariable-adjusted HRs were computed for 0.01-mm Hg/mm Hg AASI increments from the 20th to the 80th percentile of the AASI distribution. These HRs express the risk in participants, whose AASI exceeded the stepwise increasing cutoff point versus the risk in those below the cutoff

point. The HRs with 95% CI were plotted as a function of increasing AASI thresholds to assess at which AASI level the lower 95% confidence limit of the HRs consistently crossed unity, indicating significantly increased risk. Next, AASI thresholds were obtained by determining the AASI levels yielding a 10-year risk equivalent to the risk associated with an office systolic BP of 120, 125, 130, and 140 mm Hg. Model calibration was evaluated by comparing the predicted risk against overoptimism-corrected Kaplan-Meier estimates across AASI quintiles.[29] In the subgroup (n=888), who had both PWV and AASI measured, concordance between the 2 vascular indices was studied by correlation analysis and by running a κ statistic to assess concordance in categorizing participants as having increased arterial stiffness, using thresholds ≥9 m/s for PWV[4] and ≥0.50 for AASI.

Performance of AASI and R_MAP in risk stratification was assessed using nested Cox models and the log-likelihood test, the C-index, the integrated discrimination improvement (IDI), and net reclassification improvement (NRI) indexes.[30] Finally, in subgroup analyses, the results for the coprimary end points were dichotomized by sex, age, ambulatory hypertension, antihypertensive treatment, previous cardiovascular disease, dipping status, and reduced estimated glomerular filtration rate (<60 mL/min per 1.73 m^2).[31–33] A sensitivity analysis excluded one cohort at a time to ascertain that no study had an unduly disproportionate influence on the HRs.

RESULTS

Baseline Characteristics of Participants

Table 1 lists the main characteristics of the 12558 participants. Women represented 48.8% of the total study population. Mean age was 59.3 (SD, 13.3) years, and median age was 61.6 (interquartile range, 49.4–70.9) years. Table S2 lists the number of 24-hour ambulatory BP readings by center. The 24-hour ambulatory BP averaged 124.3-mm Hg systolic and 74.0-mm Hg diastolic. The number of participants with ambulatory hypertension amounted to 6373 (50.8%), of whom 3596 (56.4%) were on antihypertensive drug treatment. AASI averaged 0.43 (SD, 0.17) mm Hg/mm Hg (Table 1). Median AASI was 0.43 (interquartile range, 0.32–0.55) mm Hg/mm Hg. Considering other risk factors (Table 1), 2986 (23.8%) participants were smokers, 7118 (56.7%) reported habitual alcohol intake, 1331 (10.6%) had diabetes, and 1676 (13.4%) reported a history of cardiovascular disease.

The random categorization of participants in the discovery (n=8189) and replication (n=4369) data sets (Table 1) produced 2 samples without any significant between-group difference ($0.10 \le P \le 0.83$). Across increasing quartiles of AASI (Table S4), risk factors increased in magnitude or prevalence ($P \le 0.053$). The correlation coefficients between the measures derived from the ambulatory recordings ($-0.043 \le r \le 0.985$) were significant ($P < 0.001$), but R_MAP was uncorrelated with AASI ($r < 0.001$; $P = 0.99$; Table S5).

Primary End Points

Analysis of All Participants

Median follow-up of the whole study population was 10.7 (fifth to 95th percentile interval, 3.6–25.8) years, and across cohorts (Table S1) ranged from 4.0 (3.5–7.6) to 24.6 (7.7–28.4) years. Over 154998 person-years of follow-up (Table S6), 3027 participants died (19.5 per 1000 person-years), and 2183 experienced the coprimary cardiovascular end point (14.9 per 1000 person-years). The events contributing to the primary and secondary end points are given in Table S6. Across increasing AASI quartiles (Table 2), the standardized mortality rate increased from 9.4 (95% CI, 9.2–9.7) to 29.6 (95% CI, 29.2–30.3) deaths per 1000 person-years and the standardized incidence of the cardiovascular end point from 7.8 (95% CI, 7.6–8.1) to 25.4 (95% CI, 25.0–26.1) events per 1000 person-years ($P < 0.001$). In all models, AASI met the proportional hazard assumption (test statistic, ≤0.76; $P \ge 0.32$). In Cox regression (Figure S3), with adjustments applied for cohort, sex, and age, the cumulative incidence of the coprimary end points confirmed the trends in the standardized rates, as reported in Table 2. With basic adjustments applied, the HRs expressing risk per 1-SD increment in AASI were 1.07 (95% CI, 1.02–1.12) for total mortality and 1.12 (95% CI, 1.07–1.18) for the cardiovascular end point (Table 3). With extended adjustment, these HRs were 1.08 (95% CI, 1.04–1.13) and 1.13 (95% CI, 1.07–1.18), respectively. A further categorical analysis in all participants assessed the risk across AASI quartiles relative to the average risk in the whole population (Table S7) and produced confirmatory results for both coprimary end points with a significant gradient ($P \le 0.002$) from HRs lower than unity in the lowest AASI category to HRs greater than unity in the highest AASI quartile, indicating greater risk of death or a cardiovascular end point with higher arterial stiffness.

Analysis of the Discovery Data Set

To determine an end point–based AASI threshold, first, multivariable-adjusted HRs for total mortality (Figure 1A) and the coprimary cardiovascular end point (Figure 1B) were plotted against AASI levels increasing by 0.01 steps over the 20th to 80th percentile range of the AASI distribution. These multivariable-adjusted HRs express the 10-year risk of the coprimary end points in the discovery cohort (n=8189) associated with stepwise increasing AASI thresholds relative to the risk below these thresholds. The lower 95% confidence limit of the HRs crossed unity, indicating significantly increased risk, at AASI levels of 0.51 and 0.50 for total mortality and the cardiovascular end point, respectively. In the second step of the analysis, AASI thresholds yielding 10-year multivariable-adjusted risk equivalent to that associated with levels of systolic office BP, ranging from 120 mm Hg (elevated BP) up to 140 mm Hg (hypertension) according to the

Table 1. Baseline Characteristics of Participants

Characteristics	Discovery	Replication	All
No. in group	8189	4369	12558
No. with characteristic, %			
Ethnicity			
Europeans	5424 (66.2)	2897 (66.3)	8321 (66.3)
Asians	1522 (18.6)	811 (18.6)	2333 (18.6)
South Americans	1243 (15.2)	661 (15.1)	1904 (15.2)
Women	3995 (48.8)	2132 (48.8)	6127 (48.8)
Ambulatory hypertension	4133 (50.5)	2240 (51.3)	6373 (50.8)
Treated hypertension	2382 (57.4)	1214 (54.5)	3596 (56.4)
Diabetes	862 (10.5)	469 (10.7)	1331 (10.6)
History of cardiovascular disease	1082 (13.2)	594 (13.6)	1676 (13.4)
Smokers	1968 (24.0)	1018 (23.3)	2986 (23.8)
Drinkers	4619 (56.4)	2499 (57.2)	7118 (56.7)
Mean of characteristic (SD)			
Age, y	59.3 (13.3)	59.4 (13.3)	59.3 (13.3)
Body mass index, kg/m^2	26.0 (4.4)	26.0 (4.4)	26.0 (4.4)
Total serum cholesterol, mmol/L	5.49 (1.12)	5.49 (1.12)	5.49 (1.12)
HDL serum cholesterol, mmol/L	1.37 (0.38)	1.37 (0.38)	1.37 (0.38)
Total-to-HDL serum cholesterol ratio	4.26 (1.41)	4.29 (2.55)	4.27 (1.88)
BP and heart rate			
Office systolic BP, mm Hg	134.5 (22.0)	135.0 (22.8)	134.7 (22.3)
Office diastolic BP, mm Hg	80.4 (11.6)	80.7 (11.8)	80.5 (11.7)
24-h systolic BP, mm Hg	124.2 (13.9)	124.5 (14.1)	124.3 (14.0)
24-h diastolic BP, mm Hg	74.0 (8.5)	74.1 (8.4)	74.0 (8.5)
24-h MAP, mm Hg	94.1 (9.9)	94.3 (9.9)	94.1 (9.9)
24-h pulse pressure, mm Hg	50.2 (9.9)	50.4 (10.0)	50.3 (10.0)
24-h heart rate, bpm	71.1 (9.3)	71.0 (9.2)	71.1 (9.3)
AASI, mm Hg/mm Hg	0.43 (0.17)	0.43 (0.17)	0.43 (0.17)
Median follow-up (IQR), y	10.6 (6.4–17.1)	10.8 (6.4–17.2)	10.7 (6.4–17.1)

Body mass index is weight in kilogram divided by height in meter squared. Hypertension is a 24-h ambulatory blood pressure of ≥130-mm Hg systolic or ≥80-mm Hg diastolic or the use of antihypertensive drugs. MAP is diastolic BP plus 40% of pulse pressure. Diabetes is a self-reported diagnosis, use of antidiabetic drugs, fasting blood glucose ≥7 mmol/L (≥126 mg/dL), random blood glucose ≥11.1 mmol/L (≥200 mg/dL), or diabetes documented in practice or hospital records. Smoking is the use of smoking materials on a daily basis. Use of alcohol is the habitual consumption of alcoholic beverages daily or weekly. Significance of the difference in the characteristics between the discovery and replication sample: $0.10 \leq P \leq 0.83$. AASI indicates ambulatory arterial stiffness index; BP, blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; and MAP, mean arterial pressure.

2024 guideline published by the European Society of Cardiology. The AASI levels increased with higher systolic BP and at the hypertension threshold reached 0.45 (95% CI, 0.43–0.46) for total mortality (Figure 1C) and 0.45 (95% CI, 0.43–0.47) for the coprimary cardiovascular end point (Figure 1D). The AASI thresholds differentiating low from high risk of the 2 primary end points were rounded to 0.50. The HRs contrasting high (≥0.50) versus low (<0.50) AASI were 1.11 (95% CI, 1.01–1.22) for total mortality and 1.13 (95% CI, 1.01–1.26) for the cardiovascular end point (Table 3). With extended adjustment, the corresponding HRs were 1.14 (95% CI, 1.04–1.26) and 1.13 (95% CI, 1.01–1.26), respectively. The models using 0.50 as a threshold were well calibrated for total mortality (Figure 1E) and the coprimary cardiovascular end point (Figure 1F). Notably, in the continuous analyses, the multivariable-adjusted HRs were not materially different in the discovery data set and in all participants (n=12558).

Analysis of the Replication Data Set

The continuous analysis (1-SD AASI increment) and the categorical analysis (AASI ≥0.50 versus <0.50) of the replication data set (n=4369), irrespective of adjustment, replicated the HRs observed in the discovery data set (Table 3).

Table 2. Cohort-Sex-Age-Standardized Incidence of End Points by Quartiles of the Ambulatory Arterial Stiffness Index

End points	Quartiles of the ambulatory arterial stiffness index				
	Q1	Q2	Q3	Q4	*P* value
Quartile limits, mm Hg/mm Hg	≤0.31	0.32–0.42	0.43–0.54	≥0.55	
No. of participants	3188	3070	3205	3095	
Primary end points					
Total mortality					
No. of deaths	365	678	952	1032	
Rate (per 1000 person-years)	9.4 (9.2–9.7)	16.7 (16.4–17.1)	23.9 (23.5–24.4)	29.6 (29.2–30.3)	<0.001
Cardiovascular end points					
No. of end points	278	479	659	767	
Rate (per 1000 person-years)	7.8 (7.6–8.1)	13.6 (13.4–14.0)	19.7 (19.3–20.3)	25.4 (25.0–26.1)	<0.001
Secondary end points					
Cardiovascular mortality					
No. of deaths	119	227	355	391	
Rate (per 1000 person-years)	3.1 (3.0–3.4)	5.8 (5.7–6.1)	9.3 (9.2–9.7)	11.4 (11.2–11.9)	0.038
Coronary end points					
No. of end points	188	277	395	517	
Rate (per 1000 person-years)	4.9 (4.8–5.2)	7.9 (7.8–8.3)	11.1 (10.9–11.4)	15.9 (15.6–16.5)	0.003
Stroke					
No. of strokes	103	217	287	297	
Rate (per 1000 person-years)	2.9 (2.8–3.1)	5.6 (5.5–5.8)	8.3 (7.9–8.8)	9.2 (9.1–9.7)	0.29

The analysis includes 12 558 participants. Rates are standardized by the direct method and are given with 95% CI. The *P* value is for the trend across quartiles.

Model Performance

Model performance was examined in all participants (n=12 558). For total mortality and the cardiovascular end point, adding AASI, 24-hour R_MAP, or both to the base model, including all other covariables, refined the models as evidenced by the 2 log-likelihood statistic and both NRI and IDI (Table 4). If both AASI and 24-hour R_MAP were added to the base model, NRI was 13.6% (95% CI, 6.32%–17.9%) for total mortality and 17.9% (95% CI, 13.0%–20.5%) for the coprimary cardiovascular end point, while IDI amounted to 0.43% (95% CI, 0.15%–0.90%) and 1.43% (95% CI, 0.98%–2.07%), respectively. Figure 2 shows the AUC for total mortality and the cardiovascular end point as a function of follow-up time for 3 models: (1) the base model including all covariables, (2) the base model extended by 24-hour R_MAP, and (3) the base model extended by 24-hour R_MAP and AASI. For total mortality (Figure 2A) and the coprimary cardiovascular end points (Figure 2B), the full model including both AASI and R_MAP, compared with the base model, increased (P<0.001) the AUC. For total mortality (Figure 2A), the AUC increase was similar for the base model extended by R_MAP or both R_MAP and AASI, whereas, for the cardiovascular end point, the AUC increase was greater for adding both R_MAP and AASI to the base model than for adding R_MAP only (P=0.019).

Subgroup and Sensitivity Analyses

Dichotomization of AASI by the 0.50-mm Hg/mm Hg threshold confirmed the trend observed across AASI quartiles (Table S4) in that with higher AASI category, risk factors increased. Table S8 shows that participants with AASI ≥0.50 mm Hg/mm Hg (n=4315) had a higher risk profile than those with AASI <0.50 mm Hg/mm Hg (n=8243).

Compared with the data in Table 3, HRs for total mortality and the coprimary cardiovascular end point in relation to the AASI that analyzed a continuous variable were consistent across subgroups stratified by age, sex, the presence of ambulatory hypertension, use of antihypertensive drugs, history of cardiovascular disease, or dipping status (Figure S4). The interaction between AASI and reduced estimated glomerular filtration rate on the coprimary cardiovascular end point was nonsignificant ($P_{interaction}$=0.08; Figure S4), but this finding must be cautiously interpreted given the amount of data imputation (33.3%). None of the cohorts had a disproportionate influence on the HRs (Table S9).

A subgroup analysis relating AASI to PWV included 888 individuals (Figure S5). The unadjusted correlation coefficient of AASI with PWV was 0.22 (P<0.001). With cumulative adjustment for cohort, sex, age, heart rate, and body height, the partial correlation coefficient was 0.085 (P=0.011). Using 9 m/s and 0.50 mm Hg/mm Hg

Table 3. Primary End Points in Relation to AASI Analyzed as Continuously Distributed Variable and per Threshold

	Unadjusted		Basic adjustment		Extended adjustment	
Data set: end point (number of end points)	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All participants (n=12 558)						
Total mortality (n=3027)						
AASI (+1 SD)	1.29 (1.24–1.35)	<0.001	1.07 (1.02–1.12)	0.005	1.08 (1.04–1.13)	<0.001
AASI ≥0.50 vs <0.50 mm Hg/mm Hg	1.49 (1.38–1.61)	<0.001	1.12 (1.04–1.21)	0.004	1.13 (1.05–1.22)	0.002
Cardiovascular end points (n=2183)						
AASI (+1 SD)	1.30 (1.24–1.36)	<0.001	1.12 (1.07–1.18)	<0.001	1.13 (1.07–1.18)	<0.001
AASI ≥0.50 vs <0.50 mm Hg/mm Hg	1.45 (1.32–1.59)	<0.001	1.16 (1.06–1.26)	0.002	1.14 (1.04–1.25)	0.004
Discovery data set (n=8189)						
Total mortality (n=1987)						
AASI (+1 SD)	1.29 (1.23–1.36)	<0.001	1.07 (1.01–1.13)	0.015	1.10 (1.04–1.16)	0.002
AASI ≥0.50 vs <0.50 mm Hg/mm Hg	1.45 (1.31–1.60)	<0.001	1.11 (1.01–1.22)	0.031	1.14 (1.04–1.26)	0.007
Cardiovascular end points (n=1433)						
AASI (+1 SD)	1.31 (1.24–1.39)	<0.001	1.14 (1.07–1.21)	<0.001	1.14 (1.07–1.22)	<0.001
AASI ≥0.50 vs <0.50 mm Hg/mm Hg	1.42 (1.27–1.59)	<0.001	1.13 (1.01–1.26)	0.032	1.13 (1.01–1.26)	0.035
Replication data set (n=4369)						
Total mortality (n=1040)						
AASI (+1 SD)	1.30 (1.23–1.38)	<0.001	1.07 (1.00–1.14)	0.052	1.07 (1.01–1.15)	0.033
AASI ≥0.50 vs <0.50 mm Hg/mm Hg	1.57 (1.41–1.76)	<0.001	1.15 (1.03–1.28)	0.021	1.13 (1.01–1.26)	0.034
Cardiovascular end points (n=750)						
AASI (+1 SD)	1.28 (1.20–1.37)	<0.001	1.11 (1.03–1.19)	0.011	1.11 (1.03–1.19)	0.010
AASI ≥0.50 vs <0.50 mm Hg/mm Hg	1.52 (1.33–1.74)	<0.001	1.21 (1.06–1.37)	0.008	1.19 (1.04–1.35)	0.016

Unadjusted models account for the cohort (random effect). Basic adjustment also accounts for sex, age, body mass index, and the residual of mean arterial pressure regressed on AASI. Extended adjustment additionally considers heart rate, smoking and drinking, the total-to-high-density-lipoprotein serum cholesterol ratio, antihypertensive drug treatment, diabetes, and history of cardiovascular disease. AASI indicates ambulatory arterial stiffness index; and HR, hazard ratio.

as PWV and AASI thresholds, possibly indicating arterial stiffening (Figure S5), the classification was concordant in 627 individuals (70.6%) and discordant in 261 (29.4%). The κ statistic was 0.153 (95% CI, 0.082–0.223), indicating slight agreement.

Secondary End Points

Over follow-up, 1092 cardiovascular deaths (7.0 per 1000 person-years), 1377 cardiac end points (9.2 per 1000 person-years), and 904 strokes (6.0 per 1000 person-years) occurred (Table 2). Across increasing AASI quartiles, rates of the secondary end points increased (Table S7). In Cox models, sparsely adjusted for cohort or with basic and extended adjustment applied, the secondary outcomes were related to AASI, irrespective of whether AASI was analyzed as a continuously distributed variable or per the 0.50 threshold (Table S10). Although all HRs were directionally consistent with higher risk being associated with greater AASI, some multivariable-adjusted HRs in the discovery and replication data sets did not reach formal significance, given the lower number of end points and the smaller sample size. On top of the base model (Figure S6), AASI refined the models for the cardiac end point but not for cardiovascular mortality (P=0.38) and stroke (P=0.69). However, AASI combined with R_MAP refined the models for the 3 secondary end points (Table S11), resulting in NRI values, of 19.7% (95% CI, 15.0%–24.5%) for cardiovascular mortality, 14.2% (95% CI, 10.1%–18.9%) for the cardiac end point, and 18.7% (95% CI, 14.7–23.4) for stroke (P<0.001 for all). The corresponding IDI levels were 1.13% (95% CI, 0.60%–1.95%), 1.01% (95% CI, 0.47%–1.65%), and 0.89% (95% CI, 0.32%–1.53%), respectively (P<0.001 for all).

DISCUSSION

The key findings of the current study can be summarized as follows. First, AASI, as a continuously distributed variable, refines risk stratification for a wide range of end points, including both fatal and nonfatal outcomes. Second, in support of clinical decision making, for the first time, a risk-carrying AASI threshold of 0.50 mm Hg/mm Hg was derived in a randomly defined discovery data set and confirmed in a replication data set. Across AASI quintiles in the derivation data set, the predicted risk for the coprimary end points was similar to the overoptimism-corrected Kaplan-Meier estimates, showing that the models were well calibrated. Third,

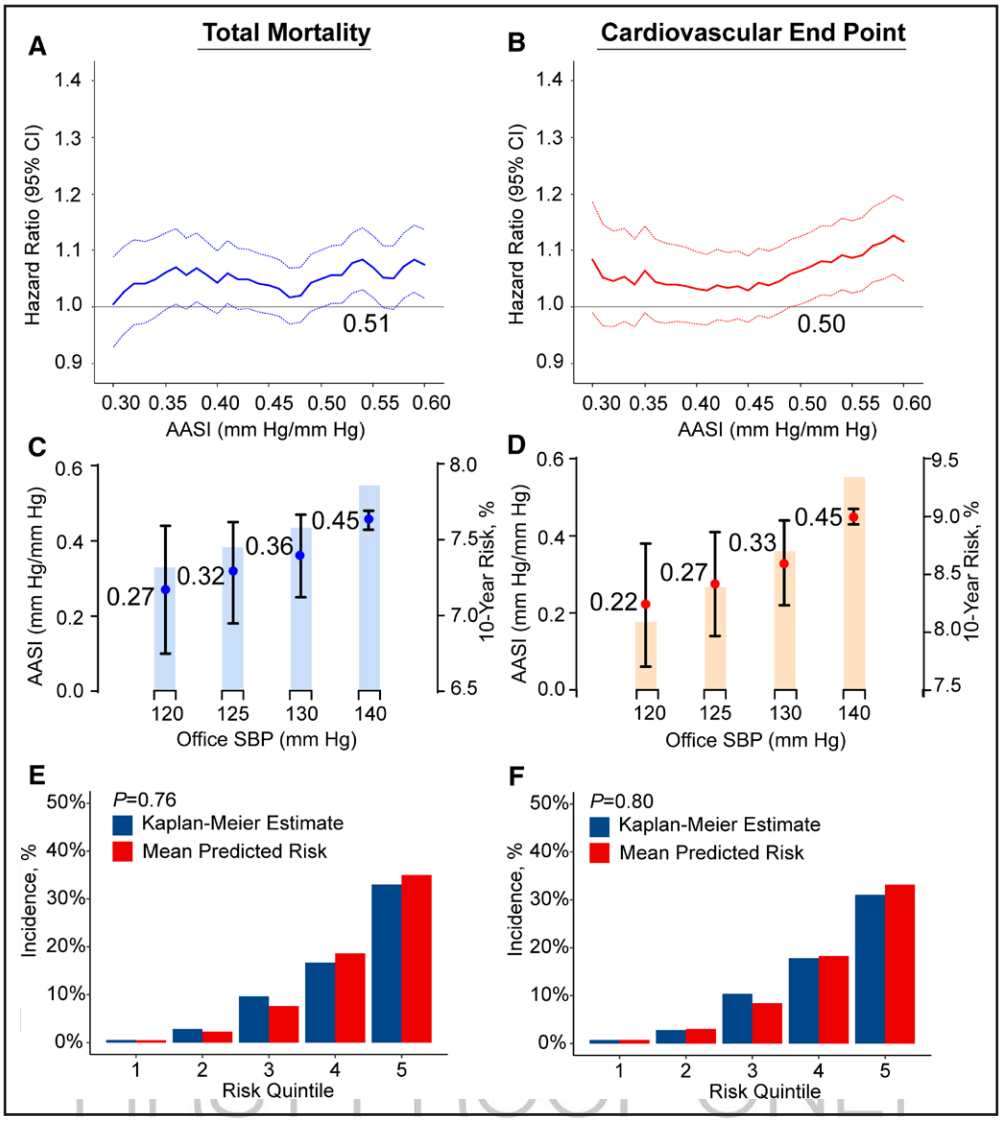

Figure 1. Derivation of an end point–based threshold for the ambulatory arterial stiffness index in the discovery data set. Hazard ratios (HRs) are given with 95% CI for total mortality (**A**) and for the coprimary cardiovascular end point (**B**) in relation to the ambulatory arterial stiffness index (AASI) increasing by 0.01 steps from the 20th to the 80th percentile of the AASI distribution. These HRs express the risk associated with stepwise increasing AASI thresholds relative to the risk below these thresholds. The AASI levels, at which the lower 95% confidence limit crossed unity, are 0.51 mm Hg/mm Hg for total mortality (**A**) and 0.50 mm Hg/mm Hg for the cardiovascular end point (**B**), indicating significantly increased risk. The AASI levels (bars-left vertical scale) yielding equivalent 10-year risk (point estimates±95% CI-right vertical scale) compared with office systolic hypertension (≥140 mm Hg) converged to 0.45 mm Hg/mm Hg for both mortality (**C**) and the cardiovascular end point (**D**). Across AASI quintiles, the predicted risk for total mortality (**E**) and the coprimary cardiovascular end point (**F**) are similar ($P \geq 0.76$) to the overoptimism-corrected Kaplan-Meier estimates, showing that the models are well calibrated. All analyses were multivariable-adjusted for cohort (random effect), sex, age, body mass index, smoking and drinking, the total-to-high-density-lipoprotein serum cholesterol ratio, antihypertensive drug treatment, diabetes, and history of cardiovascular disease.

with adjustments applied for cohort, multiple risk factors and R_MAP, AASI as continuously distributed variable or per threshold refined models as evidenced by the log-likelihood statistic, the AUC and the IDI and NRI indexes. On top of the base model, AASI refined the association with mortality and the coprimary cardiovascular end point in 5.42% and 7.62% of individuals. For AASI and R_MAP combined, the corresponding estimates were 13.6% and 17.9%, respectively. The statistically significant increase in IDI by 1.43% (for the fullest-adjusted model of the cardiovascular end point), albeit of small magnitude, reflects the increase in the average sensitivity, given no change in specificity. While AASI provides only a marginal improvement over a model that already includes MAP, it highlights the potential for more refined ABPM-derived metrics to capture unique pathophysiological information. Indeed, MAP reflects the BP level, whereas AASI is a measure of arterial stiffness. For both coprimary end points, AASI combined with R_MAP yielded the greatest increase in the C-index, AUC, NRI, and IDI.

Table 4. Model Refinement for the Coprimary End Points by the 24-h BP Indexes

End points (number of end points): base model, BP index added	−2 log-likelihood	C-index	NRI (95% CI), %	IDI (95% CI), %
Total mortality (n=3027)				
Base model	47 811.84	0.8053	…	…
AASI added	47 802.33*	0.8056	5.42 (-1.93–9.67)	0.10 (-0.01–0.30)
MAP added	47 769.97†	0.8065‡	12.8 (5.60–17.4)†	0.37 (0.09–0.78)†
R_MAP added	47 775.31†	0.8063‡	11.8 (5.7–16.1)‡	0.31 (0.05–0.68)†
R_MAP and AASI added	47 763.44†	0.8067‡	13.6 (6.32–17.9)†	0.43 (0.15–0.90)†
Cardiovascular end points (n=2183)				
Base model	35 716.39	0.7929	…	…
AASI added	35 702.08†	0.7937	7.62 (2.29–10.1)†	0.24 (0.05–0.44)†
MAP added	35 571.52†	0.8003†	18.4 (14.4–21.5)†	1.28 (0.84–1.88)†
R_MAP added	35 583.75†	0.7997†	18.1 (14.1–21.0)†	1.12 (0.71–1.70)†
R_MAP and AASI added	35 563.95†	0.8008†	17.9 (13.0–20.5)†	1.43 (0.98–2.07)†

Model performance was examined in all participants (n=12 558). The base model includes cohort, sex, age, body mass index, smoking and drinking, the total-to-high-density-lipoprotein serum cholesterol ratio, antihypertensive drug treatment, diabetes, and history of cardiovascular disease. An ellipsis indicates not applicable. AASI indicates ambulatory arterial stiffness index; BP, blood pressure; IDI, integrated discrimination improvement (95% CI); MAP, 24-h mean arterial blood pressure; NRI, net reclassification improvement (95% CI); and R_MAP, the residual of MAP regressed on AASI.

Significance of the difference with the base model:
*$P \leq 0.01$,
†$P \leq 0.001$, and
‡ $P \leq 0.05$.

The current analysis adds to the existing literature in various ways. Of 13 studies,[6,34–45] published from 2006[6,34] to 2023[45] and summarized by Boos et al[8] in a comprehensive systematic quantitative review, only 3 were population-based.[34,36,37] The other studies included patients with hypertension,[6,35,39,40,44] diabetes,[38,41] coronary heart disease,[42] high cardiovascular risk,[45] or end-stage kidney disease,[43] limiting their generalizability. In 4 cohorts, end points were limited to all-cause and stroke mortality.[6,37,38,43] Disregarding nonfatal end points underestimates the true incidence of adverse health outcomes because, over the past 30 years, the application of invasive interventions in coronary and stroke units substantially enhanced the survival rate of major coronary and cerebrovascular complications. The Cox models in the current study accounted for a broad range of risk factors and confounders (n=11), whereas, in 6 previous publications,[35,39,40,42–44] the number of covariables considered amounted to 7[37] down to 3.[35]

Despite its established prognostic value,[8] the true physiological mechanism, via which AASI reflects arterial stiffness, remains elusive.[46,47] In 2 cross-sectional studies of 515[48] and 824[49] patients with hypertension, AASI was weakly correlated with PWV, which, according to expert opinion, represents a direct measure of arterial stiffness.[1–4] The correlation coefficients were 0.28 (95% CI, 0.20–0.36)[48] and 0.28 (95% CI, 0.22–0.34),[49] respectively, but lost significance after adjustment for age. In the current study of 888 individuals, the unadjusted correlation coefficient was 0.22 (95% CI, 0.16–0.28) and remained significant after adjustment for cohort, sex, age, heart rate, and body height (partial r=0.085 [95% CI, 0.02–0.15]). In the SPARTE study (Strategy for Preventing Cardiovascular and Renal Events Based on Arterial Stiffness),[50] patients with hypertension were randomized to a BP-lowering strategy targeting the normalization of PWV, measured every 6 months (n=264), or a therapeutic strategy implementing the contemporary European Hypertension Guidelines (n=272). After a median follow-up of 48.3 months, the PWV-based treatment for hypertension reduced the office and ambulatory BP, whereas PWV slightly increased. Thus, the argument that AASI does not reflect arterial stiffness, because it is not or only slightly reduced by antihypertensive drugs,[47,51] is invalidated by the new evidence from the SPARTE trial.[50] A reasonable explanation for the weak correlation between AASI and PWV is that AASI is measured under ambulatory conditions, when individuals engage in their usual diurnal activities, whereas PWV is recorded in standardized laboratory conditions. In 167 Uruguayans, PWV showed a diurnal rhythm with a decrease by 0.7 m/s (P<0.001) from day (10–20 hours) to nighttime (0–6 hours),[52] highlighting that the time of day at which PWV is measured is a potential confounder in many studies.

Clinical Implications

The relation between end points and AASI is continuous and log-linear without a sudden increase in risk at an AASI level of 0.50. In the deviation-from-mean analyses (Table S7), there was a highly significant trend in relative risk across increasing AASI quartiles with a fully adjusted HR of 1.13 for total mortality and 1.15 for the cardiovascular end point in the top quartile. Similarly, absolute risk as captured by the incidence rates of the primary and secondary end points (Table 2) substantially

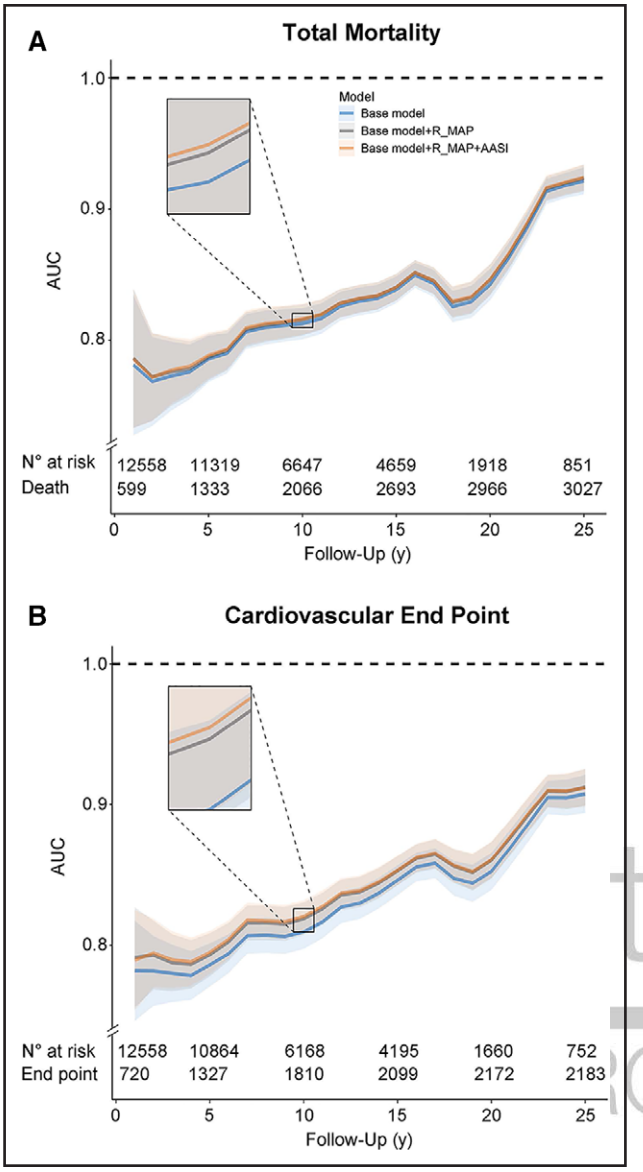

Figure 2. Time-dependent receiver operator characteristic curves for the coprimary end points in relation to the ambulatory arterial stiffness index.

The area under the curve (AUC) is plotted for total mortality (**A**) and the coprimary cardiovascular end point (**B**) as a function of follow-up time for 3 models: (1) the base model including cohort (random effect), sex, age, body mass index, smoking and drinking, the total-to-high-density-lipoprotein serum cholesterol ratio, antihypertensive drug treatment, diabetes, and history of cardiovascular disease; (2) the base model extended by the residual of mean arterial pressure regressed on ambulatory arterial stiffness index (AASI; R_MAP); and (3) the base model extended by both R_MAP and the AASI. For total mortality (**A**) and the coprimary cardiovascular end point (**B**), the full model including both AASI and R_MAP, compared with the base model, increases ($P<0.001$) the AUC. For total mortality (**A**), the AUC increase is similar for the base model extended by R_MAP or both R_MAP and AASI, whereas, for the cardiovascular end point, the AUC increase is greater for adding both R_MAP and AASI to the base model than for adding R_MAP only ($P=0.019$). The insert is a magnification of the 3 plotted lines at 10 years of follow-up. The number of participants at risk and the number of deaths and cardiovascular end points are tabulated for 5-year intervals.

increased from the bottom to the top quartile of AASI. The AASI threshold of 0.50 mm Hg/mm Hg is event-based and, therefore, more precise in risk prediction compared with previously investigator-determined AASI cutoff levels, predominantly derived in diseased patients.[6,34–36,38,39,41,43–45] In some studies, AASI was categorized by the mean,[34] median,[39,41,43–45] tertiles,[35,38] or quartiles.[36] Another approach referred to the upper limit of the 95% prediction interval of AASI regressed on age.[6,34] In the current study, an age-dependent threshold[6,34] or a quartile interval with the lowest end point rate[36] was not considered because, in view of clinical applicability, a single threshold is easier to remember compared with AASI thresholds varying with age. Notably, in the derivation of the current end point–based threshold, all models were adjusted for age. This person-level meta-analysis, including 12 558 participants recruited in Asia, Europe, and South America, produced robust evidence that AASI contributes to risk stratification over and beyond the BP level and other traditional risk factors. Moreover, AASI can be extracted without additional costs from ABPM data, which experts consider the BP measurement most closely associated with adverse cardiovascular outcomes. To facilitate clinic application, the Supplemental Material includes a video showing how AASI is calculated and an Excel sheet, which allows doctors to compute the 10-year AASI-related cardiovascular risk while accounting for all covariables applied in this study.

Strengths and Limitations

Participants were randomly recruited from populations in 14 countries and 3 continents. End points were collected over a median of 10.7 years of follow-up and encompassed both fatal and nonfatal events, which were all adjudicated against the source documents in each country. Notwithstanding these strengths, this study must also be interpreted within the context of its limitations. First, the pathophysiological mechanisms underlying AASI and its association with adverse health outcomes need further clarification. An experimental study, using random number generators to emulate the arterial cross-sectional area over 24 hours, suggested that the nonlinear elastic properties of the arterial wall might explain why AASI reflects arterial stiffness.[53] Second, 2 reports questioned the reproducibility of AASI.[54,55] The repeatability coefficients for the 24-hour AASI derived by the Bland and Altman method were 0.30[54] and 0.24,[55] at intervals ranging from 2 months[54] down to 2 weeks,[55] respectively. Finally, although IDACO is a multiethnic cohort, Blacks were not represented in the current analysis. Compared with Whites, African-Americans and Blacks born and living in sub-Saharan Africa[56] are more prone to hypertension and its associated complications. The current

findings, therefore, need to be cautiously extrapolated to other ethnic groups than those included in IDACO.

Perspectives

Over and beyond traditional risk factors, AASI improves risk stratification in representative population cohorts. Exceeding the risk-carrying 0.50 AASI threshold should motivate clinicians to manage risk factors causing stiffening of the large arteries in a timely manner before irreversible cardiovascular complications occur. A recommendation originating from the current observations is that the software, which manufacturers provide as a companion to portable BP recorders, should include an option to compute AASI. Finally, the pathophysiological mechanisms, by which AASI reflects arterial stiffness, deserve further exploration, given its prognostic value in risk stratification and given that earlier arguments to classify AASI as a surrogate marker[46–49] are invalidated by the more recent trial evidence[50] and the present findings.

ARTICLE INFORMATION

Received June 9, 2025; accepted December 15, 2025.

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Acknowledgments

The Non-Profit Research Alliance for the Promotion of Preventive Medicine (www.appremed.org) received a nonbinding grant from OMRON Healthcare Co, Ltd, Kyoto, Japan. The Guangci Laureate Professorship of J.A.Staessen is supported by the Guangci Deep Mind Project of Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. This article is a tribute to Prof Michel E. Safar and Prof Michael F. O'Rourke, whose legacy is a continuing source of inspiration in cardiovascular research.

Sources of Funding

This work was supported by the following funding: Belgium: the European Union (grant HEALTH-F7-305507 HOMAGE), the European Research Council (Advanced Researcher Grant 2011-294713-EPLORE and Proof-of-Concept Grant 713601-uPROPHET), the European Research Area Net for Cardiovascular Diseases (grant JTC2017-046-PROACT), and grant Research Foundation Flanders, Ministry of the Flemish Community, Brussels, Belgium (grant G.0881.13); China: the National Key R&D Program of China (grant 2024YFC3607200), the National Natural Science Foundation of China (grants 82070432 and 82270469), the Shanghai Commissions of Health (Leading Academics 2022LJ022 and 20234Y0036), and the Shanghai Talent Work Bureau (the Oriental Talent Program QNWS2024013 and BJWS2024086); Czech Republic: the European Union (grants LSHM-CT-2006–037093 and HEALTH-F4-2007–201550) and the Charles University Research Fund (projects P36 and Cooperation-Cardiovascular Science); Denmark: the Danish Heart Foundation (grant 01-2-9-9A-22914) and the Lundbeck Fonden (grant R32-A2740); Ireland: the Irish Allied Bank; Italy: the European Union (grants LSHM-CT-2006–037093 and HEALTH-F4-2007–201550); Japan: the Ministry of Education, Culture, Sports, Science and Technology (grants JP19K19325, JP19K19466, JP19H03908, JP19K10662, JP20K08612, JP20K18819, JP21K10452, JP21K10478, JP21H04854, JP21K17313, JP21K19670, JP23K24616 [JP22H03358], JP22K10070, JP23K27855, JP23K09698, JP23K27855 [JP23H03165], JP23K07690, JP24K02656, and JP24K13469), the internal research grants from Keio University, Japan Arteriosclerosis Prevention Fund, Ministry of Health, Labor, and Welfare, Japan (grants H29–Junkankitou–Ippan–003 and 20FA1002), ACRO Incubation Grants of Teikyo University, Academic Contributions from Pfizer Japan, Inc, and Bayer Yakuhin, Ltd, Scholarship donations from Daiichi Sankyo Co, Ltd, research support from Astellas Pharma, Inc, and Takeda Pharmaceuticals Co, Ltd, Health Science Center Research Grant, the Takeda Science Foundation, and the Mochida Memorial Foundation for Medical and Pharmaceutical Research; Poland (Gdańsk): the European Union (grants LSHM-CT-2006–037093 and HEALTH-F4-2007–201550); Poland (Kraków): the European Union (grants LSHM-CT-2006–037093 and HEALTH-F4-2007–201550) and the Foundation for Polish Science; Russia: the European Union (grants LSHM-CT-2006–037093), HEALTH-F4-2007–201550, and RAS State Target (grant FWNR-2024-0002); Spain: the Fondo de Investigación Sanitaria grant PI19/00665 and PI22/1164 (Instituto de Salud Carlos III and FEDER/FSE); Uruguay: the Asociación Española Primera en Salud, Comision Sectorial de Investigación Científica-UdelaR CSIC_I+D2010-816 and the Agencia Nacional de Investigación a Innovación: ANII FMV_2_2011_1_6414, ANII FMV_1_2017_1_136735; and Venezuela: The National Institute of Aging and the Fogarty International Center (grant 1-R01AG036469 A1), the National Institutes of Health and National Institute of Aging (grant 1 R03 AG054186-01), FONACIT, Caracas (grant G-97000726), and FundaConCiencia, Maracaibo (grant LOCTI). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures

K. Asayama received payment or honoraria for lectures, presentations, and speakers bureaus from A&D, CureApp, Taisho Pharmaceutical Holdings, and Terumo Corporation and consulting fees from Omron. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Tables S1–S11
Figures S1–S6
Video

APPENDIX

International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators

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