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, 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, 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. 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 Pressurimeter III (Del Mar Avionics). From 1985 onward, we used validated oscillometric devices (SpaceLabs 90202
Diestronic Medical Systems 15 or CH-Druck/Pressure ERKA, to 0.56. For similar levels of 24-hour BP and PP, AASI varied from 0.33 to 0.72 at 80 years for AASI and from 55 mm Hg at 20 years to 80 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 (±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-
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).

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 1. Clinical Characteristics Across Quintiles of the AASI

<table>
<thead>
<tr>
<th>AASI Percentile Limits</th>
<th>&lt;0.28</th>
<th>≥0.28/&lt;0.37</th>
<th>≥0.37/&lt;0.45</th>
<th>≥0.45/&lt;0.55</th>
<th>≥0.55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, %</td>
<td>50.3</td>
<td>48.0</td>
<td>50.3</td>
<td>56.4</td>
<td>59.2</td>
</tr>
<tr>
<td>Age, y</td>
<td>43.9±13.1</td>
<td>51.5±13.5</td>
<td>56.1±13.0</td>
<td>58.9±12.5</td>
<td>62.6±13.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.7±4.8</td>
<td>27.5±4.6</td>
<td>27.5±4.7</td>
<td>27.3±4.7</td>
<td>27.0±4.7</td>
</tr>
</tbody>
</table>

Risk factors

- Smoking, %
  - <0.28: 24.0
  - 0.28/<0.37: 21.2
  - 0.37/<0.45: 20.4
  - 0.45/<0.55: 19.2
  - ≥0.55: 16.6
- Hypertension, %
  - <0.28: 71.4
  - 0.28/<0.37: 73.7
  - 0.37/<0.45: 76.2
  - 0.45/<0.55: 78.5
  - ≥0.55: 78.4
- Diabetes mellitus, %
  - <0.28: 4.1
  - 0.28/<0.37: 5.4
  - 0.37/<0.45: 8.2
  - 0.45/<0.55: 9.5
  - ≥0.55: 10.9
- History of cardiovascular disease, %
  - <0.28: 6.9
  - 0.28/<0.37: 10.3
  - 0.37/<0.45: 12.7
  - 0.45/<0.55: 15.5
  - ≥0.55: 18.9

24-hour ambulatory measurements

- Systolic blood pressure, mm Hg
  - <0.28: 131.1±16.5
  - 0.28/<0.37: 143.3±17.2
  - 0.37/<0.45: 143.3±17.2
  - 0.45/<0.55: 146.4±19.0
  - ≥0.55: 146.4±19.0
- Diastolic blood pressure, mm Hg
  - <0.28: 83.3±10.9
  - 0.28/<0.37: 83.5±11.4
  - 0.37/<0.45: 82.6±11.7
  - 0.45/<0.55: 80.8±12.2
  - ≥0.55: 80.8±12.2
- Mean arterial pressure, mm Hg
  - <0.28: 99.2±13.3
  - 0.28/<0.37: 102.6±13.0
  - 0.37/<0.45: 102.2±12.4
  - 0.45/<0.55: 102.6±13.3
  - ≥0.55: 102.6±13.3
- Pulse pressure, mm Hg
  - <0.28: 47.9±7.6
  - 0.28/<0.37: 52.3±9.2
  - 0.37/<0.45: 56.2±10.3
  - 0.45/<0.55: 60.7±11.7
  - ≥0.55: 65.6±13.9

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

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**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 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 stiffness and an established cardiovascular risk factor. The finding that in middle-aged and older patients cardiovascular prognosis worsens with higher pulse pressure is consistent in men and women, in treated and untreated hypertensive individuals, and in patients with a history of myocardial infarction or renal failure. 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. The observation that pulse pressure was closely related to cardiac mortality also confirms previous findings from the Framingham Heart Study. Indeed, Franklin et al 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, and an established cardiovascular risk factor. The finding that pulse pressure becomes a transition period when systolic, diastolic, and pulse pressures were similar predictors of cardiovascular risk, and an established cardiovascular risk factor. The finding that pulse pressure becomes a better predictor than systolic pressure. We assume that, in our study population with mean age of 54.6 years, pulse pressure increases, stiffness increases exponentially. Mean 24-hour pulse pressure is an estimate of arterial stiffness at a single point on the pressure stiffness curve: it is critically
The companion article supports this contention that might predict outcome in patients with well-controlled hypertensive subjects and prompts speculation that AASI to the improved prognostication of stroke by AASI in ambulatory blood pressure monitoring. 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 blood pressure monitoring subjects and prompts speculation that AASI might predict outcome in patients with well-controlled hypertension. The companion article supports this contention that, 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, 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. 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. However, with the exception of pulse pressure, 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. The present study, therefore, adds to evidence already supporting the use of ambulatory blood pressure monitoring in routine clinical practice.

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 of treatment using different validated devices. More than 90% of the recordings were obtained with oscillometric SpaceLabs monitors. 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 clinical studies and confirmation of the present outcome results in other
cohorts, AAAS might add to the stratification of risk based on ambulatory blood pressure monitoring.

Acknowledgments

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