

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Hypertension 2006;47;365-370; originally published online Jan 23, 2006;

DOI: 10.1161/01.HYP.0000200699.74641.c5

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Ambulatory Arterial Stiffness Index as a Predictor of Cardiovascular Mortality in the Dublin Outcome Study

Eamon Dolan, Lutgarde Thijs, Yan Li, Neil Atkins, Patricia McCormack, Sean McClory, Eoin O'Brien, Jan A. Staessen, Alice V. Stanton

Abstract—We hypothesized that the dynamic relation between diastolic and systolic blood pressure over 24 hours provides a measure of arterial stiffness and might, therefore, predict cardiovascular mortality over and above pulse pressure. At baseline, while not on antihypertensive medication, 11 291 patients (mean age, 54.6 years; 5965 women) underwent ambulatory blood pressure monitoring. Using all of the blood pressure readings, we plotted diastolic against systolic blood pressure from each individual and calculated the regression slope. The ambulatory arterial stiffness index (AASI) was defined as 1 minus this regression slope. Over a median follow-up of 5.3 years, 566 cardiovascular deaths occurred, including 151 from stroke and 358 from cardiac disorders. Before and after adjustment for other cardiovascular risk factors, AASI and pulse pressure significantly predicted total cardiovascular mortality. AASI was a stronger predictor than pulse pressure for stroke (mutually adjusted relative hazard ratios for 1 SD increase, 1.21 versus 1.04; $P=0.02$ versus 0.66) with the opposite trend for cardiac mortality (relative hazard ratios, 1.03 versus 1.21; $P=0.63$ versus 0.002). In subjects with normal daytime ambulatory blood pressure ($<135/<85$ mm Hg), AASI was more predictive than pulse pressure of cardiovascular mortality (1.26 versus 0.96; $P=0.04$ versus 0.70) and of stroke mortality (1.81 versus 1.12; $P=0.007$ versus 0.58), whereas neither independently predicted cardiac mortality (1.11 versus 0.89; $P=0.47$ versus 0.40). AASI is a novel measure of arterial stiffness, which can be readily determined from ambulatory blood pressure recordings and which independently predicts cardiovascular mortality, even in normotensive subjects. (*Hypertension*. 2006;47:365-370.)

Key Words: arteries ■ blood pressure monitoring, ambulatory ■ epidemiology ■ mortality

Current guidelines for the management of hypertension recommend the use of ambulatory blood pressure monitoring to identify white-coat reactors and to establish the need for antihypertensive drug treatment. Although arterial stiffness is a strong predictor of cardiovascular complications,¹⁻⁷ it is underused in routine clinical practice for risk stratification. Its measurement, with the exception of pulse pressure, requires special equipment and trained observers. We hypothesized that the dynamic relation between diastolic and systolic blood pressure over 24 hours provides insights into the stiffness of the arterial wall. In this article, we describe the derivation of the ambulatory arterial stiffness index (AASI), and we explore the additional predictive value of AASI, over and above pulse pressure and established risk factors, for fatal cardiovascular outcomes among a large cohort of patients referred to a single center in Dublin, Ireland. In a companion article,⁸ we demonstrate that AASI closely correlated with aortic pulse wave velocity and the central and peripheral systolic augmentation indexes, and we

propose reference values for AASI based on observations in Chinese and European subjects.

Methods

Study Population

From 1980 to 2002, we enrolled 14 414 subjects into the Dublin Outcome Study.⁹ At referral, all of the patients were untreated. We excluded 3123 participants because their 24-hour ambulatory registration included <10 daytime or 5 nighttime blood pressure readings ($n=2612$), because at baseline not all of the cardiovascular risk factors had been recorded ($n=433$), or because vital status could not be ascertained ($n=78$). Thus, the total number of participants included in the present analysis was 11 291. The Ethics Committee of the Beaumont Hospital approved the study.

Ambulatory Blood Pressure Measurement

From 1980 until 1984, we recorded daytime and nighttime ambulatory blood pressure by microphonic detection of the Korotkoff sounds with the prototype automated ambulatory blood pressure recorder, the Del Mar Avionics Pressurometer III (Del Mar Avionics).¹⁰ From 1985 onward, we used validated oscillometric devices (SpaceLabs 90202

Received May 19, 2005; first decision June 13, 2005; revision accepted October 25, 2005.

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Eoin O'Brien and Neil Atkins have contributed financially to the development of the dabl ABPM software program and are members of the Board of dabl Limited. Neil Atkins is an employee of dabl Limited.

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Hypertension is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000200699.74641.c5

or 90207, SpaceLabs^{11,12} or A&D TM-2430, A&D Engineering Company¹³) or auscultatory monitors (Spacelabs 5200,¹⁴ Profilomat, Diestronic Medical Systems¹⁵ or CH-Druck/Pressure ERKA, Diestronic Medical Systems¹⁶). We programmed the recorders to obtain blood pressure readings at 30-minute intervals throughout the whole day.⁹ In keeping with JNC7 guidelines,¹⁷ hypertension was a daytime (10:00 AM until 8:00 PM) ambulatory blood pressure averaging ≥ 135 mm Hg systolic or 85 mm Hg diastolic. For database management, all of the clinical data were transferred into the dabl Cardiovascular software package (dabl Ltd).

Derivation of AASI

Arterial stiffness varies nonlinearly with distending pressure: as mean arterial pressure increases, stiffness increases exponentially.¹⁸ Mean arterial pressure shows considerable diurnal variability, usually increasing with activity and declining with rest and sleep. In subjects with elastic arteries, with variation in mean arterial pressure, changes in systolic and diastolic blood pressures occur in parallel throughout the blood pressure range. In subjects with less compliant arteries, increases in the distending pressure, above a certain threshold, are associated with a greater increase in systolic pressure than diastolic pressure. In those with very stiff vessels, although systolic pressure sharply rises with each increase in mean arterial pressure, diastolic pressure may even decline.

From unedited 24-hour recordings, we computed for each participant the regression slope of diastolic on systolic blood pressure. We did not force the regression line through the origin (intercept=0),⁸ because during diastole when flow drops to zero, such a phenomenon does not occur for blood pressure.¹⁹ 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. Figure 1 demonstrates that for similar levels of the 24-hour ambulatory blood pressure and pulse pressure, AASI can vary considerably and, therefore, suggests that AASI might provide additional hemodynamic information.

Mortality Outcomes

In the absence of a unique identifier permitting ready identification of subjects in the Irish death register, vital status was ascertained by searching this computerized death register for each individual whose name also appeared in the dabl database. This process was completed in a number of steps, which have been described previously.²⁰ Briefly, the death register was first searched for patients having both a similar name and approximate date of birth. This procedure accounted for different versions of first and surnames and/or misspelling. To overcome imprecision in the date of birth, we allowed a 2-year margin of error. If there was no match using these 2 criteria, the individual was considered to be alive. Where there was a positive

match, additional confirmation of death was sought by checking addresses and records of hospitals and family doctors. This process provided definite evidence that, of the 11 291 subjects in the study cohort, 948 had died by September 30, 2002.

Because Irish death certificates state the cause of death but are not coded, the death certificate of each individual was examined, and the cause of death was coded according to the World Health Organization's International Classification of Diseases, 9th Revision. Of the 948 deaths, 566 were from cardiovascular causes; 358 were attributed to cardiac illness and 151 to stroke. Cardiac mortality included myocardial infarction (International Classification of Diseases, 9th Revision, 4100 to 4109), chronic coronary heart disease (4140 to 4149), heart failure (4280 to 4289), and sudden death (7980 to 7989). Cardiovascular mortality consisted of cardiac mortality, fatal stroke (4300 to 4389), and other vascular deaths.

Statistical Analysis

For statistical analysis, we used SAS software, version 9.1 (SAS Institute Inc). We compared means and proportions by the large sample z test and the χ^2 -statistic, respectively. In exploratory analyses, we plotted the rates of cardiovascular mortality in quintiles of AASI or pulse pressure while standardizing for sex and age by the direct method. We calculated relative hazard ratios by multiple Cox regression with adjustment for baseline characteristics including sex, age, mean arterial pressure, body mass index, smoking, diabetes mellitus, and history of cardiovascular disease. We treated AASI and pulse pressure as continuous variables. In additional analyses, we dichotomized AASI⁸ and pulse pressure using the upper boundary of the 95th prediction interval for individual data points in relation to age in the Belgian, Chinese, and Irish normotensive subjects enrolled in the International Database on Ambulatory Blood Pressure Monitoring.²¹ Cutoff limits by decade of age ranged from 0.53 at 20 years to 0.72 at 80 years for AASI⁸ and from 55 mm Hg at 20 years to 60 mm Hg at 80 years for pulse pressure. We modeled the probability of the 5-year incidence of cardiovascular mortality using the Weibull distribution for time-failure data.

Results

Baseline Characteristics

At enrollment, the 11 291 subjects had a mean (\pm SD) age of 54.6 ± 14.6 years (range, 16 to 96 years). AASI was higher ($P < 0.001$) in women than men (0.42 versus 0.40) in the presence as opposed to the absence of diabetes mellitus (0.46 versus 0.41) or a history of cardiovascular disease (0.47 versus 0.41). The corresponding differences in pulse pres-

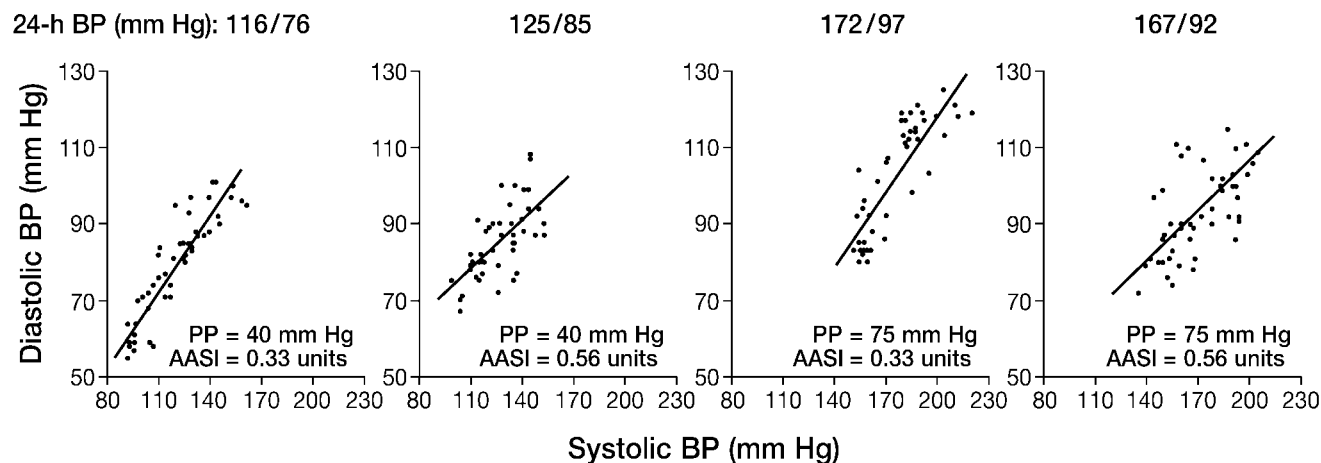


Figure 1. Plots of diastolic blood pressure regressed on systolic blood pressure in 4 different subjects. BP, PP, and AASI indicate blood pressure, the 24-hour pulse pressure, and the AASI, respectively. For similar levels of 24-hour BP and PP, AASI varied from 0.33 to 0.56.

TABLE 1. Clinical Characteristics Across Quintiles of the AASI

AASI Percentile Limits	<0.28	≥0.28/<0.37	≥0.37/<0.45	≥0.45/<0.55	≥0.55
Women, %	50.3	48.0	50.3	56.4	59.2
Age, y	43.9±13.1	51.5±13.5	56.1±13.0	58.9±12.5	62.6±13.0
Body mass index, kg/m ²	27.7±4.8	27.5±4.6	27.5±4.7	27.3±4.7	27.0±4.7
Risk factors					
Smoking, %	24.0	21.2	20.4	19.2	16.6
Hypertension, %	71.4	73.7	76.2	78.5	78.4
Diabetes mellitus, %	4.1	5.4	8.2	9.5	10.9
History of cardiovascular disease, %	6.9	10.3	12.7	15.5	18.9
24-hour ambulatory measurements					
Systolic blood pressure, mm Hg	131.1±14.8	136.1±15.7	139.7±16.5	143.3±17.2	146.4±19.0
Diastolic blood pressure, mm Hg	83.3±10.9	83.8±11.0	83.5±11.4	82.6±11.7	80.8±12.2
Mean arterial pressure, mm Hg	99.2±11.8	101.2±12.0	102.2±12.4	102.8±12.7	102.6±13.3
Pulse pressure, mm Hg	47.9±7.6	52.3±9.2	56.2±10.3	60.7±11.7	65.6±13.9

Plus-minus values are mean±SD. Differences between the quintiles were significant ($P<0.01$) except for body mass index.

sure (57.4 versus 55.6 mm Hg, 61.3 versus 56.2 mm Hg, and 59.6 versus 56.1 mm Hg, respectively) were also significant ($P<0.001$). Table 1 shows the characteristics of the study population across fifths of the AASI distribution. The differences between the quintiles were significant ($P<0.01$) except for body mass index. Systolic blood pressure and mean arterial pressure rose with increasing AASI, whereas diastolic blood pressure fell slightly. Those with higher AASI also had higher pulse pressure.

Prediction of Cardiovascular Mortality

Over a median follow-up of 5.3 years (range, 2 days to 21.4 years), 566 cardiovascular deaths occurred. In exploratory nonparametric analyses, the sex- and age-adjusted incidence of cardiovascular mortality increased with AASI and pulse pressure (Figure 2). In Cox regression, both before and after adjustment for sex, age, mean arterial pressure, body mass index, smoking, diabetes mellitus, and previous cardiovascular disease, AASI and pulse pressure analyzed as continuous variables predicted cardiovascular mortality (Table 2). In adjusted analyses, AASI predicted fatal stroke, whereas pulse pressure predicted cardiac mortality (Table 2).

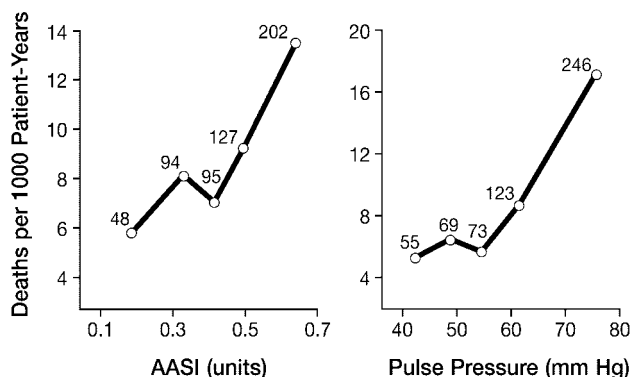


Figure 2. Sex- and age-standardized rates of cardiovascular mortality across quintiles of the AASI (left) and the 24-hour pulse pressure (right). The number of deaths is given for each quintile.

In adjusted analyses of AASI treated as a binary variable, elevated values significantly and independently predicted mortality from all of the cardiovascular causes, stroke and cardiac disease. Pulse pressure, also as a binary variable, only predicted cardiac mortality. Figure 3 shows the absolute risk of overall and cause-specific cardiovascular mortality in relation to AASI and pulse pressure.

Sensitivity Analyses

When in continuous analyses we additionally adjusted AASI for pulse pressure and vice versa, AASI maintained its prognostic value for stroke, whereas pulse pressure remained predictive for cardiovascular and cardiac mortality (Table 2). Furthermore, in dichotomized analyses with mutual adjustments applied as before, elevated values of AASI still predicted cardiovascular and stroke mortality, whereas a high pulse pressure lost its predictive value for the 3 fatal outcomes under study (Table 2).

Additional analyses stratified for the presence of ambulatory hypertension at baseline (Table 3) showed that AASI and pulse pressure analyzed as continuous variables predicted cardiovascular and stroke mortality in normotensive subjects and cardiovascular and cardiac mortality in hypertensive patients, respectively. In dichotomized analyses, elevated values of AASI predicted cardiovascular and stroke mortality in normotensive and hypertensive subjects, whereas an elevated pulse pressure only predicted cardiac mortality in hypertensive patients (Table 3).

When, in the fully adjusted models shown in Tables 2 and 3, we substituted mean arterial pressure with systolic blood pressure as an explanatory variable, the relative hazard ratios for AASI did not materially change, whereas those for pulse pressure weakened to a nonsignificant level (data not shown). The introduction of mean 24-hour heart rate in the Cox models did not materially alter the relative hazard ratios (data not shown). The results shown in Tables 2 and 3 also remained consistent, when in the computation of AASI we applied robust regression (least-trimmed squares) or excluded influential data points ($DF\beta>2/\sqrt{n}$).

TABLE 2. Relative Hazard Ratios for Mortality in Relation to the AASI and Pulse Pressure

Cause of Deaths (No. of Deaths)	AASI (Units) RHR (95% CI)	24-Hour Pulse Pressure (mm Hg) RHR (95% CI)	Dichotomized AASI (0, 1) RHR (95% CI)	Dichotomized 24-Hour Pulse Pressure (0, 1) RHR (95% CI)
Cardiovascular (n=566)				
Unadjusted	1.59 (1.47 to 1.71)	1.66 (1.58 to 1.74)	2.05 (1.60 to 2.63)	2.81 (2.37 to 3.34)
Adjusted*	1.14 (1.04 to 1.24)§	1.19 (1.09 to 1.30)	1.71 (1.33 to 2.19)	1.19 (0.98 to 1.44)
Fully adjusted†	1.08 (0.98 to 1.19)	1.16 (1.05 to 1.27)§	1.59 (1.23 to 2.04)	1.11 (0.90 to 1.35)
Stroke (n=151)				
Unadjusted	1.71 (1.47 to 1.97)	1.68 (1.52 to 1.84)	3.06 (2.01 to 4.64)	2.70 (1.95 to 3.76)
Adjusted*	1.23 (1.04 to 1.45)‡	1.12 (0.94 to 1.32)	2.49 (1.64 to 3.80)	0.99 (0.69 to 1.44)
Fully adjusted†	1.21 (1.01 to 1.45)‡	1.04 (0.87 to 1.25)	2.42 (1.58 to 3.72)	0.87 (0.59 to 1.28)
Cardiac (n=358)				
Unadjusted	1.57 (1.42 to 1.73)	1.66 (1.56 to 1.77)	1.78 (1.29 to 2.47)	3.04 (2.45 to 3.78)
Adjusted*	1.11 (0.99 to 1.24)	1.22 (1.10 to 1.37)	1.44 (1.03 to 2.00)‡	1.34 (1.05 to 1.71)‡
Fully adjusted†	1.03 (0.91 to 1.16)	1.21 (1.08 to 1.36)§	1.32 (0.94 to 1.84)	1.28 (0.99 to 1.65)

RHR (95% CI) indicates the relative hazard ratios (95% CI) associated with a 1 SD increase in AASI or 24-hour pulse pressure or with an abnormal AASI or 24-hour pulse pressure dichotomized based on the upper boundary of the 95% prediction interval for individual data in relation to age in a normotensive reference population.⁸

*Adjusted for sex, age, mean arterial pressure, body mass index, smoking, diabetes mellitus, and a history of cardiovascular disease.

†AASI additionally adjusted for pulse pressure and vice versa.

Significance of the RHRs: ‡ $P < 0.05$, § $P < 0.01$, || $P < 0.001$.

Discussion

In this study we have demonstrated that AASI, a measure of the dynamic relation between diastolic and systolic blood pressure throughout the whole day, predicted cardiovascular mortality in a large cohort of hypertensive individuals. For cardiovascular and stroke mortality in dichotomized analyses and for stroke mortality in continuous analyses, this prediction withstood additional adjustment for other risk factors, including pulse pressure. Furthermore, compared with pulse pressure, AASI was a stronger predictor of fatal stroke in

those with ambulatory normotension than in patients with hypertension.

Pulse pressure is a surrogate measure of arterial stiffness²² and an established cardiovascular risk factor.^{23–30} The finding that in middle-aged and older patients cardiovascular prognosis worsens with higher pulse pressure is consistent in men and women,^{23,24,26,30} in treated and untreated hypertensive individuals,^{23,27,30} and in patients with a history of myocardial infarction²⁵ or renal failure.⁷ Our finding that pulse pressure was more predictive at higher than lower levels of blood pressure is in line with the concept that an elevated pulse pressure already represents generalized stiffening of the large arteries and more advanced arterial disease.^{22,23} The observation that pulse pressure was closely related to cardiac mortality also confirms previous findings from the Framingham Heart Study. Indeed, Franklin et al²⁹ demonstrated that in subjects <50 years of age, diastolic blood pressure was a strong predictor of coronary heart disease. Age 50 to 59 years was a transition period when systolic, diastolic, and pulse pressures were similar predictors of cardiovascular risk, whereas from 60 years on, diastolic pressure was negatively related to the risk of coronary events so that pulse pressure became a better predictor than systolic pressure. We assume that, in our study population with mean age of 54.6 years, these age-related trends²⁹ contributed to the prognostic significance of pulse pressure.

In this current study, we have shown that AASI improves on pulse pressure in the prediction of stroke, particularly in individuals with lower average pressures. Arterial stiffness varies nonlinearly with distending pressure; as mean arterial pressure increases, stiffness increases exponentially.¹⁸ Mean 24-hour pulse pressure is an estimate of arterial stiffness at a single point on the pressure stiffness curve: it is critically

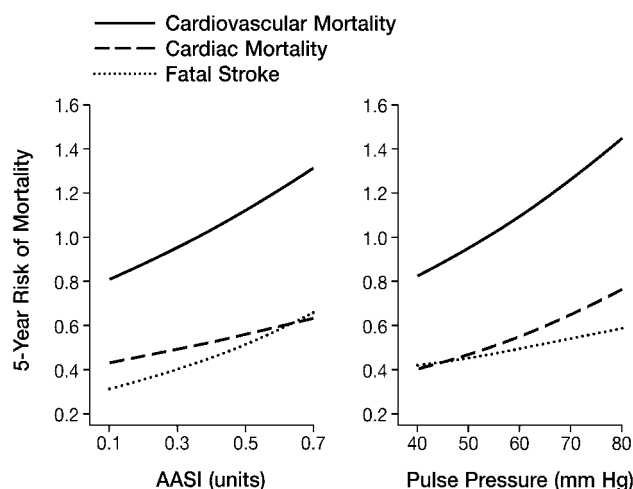


Figure 3. Five-year risk of cardiovascular (full lines), cardiac (dashed lines), and cerebrovascular (dotted lines) mortality per 100 subjects, according to the AASI (left) and the 24-hour pulse pressure (right). Using Cox regression analysis, the death rate was standardized to female sex, mean age, average of mean arterial pressure, mean body mass index, nonsmoking status, absence of diabetes mellitus, and no previous cardiovascular complications.

TABLE 3. Adjusted Relative Hazard Ratios for Cardiovascular Mortality in Relation to the AASI and Pulse Pressure in 2757 Normotensive and 8534 Hypertensive Subjects

Subgroup/Cause (No. of Deaths)	AASI (Units) RHR (95% CI)	24-Hour Pulse Pressure (mm Hg) RHR (95% CI)	Dichotomized AASI (0, 1) RHR (95% CI)	Dichotomized 24-Hour Pulse Pressure (0, 1) RHR (95% CI)
Normotensive subjects (n=2757)				
Cardiovascular (n=101)	1.26 (1.01 to 1.57)†	0.96 (0.78 to 1.18)	2.06 (1.17 to 3.61)‡	1.46 (0.87 to 2.45)
Stroke (n=26)	1.81 (1.18 to 2.78)‡	1.12 (0.75 to 1.66)	5.60 (2.41 to 13.0)§	1.21 (0.46 to 3.16)
Cardiac (n=65)	1.11 (0.83 to 1.47)	0.89 (0.69 to 1.16)	1.31 (0.55 to 3.08)	1.49 (0.76 to 2.92)
Hypertensive patients* (n=8534)				
Cardiovascular (n=465)	1.03 (0.92 to 1.15)	1.25 (1.12 to 1.38)§	1.47 (1.11 to 1.95)‡	1.19 (0.95 to 1.50)
Stroke (n=125)	1.08 (0.88 to 1.32)	1.12 (0.91 to 1.37)	1.81 (1.08 to 3.02)†	0.96 (0.62 to 1.48)
Cardiac (n=293)	1.02 (0.89 to 1.16)	1.31 (1.15 to 1.49)§	1.31 (0.91 to 1.88)	1.40 (1.04 to 1.89)†

RHR (95% CI) is the relative hazard ratios (95% CI) associated with a 1 SD increase in AASI or pulse pressure or with an abnormal AASI or pulse pressure dichotomized based on the upper boundary of the 95% prediction interval for individual data in relation to age in a normotensive reference population. Adjustments included sex, age, mean arterial pressure, body mass index, smoking, diabetes mellitus, and a history of cardiovascular disease. AASI was additionally adjusted for pulse pressure and vice versa.

*Hypertension was a daytime ambulatory blood pressure of ≥ 135 mm Hg systolic or 85 mm Hg diastolic.

Significance of the RHRs: † $P < 0.05$, ‡ $P < 0.01$, § $P < 0.001$.

dependent on the average distending pressure over the 24 hours of measurement. By contrast, AASI rests on the concepts that average 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 structural and functional characteristics of the large arteries.³¹ AASI consequently provides insight into the position of the pressure stiffness curve and, therefore, into intrinsic wall stiffness. This feature may importantly contribute to the improved prognostication of stroke by AASI in ambulatory normotensive subjects and prompts speculation that AASI might predict outcome in patients with well-controlled hypertension. The companion article⁸ supports this contention that AASI, but not pulse pressure, correlates with systolic augmentation < 40 years of age, raising the possibility that AASI might be a more sensitive indicator of arterial stiffening in younger patients. Moreover, particularly in younger subjects, pulse pressure measured at the brachial artery is higher than the central pulse pressure,¹⁹ which is an important determinant of cardiac complications. Indeed, lowered diastolic pressure in the ascending aorta can impair coronary blood flow and predispose to myocardial ischemia, whereas increased central systolic pressure augments cardiac work and can lead to heart failure.^{19,30} Other prospective studies of both normotensive and hypertensive subjects are required to test the hypothesis that the predictive value of AASI and pulse pressure differ according to age, level of central arterial pressure, and target organ damage.

We propose AASI as a novel index of arterial stiffness. Outcome data support the predictive value of other indirect measures of arterial stiffness.^{1-7,23-30} However, with the exception of pulse pressure,²³⁻³⁰ these measures are not presently readily available in clinical practice. Our new measure of arterial stiffness may be easily and directly derived from ambulatory blood pressure monitoring, which is implemented in most hospitals and a growing number of family practices. AASI is not operator dependent. Most hypertension guidelines already recommend the use of ambulatory blood pressure monitoring in patients referred with elevated clinic blood pressures.¹⁷ The

present study, therefore, adds to evidence already supporting the use of ambulatory blood pressure monitoring in routine clinical practice.^{9,32-35}

Some limitations of our study should be addressed. We did not collect nonfatal health outcomes. Also, given the process used to ascertain fatal outcomes, some deaths may not have been recorded because of emigration or marriage. Ambulatory blood pressure monitoring was performed at baseline off treatment using different validated¹⁰⁻¹⁶ devices. More than 90% of the recordings were obtained with oscillometric SpaceLabs monitors.^{11,12} Obviously those patients found to be truly hypertensive were offered blood pressure-lowering pharmacological treatment. However, the aforementioned confounders would have led to an underestimation rather than an overestimation of the observed associations. Other conditions could lead to an erroneous estimate of AASI, such as the variable stroke volume in patients with atrial fibrillation. Yet, AASI did not differ between 20 individuals with atrial fibrillation and 20 age- and sex-matched individuals in sinus rhythm (data not shown). A limited range of systolic blood pressure values throughout the 24 hours would tend to flatten the regression slope and erroneously increase AASI. However, in our study population, the systolic blood pressure range tended to increase across the fifths of the AASI distribution rather than the converse. Outlying data points can greatly influence linear regression, but our results remained consistent when we applied robust regression or discarded outliers in the derivation of AASI.

Perspectives

We studied AASI as a novel index of arterial stiffness, which reflects the diurnal variation in the relation between the diastolic and systolic inflection points of the arterial pressure wave. We validated AASI as a prognostic indicator of total and cause-specific cardiovascular mortality. Its predictive value may complement that provided by pulse pressure in that it appears to be a stronger predictor of stroke mortality, especially in normotensive subjects. Pending additional physiological and clinical⁸ studies and confirmation of the present outcome results in other

cohorts, AASI might add to the stratification of risk based on ambulatory blood pressure monitoring.

Acknowledgments

We are indebted to the staff of the Blood Pressure Unit, Beaumont Hospital (Ireland) and the General Register Office, Department of Health and Children, Ireland, for data collection. We also gratefully acknowledge the clerical assistance of Sandra Covens. The Higher Education Authority (Ireland) and the Charitable Infirmary Charitable Trust (Ireland) supported The Dublin Mortality Outcome Study. The Bilateral Scientific and Technological Cooperation between China and Flanders (grant BIL02/10, Ministry of the Flemish Community, Brussels, Belgium) supported the postdoctoral research of Dr Yan Li in Leuven and travel of Dr Jan A. Staessen to Shanghai.

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