Ambulatory Arterial Stiffness Index and 24-Hour Ambulatory Pulse Pressure as Predictors of Mortality in Ohasama, Japan

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Background and Purpose—Ambulatory arterial stiffness index (AASI) and pulse pressure (PP) are indexes of arterial stiffness and can be computed from 24-hour blood pressure recordings. We investigated the prognostic value of AASI and PP in relation to fatal outcomes.

Methods—In 1542 Ohasama residents (baseline age, 40 to 93 years; 63.4% women), we applied Cox regression to relate mortality to AASI and PP while adjusting for sex, age, BMI, 24-hour MAP, smoking and drinking habits, diabetes mellitus, and a history of cardiovascular disease.

Results—During 13.3 years (median), 126 cardiovascular and 63 stroke deaths occurred. The sex- and age-standardized incidence rates of cardiovascular and stroke mortality across quartiles were U-shaped for AASI and J-shaped for PP. Across quartiles, the multivariate-adjusted hazard ratios for cardiovascular and stroke death significantly deviated from those in the whole population in a U-shaped fashion for AASI, whereas for PP, none of the HRs departed from the overall risk. The hazard ratios for cardiovascular mortality across ascending AASI quartiles were 1.40 (P=0.04), 0.82 (P=0.25), 0.64 (P=0.01), and 1.35 (P=0.03). Additional adjustment of AASI for PP and sensitivity analyses by sex, excluding patients on antihypertensive treatment or with a history of cardiovascular disease, or censoring deaths occurring within 2 years of enrollment, produced confirmatory results.

Conclusions—In a Japanese population, AASI predicted cardiovascular and stroke mortality over and beyond PP and other risk factors, whereas in adjusted analyses, PP did not carry any prognostic information. (Stroke. 2007;38:1161-1166.)

Key Words: ambulatory blood pressure ■ epidemiology ■ hypertension ■ prognosis ■ stroke

Recent reports have highlighted that the stiffness of central arteries, as reflected by aortic pulse wave velocity, reflects the incidence of cardiovascular disease and over and beyond 24-hour mean arterial pressure (MAP) and traditional risk factors.1 We recently proposed the ambulatory arterial stiffness index (AASI) as a measure reflecting arterial stiffness.2,3 This novel index, defined as 1 minus the regression slope of diastolic on systolic blood pressure in individual subjects, can be determined from 24-hour ambulatory blood pressure recordings.2,3 AASI shows high correlations with several measures of arterial stiffness, including aortic pulse wave velocity, central and peripheral pulse pressures, and the systolic augmentation index.3 In the Dublin Outcome Study,2 both AASI and 24-hour pulse pressure (PP), with adjustments applied for other risk factors, predicted cardiovascular death. Furthermore, compared with the 24-hour PP, AASI was a stronger predictor of fatal stroke, especially in normotensive subjects, whereas the opposite was true for 24-hour PP in relation to cardiac mortality.2 Although AASI might refine risk stratification based on ambulatory blood pressure measurements, its use cannot be recommended before the Irish outcome results2 are replicated in population cohorts of different ethnic extraction. We therefore investigated in Japanese subjects, randomly recruited from the population of Ohasama, Japan, to what extent AASI and 24-hour PP predicted mortality.

Subjects and Methods

Study Population

The institutional review boards of the Tohoku University School of Medicine and the Department of Health of the Ohasama Municipal Government approved the study. All participants gave informed, written consent.

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From 1988 to 1994, we contacted all 2716 subjects age 40 years or older and living in 3 of 4 Ohasama districts. Subjects who were not at home during the normal working hours of the study nurses (n=575) and those who were hospitalized (n=121) or incapacitated (n=31) were ineligible. Of the remaining 1989 residents, 1552 (78.0%) participated in the baseline examinations and were followed up. We excluded 10 subjects from the present analysis because their ambulatory blood pressure recording included less than 8 and 4 hours during the awake and asleep periods, respectively. Thus, the number of participants statistically analyzed totaled 1542.

Data Collection
At public health centers, trained nurses measured anthropometric characteristics. Body mass index (BMI) was weight in kilograms divided by height in meters squared. We programmed validated4 ABPM-630 recorders (Nippon Colin) to obtain oscillometric blood pressure reading at 30-minute intervals throughout the whole day. We computed the within-subject 24-hour means of the ambulatory measurements with weights according to the duration of the awake and asleep periods. Ambulatory hypertension was an awake blood pressure of at least 135 mm Hg systolic or 85 mm Hg diastolic or the use of antihypertensive drugs.

From 24-hour recordings edited according to previously published criteria,6 we computed for each participant the regression slope of diastolic on systolic blood pressure.7,8 We did not force the regression line through the origin (intercept=0), because during diastole when flow drops to 0, such a phenomenon does not occur for blood pressure.9 We defined AASI as 1 minus the regression slope. The stiffer the arterial tree, the closer the regression slope and AASI are to 0 and 1, respectively. In addition, from individual recordings and the same readings as used for AASI, we computed PP as the difference between the 24-hour systolic and diastolic blood pressures and 24-hour MAP as 24-hour diastolic blood pressure plus one third of the 24-hour PP. The “white-coat window” was the first hour of each ambulatory blood pressure recording.

The study nurses administered a standardized questionnaire, inquiring into each subject’s medical history, intake of medications, and smoking and drinking habits. For our primary analyses, we defined smoking as past or present use of tobacco9 and likewise drinking as past or current consumption of alcoholic beverages. In sensitivity analyses, we also considered only current smoking and drinking. Prevalent cardiovascular disease included stroke, transient ischemic attack, coronary heart disease, and atrial fibrillation.

Venous blood samples were analyzed by automated enzymatic methods for total cholesterol and blood glucose. According to published criteria,9 diabetes mellitus was a fasting or random blood glucose value of at least 7.0 or 11.1 mmol/L, respectively, or use of antidiabetic drugs. Hypercholesterolemia was a serum cholesterol level of at least 5.68 mmol/L (220 mg/dL) or use of lipid-lowering drugs.

Ascertainment of Events
We ascertained vital status until December 31, 2004, from the residents’ registration cards, which are the bases for pension and social security benefits. We obtained cause-of-death information from the National Japanese Mortality Registry. We verified the diagnoses on the death certificates against the medical records of Ohasama Hospital, where >90% of Ohasama residents undergo regular health check-ups. The end points considered in the present analysis were death from all causes, cardiovascular (ICD-10 codes ‘I’ and noncardiovascular mortality, and mortality from stroke (ICD-10 codes, “I6”), and cardiac disorders (ICD-10 codes I08, I11, 121, 122, 124, 125, 135, 142, 144, 146, 147, 149, 150, 160, 161, 163, 164, and 168).

Statistical Analysis
For statistical analysis, we used SAS software, version 9.1 (SAS Institute). We compared means and proportions by ANOVA and the χ² statistic, respectively. We evaluated unadjusted associations from Pearson’s correlation coefficient. To explore the plausibility of the Cox model in the overall study population, in exploratory analyses we plotted mortality rates by quartiles of AASI or 24-hour PP while standardizing for sex and age by the direct method.

Next, we calculated hazard ratios (HRs) by multiple Cox regression by comparing the risk in each quartile to the overall risk in the whole cohort. We used deviation from the mean coding10 because the association between cardiovascular mortality and AASI was curvilinear. This approach also allows computation of confidence intervals (CIs) for the HR in each quartile without definition of an arbitrary reference group. We adjusted the HRs for baseline characteristics, including sex, age, 24-hour MAP, BMI, current and past smoking and drinking habits, diabetes mellitus, and a previous history of cardiovascular disease. In fully adjusted models, we also accounted for PP when analyzing AASI and vice versa.

By repeat examination of 19 healthy and untreated subjects (mean±SD age, 65.6±3.0 years; 79.0% women) within an interval of 5 years (range, 3.1 to 4.6 years), we computed the repeatability coefficient as twice the SD of the differences between paired measurements.11 To allow comparison between AASI and 24-hour PP, we expressed the repeatability coefficients as percentages of near-maximal biological variation, ie, 4 times the SD of the first measurement.12

Results
Baseline Characteristics of the Subjects
The 1542 participants included 977 (63.4%) women and 760 (49.3%) patients with ambulatory hypertension, of whom 473 (62.2%) were taking antihypertensive drugs. Mean values (±SD) were 61.7±10.7 years for age, 0.46±0.10 U for AASI, and 51.3±7.4 mm Hg for 24-hour PP. Table 1 shows the characteristics of the study population across quartiles of the AASI distribution. Anthropometric characteristics and prevalence of a history of cardiovascular disease were different between quartiles (P<0.03 or less). Diastolic blood pressure decreased with increasing AASI, whereas systolic and 24-MAP increased with higher AASI (Table 1). AASI was not significantly different between women and men (0.46 versus 0.45, P<0.16) or between normotensive and hypertensive subjects (0.45 versus 0.46, P<0.19). AASI increased with age (r=0.26, P<0.001) but decreased with body height (r=−0.17, P<0.001). There was a positive association between AASI and 24-hour PP (r=0.24, P<0.001).

The number of readings available per recording for the calculation of AASI, 24-hour PP, and 24-hour MAP averaged 44.6. The 50th, 25th, 10th, 5th, and 1st percentile values were 46, 42, 38, 36, and 30, respectively. When we randomly reduced the number of blood pressure measurements per recording in steps of 1, only after we excluded 7 readings, mean AASI significantly departed from the currently reported values. In the reproducibility study, the repeatability coefficients for AASI and 24-hour PP were 53.2% and 55.5%, respectively.

Analysis of Mortality
During follow-up (median, 13.3 years; 5th to 95th percentile CI, 4.7 to 16.3 years), 19 024 person-years accrued. Of 345 deaths, 126 (36.5%) were cardiovascular, including 63 stroke and 59 cardiac. Stroke deaths were due to cerebral infarction in 38 subjects, intracerebral or subarachnoid hemorrhage in 22, and other cerebrovascular or ill-defined causes in 3. Cardiac mortality included myocardial infarction (n=20), chronic coronary heart disease (n=4), heart failure (n=15),
TABLE 1. Clinical Characteristics Across Quartiles of AASI

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>AASI Quartile Limits</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>0.16–0.38</td>
<td>0.39–0.45</td>
</tr>
<tr>
<td>Women, %</td>
<td>385</td>
<td>386</td>
</tr>
<tr>
<td>Age, y</td>
<td>57.6±10.5</td>
<td>61.1±10</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.1±3.2</td>
<td>23.6±3.3</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>154.2±8.6</td>
<td>152.5±8.6</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/past smokers, %</td>
<td>20.5/2.6</td>
<td>21.0/2.9</td>
</tr>
<tr>
<td>Current/past drinkers, %</td>
<td>25.8/0.0</td>
<td>24.3/0.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>44.9</td>
<td>50.8</td>
</tr>
<tr>
<td>Diabetes mellitus, %†</td>
<td>18.4</td>
<td>17.4</td>
</tr>
<tr>
<td>Previous cardiovascular disease, %</td>
<td>6.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>6.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Hypercholesterolemia, %‡</td>
<td>22.3</td>
<td>24.6</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.0±0.8</td>
<td>5.0±0.8</td>
</tr>
<tr>
<td>24-hour ambulatory measurements, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>121.6±12.3</td>
<td>123.5±13.3</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>72.7±7.3</td>
<td>72.8±7.7</td>
</tr>
<tr>
<td>PP</td>
<td>48.9±6.8</td>
<td>50.7±7.2</td>
</tr>
<tr>
<td>MAP</td>
<td>89±8.7</td>
<td>89.7±9.3</td>
</tr>
</tbody>
</table>

Larger values of AASI indicate stiffer arteries. Plus-minus values are mean±SD. P values are for overall differences across quartiles.

*Hypertension was an awake blood pressure of at least 135 mm Hg systolic or 85 mm Hg diastolic or the use of antihypertensive drugs.
†Diabetes mellitus was a fasting or random blood glucose value of ≥7.0 or ≥11.1 mmol/L, respectively, or the use of antidiabetic drugs.
‡Hypercholesterolemia was a serum cholesterol level of ≥5.68 mmol/L (220 mg/dL) or the use of lipid-lowering drugs.

sudden death (n=6), arrhythmia (n=6), and various other cardiac disorders (n=8).

Across quartiles, exploratory analyses revealed U-shaped associations of the sex- and age-standardized incidence rates of cardiovascular and stroke mortality for AASI and J-shaped associations for PP (Figure 1). Next, we computed the HRs for quartiles of AASI and PP, unadjusted (Table 2) and while adjusting for sex, age, BMI, 24-hour MAP, past and current smoking and drinking habits, diabetes mellitus, and a previous history of cardiovascular disease (Figure 2). With such adjustments applied, for AASI, multiple Cox regression confirmed U-shaped deviations in the risk of cardiovascular and stroke mortality across quartiles relative to the risk in the whole cohort. For 24-hour PP, the adjusted HRs in the quartiles did not significantly (P>0.20) depart from the risk in the whole population (Figure 2). When we additionally adjusted AASI for 24-hour PP, and vice versa, our findings remained consistent (Table 2). In adjusted (Figure 2) and fully adjusted (Table 2) analyses, we did not find any association of cardiac or noncardiovascular mortality with AASI or PP (data not shown).

In sensitivity analyses of cardiovascular mortality in relation to AASI, we considered women and men separately, we excluded patients taking antihypertensive drugs at baseline or those with a history of cardiovascular disease or diabetes mellitus, we adjusted for current instead of ever-smoking and ever-smoking, or we additionally adjusted for clinic blood pressure, systolic blood pressure during the white-coat window,

Kikuya et al AASI and PP as Predictors of Fatal Stroke

In middle-aged and older subjects recruited from a Japanese population, AASI, a measure of the dynamic relation between diastolic and systolic blood pressure throughout the day, predicted cardiovascular and stroke mortality over and beyond 24-hour MAP, anthropometric characteristics, and cardiovascular risk factors. With similar adjustments applied, 24-hour PP lost its prognostic value. AASI remained a significant predictor of cardiovascular and stroke mortality even in fully adjusted models, which also incorporated 24-hour PP. Our findings extend the validation of AASI against fatal outcomes from the hypertensive patients enrolled in the Dublin Outcome Study to a general population of Japanese extraction.

AASI as a Predictor of Stroke Mortality

In line with the present observations, in the Dublin Outcome Study, AASI also behaved as a stronger predictor of stroke mortality than did 24-hour PP. However, in the Irish patients,
the association between stroke mortality and AASI was log-linear, whereas in the current study, it was U-shaped. We can only speculate why in Ohasama these associations departed from linearity. First, our study population consisted mainly of older women (63.4%), whereas among the Irish patients, only 52.8% were female. The proportion of Ohasama residents with a history of cardiovascular disease in the second quartile of AASI was about half of that observed in the bottom and top quartiles. However, the relation between AASI and cardiovascular mortality remained U-shaped, even after exclusion of patients with a history of cardiovascular disease. Residual confounding and/or differences between European and Asian populations in the competing risks of stroke and coronary heart disease might also have played a role.

24-Hour PP as a Predictor of Stroke

In keeping with other studies, we noticed that in the Ohasama population, PP did not predict stroke mortality. Miura and colleagues assessed the incidence of fatal and nonfatal stroke for 10 years in 4989 Japanese (69.5% women; age range at baseline, 35 to 79 years) in relation to systolic

### TABLE 2. HRs for Mortality by Quartiles of AASI and 24-Hour PP

<table>
<thead>
<tr>
<th>Mortality (No. of deaths)</th>
<th>AASI</th>
<th>24-Hour PP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.39</td>
<td>0.39–0.45</td>
</tr>
<tr>
<td>All causes (n=345)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.81 (0.67, 0.99)†</td>
<td>0.87 (0.72, 1.06)</td>
</tr>
<tr>
<td>Fully adjusted‡</td>
<td>1.18 (0.96, 1.45)</td>
<td>0.94 (0.77, 1.14)</td>
</tr>
<tr>
<td>Cardiovascular (n=126)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.92 (0.67, 1.27)</td>
<td>0.77 (0.55, 1.08)</td>
</tr>
<tr>
<td>Fully adjusted‡</td>
<td>1.41 (1.01, 1.96)†</td>
<td>0.85 (0.61, 1.20)</td>
</tr>
<tr>
<td>Stroke (n=63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.02 (0.65, 1.59)</td>
<td>0.81 (0.50, 1.30)</td>
</tr>
<tr>
<td>Fully adjusted‡</td>
<td>1.56 (0.98, 2.47)†</td>
<td>0.89 (0.54, 1.45)</td>
</tr>
</tbody>
</table>

HRs (95% CIs) express the risk in each quartile vs the overall risk in the whole study population. Fully adjusted models accounted for sex, age, BMI, 24-hour MAP, past and current smoking and drinking, diabetes mellitus, and previous cardiovascular disease and included both AASI and 24-hour PP.

Significance of HRs: *P < 0.01, †P < 0.05, ‡P < 0.06.
and diastolic blood pressures, MAP, and PP. The adjusted HRs for all strokes associated with a 1-SD higher value for each blood pressure index were 1.68, 1.72, 1.80, and 1.34, respectively. Benetos and colleagues16 followed up cardiovascular mortality for 19.5 years in 19,083 men, age 40 to 69 years. A wider PP, evaluated either by quartiles or on a continuous scale, was a significant predictor of all-cause, cardiovascular, and especially coronary mortality, whereas PP did not predict cerebrovascular mortality. In the study of Verdecchia et al.,17 of 2311 patients with essential hypertension and diastolic blood pressure, MAP, and PP. The adjusted HRs for all strokes associated with a 1-SD higher value for each blood pressure index were 1.68, 1.72, 1.80, and 1.34, respectively. Benetos and colleagues16 followed up cardiovascular mortality for 19.5 years in 19,083 men, age 40 to 69 years. A wider PP, evaluated either by quartiles or on a continuous scale, was a significant predictor of all-cause, cardiovascular, and especially coronary mortality, whereas PP did not predict cerebrovascular mortality. In the study of Verdecchia et al.,17 of 2311 patients with essential hypertension, adjustment for MAP weakened the association of PP with the risk of cerebrovascular complications to a nonsignificant level.

**AASI as a Proxy for Arterial Stiffness**

Taking into account differences in the distributions of sex, age, and height, average values of AASI in the present Japanese population were comparable with those observed in Chinese volunteers,3 a European reference population,2,3 and a Chinese population.3 AASI rests on the concepts that arterial distending pressure varies during the day and that the relation between diastolic and systolic blood pressure, with this changing distending pressure, largely depends on the functional and structural characteristics of large arteries. In addition, AASI must also depend on stroke volume, left ventricular ejection rate, and the reflection of the arterial pulse wave. We previously demonstrated in healthy Chinese volunteers that the correlation coefficient between AASI and aortic pulse wave velocity was 0.51.3 In a randomly recruited Chinese population, both before and after adjustment for arterial wave reflections by considering height and heart rate as covariates, AASI was correlated better with central and peripheral systolic augmentation indexes than with 24-hour PP.1 In 19 healthy and unmedicated study participants who underwent a repeat ambulatory blood pressure recording within 5 years of the baseline examination, the repeatability coefficient expressed as a percentage of nearly-maximum variation in the first measurement was similar for AASI and 24-hour PP. Despite similar reproducibility, the associations of cardiovascular and stroke mortality with AASI were closer than those with 24-hour PP. These findings suggest that from a physiological point of view, AASI might be more meaningful than 24-hour PP, which in contrast to AASI does not account for the diurnal variability in the relation between diastolic and systolic blood pressure.

**Study Limitations**

The present study must be interpreted within the context of its potential limitations. First, we did not collect updated information on nonfatal health outcomes beyond December 31, 2001. Our present analysis, as in the Irish study,2 was therefore exclusively based on mortality. Second, middle-aged or older women made up the majority of the Ohasama participants. To some extent, this imbalance in the sex and age distribution might limit the generalizability of the current findings. On the other hand, our population-based survey probably included fewer subjects starting or continuing antihypertensive drug treatment than in the Dublin Outcome Study.2 Moreover, we validated the diagnoses on the death certificates against the medical records of the only hospital of Ohasama. By censoring deaths occurring within 2 years of enrollment, we also

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**TABLE 3. HRs for Cardiovascular Mortality by Quartiles of AASI in Sensitivity Analyses**

<table>
<thead>
<tr>
<th>Subgroup (No. of subjects analyzed)</th>
<th>No. of Deaths</th>
<th>HRs (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Quartile 1</td>
</tr>
<tr>
<td>Women (n=977)</td>
<td>65</td>
<td>1.42 (0.90, 2.24)</td>
</tr>
<tr>
<td>Men (n=565)</td>
<td>61</td>
<td>1.53 (0.93, 2.53)</td>
</tr>
<tr>
<td>Participants not taking antihypertensive medications (n=1069)</td>
<td>55</td>
<td>1.89 (1.17, 3.07)*</td>
</tr>
<tr>
<td>Participants without diabetes mellitus (n=1274)</td>
<td>98</td>
<td>1.44 (0.98, 2.13)</td>
</tr>
<tr>
<td>Participants without a history of cardiovascular disease (n=1444)</td>
<td>101</td>
<td>1.68 (1.17, 2.41)*</td>
</tr>
<tr>
<td>Censoring deaths within 2 years of enrollment (n=1542)</td>
<td>115</td>
<td>1.49 (1.05, 2.10)*</td>
</tr>
</tbody>
</table>

Alternative/additional factors accounted for†

- Current instead of ever-smoking and -drinking (n=1542) | 126 | 1.39 (1.00, 1.94) | 0.85 (0.60, 1.20) | 0.65 (0.46, 0.92)* | 1.30 (0.98, 1.72) |
- Plus clinic systolic blood pressure (n=1332) | 99  | 1.59 (1.10, 2.30)* | 0.77 (0.53, 1.13) | 0.64 (0.43, 0.94)* | 1.28 (0.93, 1.76) |
- Plus systolic blood pressure in the white-coat window (n=1542) | 126 | 1.47 (1.06, 2.05)* | 0.90 (0.64, 1.27) | 0.64 (0.46, 0.90)* | 1.18 (0.89, 1.57) |
- Plus total cholesterol at baseline (n=1542) | 126 | 1.41 (1.01, 1.96)* | 0.85 (0.61, 1.20) | 0.65 (0.46, 0.91)* | 1.29 (0.97, 1.70) |
- Plus hypercholesterolemia (n=1542) | 126 | 1.41 (1.01, 1.96)* | 0.85 (0.61, 1.20) | 0.65 (0.46, 0.91)* | 1.29 (0.97, 1.70) |

No. indicates the number of cardiovascular deaths. HRs express the risk in each quartile vs the overall risk in the whole group or subgroup.

Significance of the HRs: *P<0.05.

†See fully adjusted models in Table 2.
excluded the possibility that reverse causality might have contributed to the present findings.

Perspective
In line with the Dublin Outcome Study in hypertensive patients, we confirmed in a Japanese population that AASI adds to the stratification of risk based on ambulatory blood pressure monitoring. AASI can be derived without the need of complex devices and skilled observers. In previous studies, we noticed that the upper boundary of the 95% prediction interval for individual values of AASI in relation to age ranged from 0.53 at 20 years to 0.72 at 80 years. A worldwide consortium of investigators is currently constructing an international database of ambulatory blood pressure recordings in relation to cardiovascular outcomes and will among, other things, further study the predictive value of AASI in population-based cohorts of different ethnicity.

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Disclosures
None.

References
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