Prognostic Value of Aortic Pulse Wave Velocity as Index of Arterial Stiffness in the General Population

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Background—Few population studies addressed the prognostic significance of aortic pulse wave velocity (APWV) above and beyond other cardiovascular risk factors.

Methods and Results—We studied a sex- and age-stratified random sample of 1678 Danes aged 40 to 70 years. We used Cox regression to investigate the prognostic value of APWV, office pulse pressure (PP), and 24-hour ambulatory PP while adjusting for mean arterial pressure (MAP) and other covariates. Over a median follow-up of 9.4 years, the incidence of fatal and nonfatal cardiovascular end points, cardiovascular mortality, and fatal and nonfatal coronary heart disease amounted to 154, 62, and 101 cases, respectively. We adjusted for sex, age, body mass index, MAP measured in the office (conventional PP and APWV) or by ambulatory monitoring (24-hour PP), smoking, and alcohol intake. With these adjustments, APWV maintained its prognostic significance in relation to each end point (P < 0.05), whereas office and 24-hour PP lost their predictive value (P > 0.19), except for office PP in relation to coronary heart disease (P = 0.02). For each 1-SD increment in APWV (3.4 m/s), the risk of an event increased by 16% to 20%. In sensitivity analyses, APWV still predicted all cardiovascular events after standardization to a heart rate of 60 beats per minute, after adjustment for 24-hour MAP instead of office MAP, and/or after additional adjustment for the ratio of total to HDL serum cholesterol and diabetes mellitus at baseline.

Conclusions—In a general Danish population, APWV predicted a composite of cardiovascular outcomes above and beyond traditional cardiovascular risk factors, including 24-hour MAP. (Circulation. 2006;113:664-670.)

Key Words: arterial stiffness | cardiovascular diseases | epidemiology | pulse pressure | risk factors

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In 1993–1994, we recorded pulse pressure from office blood pressure readings and 24-hour ambulatory recordings as well as APWV in a sex- and age-stratified random sample of the general Danish population. Follow-up continued until October 2003. In the present analysis, we studied the extent to which the office and 24-hour pulse pressures and APWV predicted cardiovascular outcome above and beyond mean arterial pressure as an index of the blood pressure level.

Methods

Study Population
The Ethics Committee of Copenhagen County approved the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) health survey. The study was conducted in accordance with the Helsinki Declaration. Participants provided informed written consent. In 1982–1984, we selected a random sample of the residents of Glostrup County with the goal to recruit an equal number
of women and men aged 30, 40, 50, and 60 years. At baseline, the participation rate was 82.6%. In 1993–1994, the 3785 former participants were invited for a follow-up examination at the Research Center for Prevention and Health in Glostrup, of whom 2656 (70.2%) renewed informed written consent and were examined.20 For the present analysis, we excluded 978 subjects because APWV had not been recorded (n=36), because they were unwilling to have their 24-hour ambulatory blood pressure measured (n=568), because they had <14 daytime or <7 nighttime blood pressure readings (n=232),21 because their ambulatory blood pressure had been recorded during nighttime shifts (n=13), or because they had a previous history of myocardial infarction or stroke (n=106) or were taking digoxin or nitrates (n=23). Thus, the number of subjects statistically analyzed totaled 1678 (63.2% of those with a follow-up examination).

Data Collection
At the research center, a trained nurse measured anthropometric characteristics. Body mass index was weight in kilograms divided by height in meters squared. After the subjects had rested for 5 minutes in the supine position, 2 consecutive blood pressure readings were obtained with a random zero mercury sphygmomanometer fitted with an appropriate cuff size. The 2 readings were averaged for analysis. Hypertension was defined as an office blood pressure of ≥140 mm Hg systolic or 90 mm Hg diastolic22 or as the use of antihypertensive drugs. Heart rate was counted at the radial artery over 15 seconds. Immediately thereafter, the same trained nurse used 2 piezoelectric pressure transducers (Hellige GmbH) to record in all subjects the arterial wave simultaneously at the left common carotid and femoral arteries.23 APWV was the travel distance between the 2 transducers, measured on the body surface, divided by the transit time, determined manually by the foot-to-foot velocity method.23 For analysis, we averaged from 2 to 15 heart cycles. As reported by Asmar and colleagues,23 the intraobserver repeatability coefficient of APWV, computed according to the method for the distribution of APWV, and the office and 24-hour pulse pressures, unadjusted or with adjustment for sex and age. We used the deviation from mean coding29,30 to compute hazard ratios in quintiles relative to the overall risk in the study population. This approach avoids any assumption about the shape of the association between outcome and APWV or pulse pressure.30 Next, to identify significant predictors of outcome, we used forward and backward selection in Cox regression with the probability value for independent covariates to enter or stay in the model set at 0.05. The baseline measurements considered as predictors were sex, age, body mass index, waist-to-hip ratio, mean arterial pressure, use of antihypertensive drugs, current smoking, alcohol intake, physical activity, ratio of total to HDL serum cholesterol, and diabetes mellitus. To test for heterogeneity between women and men in the associations between outcome and APWV, we forced the appropriate interaction term into the regression models. In a sensitivity analysis, we standardized each participant’s APWV to a heart rate of 60 beats per minute by means of regression analysis in women and men, separately.31 Statistical significance was a probability value of ≤0.05 on 2-sided tests.

Results
Baseline Characteristics of Participants
The 1678 participants included 800 women (47.7%), 608 hypertensive patients (36.2%), of whom 147 (24.2%) were takings antihypertensive drugs, and 48 diabetic subjects (2.8%), of whom 17 (35.4%) were on treatment with antidiabetic agents. Women compared with men had lower office and ambulatory blood pressures, lower APWV, and higher heart rate but similar pulse pressure on office and 24-hour ambulatory blood pressure measurement (Table 1). Alcohol intake in excess of 5 beverages per day was more frequent among men. In the total study population, average values (±SD) of mean arterial pressure were 97.8±12.1 and 91.6±9.9 mm Hg on office and 24-hour ambulatory measurement, respectively. The ratio of total to HDL serum cholesterol averaged 4.6±1.5 in all participants.

The 978 subjects excluded from analysis compared with the 1678 included were older (40/50/60/70 years, 30%/26%/24%/20% versus 26%/29%/27%/18%; P=0.01), were more likely to be female (54.5% versus 47.8%; P<0.01), and were more likely to have lower systolic/diastolic levels of office blood pressure (129.6/80.0 versus 131.1/81.1 mm Hg; P<0.05).

Incidence of End Points in Exploratory Analyses
During follow-up (median, 9.4 years; 5th to 95th percentile interval, 4.0 to 10.1 years), 14 838 person-years accrued. Of 171 deaths, 62 (36.3%) were due to cardiovascular illnesses. The incidence of the composite cardiovascular outcome totaled 154 events, including 43 cardiovascular deaths, 88 coronary events, and 23 strokes. Coronary heart disease consisted of 22 fatal and 79 nonfatal events, including 18 fatal and 35 nonfatal cases of acute myocardial infarction.

Ascertainment of Events
For all enrolled subjects, we ascertained vital status via the Danish Civil Registration System, the cause of death from the blinded adjudication of the diseases on the death certificates, and nonfatal events from the Danish National Health Register, which has a high sensitivity and predictive value.24 The end points considered in the present analysis were cardiovascular mortality, fatal and nonfatal coronary heart disease, and a composite end point consisting of cardiovascular mortality, coronary heart disease (ICD-8 codes 410 to 414 or ICD-10 codes I20 to I25), and stroke (ICD-8 codes 431, 433, or 434 or ICD-10 codes I61 or I63).

Statistical Analysis
For statistical analysis, we used SAS software, version 9.1 (SAS Institute). To compare means, we used the standard normal Z test for large samples or ANOVA with Tukey test for multiple comparisons. For proportions, we used the χ² statistic with Bonferroni correction of the probability values, if appropriate. In the analysis of outcome, for participants who experienced multiple events, we considered only the first event. We implemented Cox proportional hazard regression to calculate relative hazard ratios in relation to APWV and pulse pressure. First, in exploratory analyses, we calculated relative hazard ratios for the composite cardiovascular end point by quintiles of the distribution of APWV and the office and 24-hour pulse pressures, unadjusted or with adjustment for sex and age. We used the deviation from mean coding29,30 to compute hazard ratios in quintiles relative to the overall risk in the study population. This approach avoids any assumption about the shape of the association between outcome and APWV or pulse pressure.30 Next, to identify significant predictors of outcome, we used forward and backward selection in Cox regression with the probability value for independent covariates to enter or stay in the model set at 0.05. The baseline measurements considered as predictors were sex, age, body mass index, waist-to-hip ratio, mean arterial pressure, use of antihypertensive drugs, current smoking, alcohol intake, physical activity, ratio of total to HDL serum cholesterol, and diabetes mellitus. To test for heterogeneity between women and men in the associations between outcome and APWV, we forced the appropriate interaction term into the regression models. In a sensitivity analysis, we standardized each participant’s APWV to a heart rate of 60 beats per minute by means of regression analysis in women and men, separately.31 Statistical significance was a probability value of ≤0.05 on 2-sided tests.
Anthropometrics

APWV and office and 24-hour pulse pressures (Figure 1) revealed strong associations of the risk of the composite cardiovascular end point with quintiles of APWV. The explanatory analysis unadjusted or adjusted for sex and age (Figure 1) revealed strong associations of the risk of the composite cardiovascular end point with quintiles of APWV. The explanatory analysis unadjusted or adjusted for sex and age (Figure 1) revealed strong associations of the risk of the composite cardiovascular end point with quintiles of APWV. The explanatory analysis unadjusted or adjusted for sex and age (Figure 1) revealed strong associations of the risk of the composite cardiovascular end point with quintiles of APWV.

TABLE 1. Baseline Characteristics of Men and Women

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Women (n=800)</th>
<th>Men (n=878)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age class, 40/50/60/70 y, %</td>
<td>27/29/26/18</td>
<td>24/29/27/20</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.3±4.4</td>
<td>26.4±3.6</td>
</tr>
<tr>
<td><strong>Hemodynamic measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office BP systolic, mm Hg</td>
<td>126.9±19.1</td>
<td>132.5±17.2</td>
</tr>
<tr>
<td>Office BP diastolic, mm Hg</td>
<td>79.2±10.1</td>
<td>82.9±10.1</td>
</tr>
<tr>
<td>24-hour BP systolic, mm Hg</td>
<td>123.1±13.5</td>
<td>129.1±12.9</td>
</tr>
<tr>
<td>24-hour BP diastolic, mm Hg</td>
<td>71.2±8.7</td>
<td>76.9±8.5</td>
</tr>
<tr>
<td>Office heart rate, bpm</td>
<td>64.0±8.8</td>
<td>61.0±9.7</td>
</tr>
<tr>
<td>APWV, m/s</td>
<td>10.8±3.2</td>
<td>11.8±3.6</td>
</tr>
<tr>
<td>Office pulse pressure, mm Hg</td>
<td>46.9±13.2</td>
<td>47.9±13.2</td>
</tr>
<tr>
<td>24-hour pulse pressure, mm Hg</td>
<td>51.9±9.3</td>
<td>52.1±8.2</td>
</tr>
<tr>
<td><strong>Biochemical measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.7±0.9</td>
<td>5.0±1.1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.23±1.12</td>
<td>6.1±1.1</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.60±0.44</td>
<td>1.29±0.33</td>
</tr>
<tr>
<td><strong>Lifestyle factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>329 (41.1)</td>
<td>418 (47.6)</td>
</tr>
<tr>
<td>&gt;5 alcoholic beverages per week, n (%)</td>
<td>6 (0.8)</td>
<td>48 (5.6)</td>
</tr>
<tr>
<td>&lt;4 h of exercise per week, n (%)</td>
<td>650 (83.0)</td>
<td>609 (70.6)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are mean±SD or number of subjects (%). Gender differences were significant (P<0.05) except for age class, office and 24-hour pulse pressures, and total cholesterol (0.07<P<0.48).

Table 2 lists the baseline characteristics according to the quintiles of APWV. The explanatory analysis unadjusted or adjusted for sex and age (Figure 1) revealed strong associations of the risk of the composite cardiovascular end point with APWV and office and 24-hour pulse pressures (Figure 1).

Cox Regression

Using Cox regression, we computed the relative hazard ratios associated with a 1-SD increase in APWV and the office and 24-hour pulse pressures, first without any adjustment, next with adjustment for sex and age, and then additionally adjusted for body mass index, mean arterial pressure, current smoking, and alcohol intake (Table 3). In the fully adjusted models, mean arterial pressure was derived from the office measurements for office pulse pressure and APWV and from the ambulatory recordings for the 24-hour pulse pressure.

In Cox models unadjusted or only adjusted for sex and age, APWV and the office and 24-hour pulse pressures consistently predicted each of the 3 outcomes under study. In the fully adjusted models, APWV maintained its prognostic significance in relation to each end point, whereas the office and 24-hour pulse pressures no longer predicted outcome, except for the office pulse pressure in relation to coronary heart disease. Figure 2 shows the absolute risk in women and men associated with APWV at different levels of mean arterial pressure in the office, while controlling for age, body mass index, current smoking, and alcohol intake.

Sensitivity Analysis of APWV as Predictor of Outcome

The relative hazards ratios relating the 3 end points to APWV were higher in women than men (Table 4). At any level of mean arterial pressure, the absolute risk of a composite cardiovascular outcome in relation to APWV also increased more in women than men (Figure 2). However, when we formally tested the interaction between APWV and sex for the 3 end points, none of the probability values reached significance, irrespective of whether (P>0.48) or not (P>0.23) the Cox models were adjusted for other covariates. Furthermore, exclusion of subjects on antihypertensive drugs at the time of the APWV measurement weakened the relative

TABLE 2. Selected Baseline Characteristics Across Quintiles of the Distribution of APWV

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt;8.9 m/s</th>
<th>8.9–10.0 m/s</th>
<th>10.0–11.3 m/s</th>
<th>11.3–13.1 m/s</th>
<th>&gt;13.1 m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>236 (70.2)</td>
<td>173 (45.8)</td>
<td>125 (41.8)</td>
<td>137 (41.0)</td>
<td>129 (39.0)</td>
</tr>
<tr>
<td>Age class, 40/50/60/70 y, %</td>
<td>52/34/11/3</td>
<td>40/37/19/4</td>
<td>20/37/34/9</td>
<td>10/27/41/2</td>
<td>3/11/29/57</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.4±3.8</td>
<td>25.4±3.4</td>
<td>26.0±4.1</td>
<td>26.8±4.2</td>
<td>26.9±4.2</td>
</tr>
<tr>
<td><strong>Mean arterial pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office, mm Hg</td>
<td>88.3±9.5</td>
<td>93.6±8.8</td>
<td>98.3±9.6</td>
<td>102.6±10.5</td>
<td>107.1±12.1</td>
</tr>
<tr>
<td>24-hour, mm Hg</td>
<td>85.3±8.2</td>
<td>89.2±8.0</td>
<td>92.4±8.3</td>
<td>94.3±9.7</td>
<td>97.0±10.7</td>
</tr>
<tr>
<td><strong>Pulse pressure</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Office, mm Hg</td>
<td>39.9±9.8</td>
<td>41.9±9.7</td>
<td>46.8±11.8</td>
<td>50.9±11.7</td>
<td>58.5±13.7</td>
</tr>
<tr>
<td>24-hour, mm Hg</td>
<td>48.0±6.6</td>
<td>49.2±6.7</td>
<td>51.1±6.7</td>
<td>53.3±8.2</td>
<td>58.7±10.6</td>
</tr>
<tr>
<td><strong>Biochemical measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.5±0.4</td>
<td>4.7±0.8</td>
<td>4.9±1.0</td>
<td>5.0±1.2</td>
<td>5.2±1.4</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>4.1±1.1</td>
<td>4.5±1.5</td>
<td>4.6±1.5</td>
<td>4.9±1.5</td>
<td>4.9±1.5</td>
</tr>
<tr>
<td><strong>Lifestyle factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>163 (48.5)</td>
<td>177 (46.8)</td>
<td>138 (46.2)</td>
<td>154 (46.1)</td>
<td>115 (34.7)</td>
</tr>
<tr>
<td>&gt;5 alcoholic beverages per day, n (%)</td>
<td>4 (1.2)</td>
<td>9 (2.4)</td>
<td>10 (3.4)</td>
<td>15 (4.6)</td>
<td>16 (4.9)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or number of subjects (%). All P values for trend across the quintiles were statistically significant (P<0.05). Means and proportions marked with the same letter are not statistically different, with P values adjusted for multiple comparisons.
hazard ratio reported for cardiovascular mortality from 1.20 ($P=0.03$; Table 3) to 1.08 ($P=0.53$; Table 4).

Standardizing APWV to a heart rate of 60 beats per minute, adjustment for the 24-hour mean arterial pressure instead of the office measurement at the time of APWV registration, additional adjustment for the ratio of total to HDL serum cholesterol and diabetes mellitus at baseline, and the combination of the 3 former adjustments did not materially change the point estimates of relative hazard ratios reported for APWV in Table 3 but widened the CIs. However, in all instances, APWV remained a significant and independent predictor of the composite cardiovascular end point (Table 4).

**Discussion**

The key finding of our study was that in middle-aged and elderly individuals randomly recruited from a Western European population, APWV measured over a few seconds in the office was a significant predictor of cardiovascular complications, above and beyond mean arterial pressure and other risk factors, including sex, age, body mass index, current smoking, and alcohol intake. With similar adjustments applied, the office and 24-hour pulse pressures lost their prognostic value with the exception of office pulse pressure in relation to coronary heart disease. For each 1-SD increment in APWV, the risk of an event increased by 16% to 20%. In sensitivity analyses, APWV still predicted all cardiovascular events after standardization to a heart rate of 60 beats per minute, after adjustment for 24-hour instead of office mean arterial pressure, and/or after additional adjustment for the ratio of total to HDL serum cholesterol and diabetes mellitus at baseline.

Most previous studies on the role of APWV as cardiovascular risk factor involved patients with hypertension, diabetes mellitus, or end-stage renal disease or elderly hospis.

### TABLE 3. Standardized Relative Hazard Ratios Relating Various Outcomes to APWV and Office and 24-Hour Pulse Pressures

<table>
<thead>
<tr>
<th>End Point (No. of Events)</th>
<th>Office Pulse Pressure (SD = 13 mm Hg)</th>
<th>24-Hour Pulse Pressure (SD = 9 mm Hg)</th>
<th>APWV (SD = 3.4 m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite cardiovascular end point (n=154)</td>
<td>1.67 (1.46–1.92)‡</td>
<td>1.51 (1.32–1.71)‡</td>
<td>1.50 (1.38–1.63)‡</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex- and age-adjusted</td>
<td>1.31 (1.11–1.55)‡</td>
<td>1.26 (1.09–1.46)‡</td>
<td>1.26 (1.12–1.41)‡</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>1.13 (0.93–1.36)</td>
<td>1.05 (0.89–1.25)</td>
<td>1.17 (1.04–1.32)†</td>
</tr>
<tr>
<td>Cardiovascular mortality (n=62)</td>
<td>1.85 (1.50–2.28)‡</td>
<td>1.70 (1.39–2.07)‡</td>
<td>1.61 (1.44–1.79)‡</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex- and age-adjusted</td>
<td>1.28 (1.00–1.63)†</td>
<td>1.31 (1.05–1.63)†</td>
<td>1.29 (1.11–1.50)†</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>1.04 (0.78–1.37)</td>
<td>1.13 (0.89–1.44)</td>
<td>1.20 (1.01–1.41)†</td>
</tr>
<tr>
<td>Coronary heart disease (n=101)</td>
<td>1.67 (1.41–1.98)‡</td>
<td>1.38 (1.17–1.64)‡</td>
<td>1.45 (1.30–1.61)‡</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex- and age-adjusted</td>
<td>1.44 (1.18–1.76)‡</td>
<td>1.21 (1.00–1.47)‡</td>
<td>1.25 (1.08–1.44)†</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>1.30 (1.04–1.61)†</td>
<td>1.06 (0.86–1.31)</td>
<td>1.16 (1.00–1.35)†</td>
</tr>
</tbody>
</table>

Relative hazards ratios (95% CI) express the risk associated with a 1-SD increase in the measurement of arterial stiffness.

*Also adjusted for sex, age, body mass index, mean arterial pressure as measured in the office (office pulse pressure or APWV) or by ambulatory monitoring (24-hour pulse pressure), current smoking, and alcohol intake. $P<0.05$, $P<0.01$, significance of the relative hazard ratios.
the relative hazard ratios associated with a 3.4-m/s increase in APWV were 1.34 for stroke,1.38 for coronary complications,5 and 1.23 for cardiovascular mortality.5 The hazard ratios for a similar increase in APWV were 1.80 for cardiovascular mortality in elderly patients8 and 1.30 and 3.06 for total mortality in patients with diabetes8 or end-stage renal disease,7 respectively. Boutouyrie and colleagues5 reported relative hazard ratios for coronary heart disease in low-risk hypertensive patients by tertiles of APWV and adjusted for the Framingham risk score.52 With the bottom tertile as referent group, these ratios were 2.37 (95% CI, 1.45 to 3.86) and 5.60 (95% CI, 2.10 to 14.9) for the middle and top tertiles. In similarly informed calculations in our own cohort, these ratios were 2.37 (95% CI, 1.45 to 3.86) and 5.60 (95% CI, 2.10 to 14.9) for the middle and top tertiles, respectively. Boutouyrie and colleagues5 reported relative hazard ratios for coronary heart disease in low-risk hypertensive patients by tertiles of APWV and adjusted for the Framingham risk score.52 With the bottom tertile as referent group, these ratios were 2.37 (95% CI, 1.45 to 3.86) and 5.60 (95% CI, 2.10 to 14.9) for the middle and top tertiles. In similarly informed calculations in our own cohort, these ratios were 2.37 (95% CI, 1.45 to 3.86) and 5.60 (95% CI, 2.10 to 14.9) for the middle and top tertiles, respectively. These findings suggest that the relative hazard ratios in our population-based study are smaller than those in patients because we excluded subjects with previous cardiovascular disease. Moreover, the more extensive adjustment for additional risk factors also weakened the hazard ratios in our study compared with those in the patient cohorts.3,6–8

To our knowledge, only 2 population-based studies9,10 previously examined the role of APWV as an independent predictor of cardiovascular outcomes. Shokawa and colleagues9 followed a cohort of 492 Japanese Americans, including 272 women (55.3%) living in Hawaii. Their mean age was 63.7 years. Over 10 years of follow-up, all-cause and cardiovascular mortality amounted to 43 and 14 deaths, respectively. The authors determined the receiver operating characteristics curve of APWV, which best discriminated subjects who died from those who survived. They observed that the optimal threshold was 9.9 m/s. In multivariate analyses adjusted for sex, age, systolic blood pressure, diabetes mellitus, hyperlipidemia, and ECG abnormalities, the relative risk associated with an elevated APWV was 1.42 (95% CI, 0.96 to 2.11) for all-cause mortality and 4.24 (95% CI, 1.39 to 12.9) for cardiovascular mortality. However, the small number of events and the post hoc determination of the threshold value for APWV render the results of this study difficult to interpret.

Figure 2. Absolute risk associated with APWV in women and men at different levels of mean arterial pressure in the office controlling for age, body mass index, current smoking, and alcohol intake.

### Table 4. Prognostic Significance of APWV in Sensitivity Analyses

<table>
<thead>
<tr>
<th>Subgroup (No. of subjects analyzed)</th>
<th>Cardiovascular End Point</th>
<th>Cardiovascular Mortality</th>
<th>Coronary Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>RHR (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td>Women (n=800)</td>
<td>45</td>
<td>1.40 (1.07–1.82)§</td>
<td>17</td>
</tr>
<tr>
<td>Men (n=878)</td>
<td>109</td>
<td>1.13 (0.98–1.31)†</td>
<td>45</td>
</tr>
<tr>
<td>Participants not taking antihypertensive medications (n=1531)</td>
<td>130</td>
<td>1.12 (0.96–1.28)§</td>
<td>48</td>
</tr>
<tr>
<td>Additional factors accounted for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APWV standardized to heart rate 60 bpm (n=1678)</td>
<td>154</td>
<td>1.14 (1.02–1.29)‡</td>
<td>62</td>
</tr>
<tr>
<td>Adjustment for 24-hour instead of office mean arterial pressure (n=1678)</td>
<td>154</td>
<td>1.16 (1.03–1.31)‡</td>
<td>62</td>
</tr>
<tr>
<td>Additional adjustment for other risk factors (n=1678)*</td>
<td>154</td>
<td>1.15 (1.01–1.30)‡</td>
<td>62</td>
</tr>
<tr>
<td>All of the above (n=1678)</td>
<td>154</td>
<td>1.14 (1.00–1.29)‡</td>
<td>62</td>
</tr>
</tbody>
</table>

*In addition to the cumulative adjustment for sex, age, body mass index, mean arterial pressure as measured in the office, current smoking, and alcohol intake (see Table 3), the models also included the ratio of total to HDL serum cholesterol and diabetes mellitus at baseline.

10.10: P<0.05, †P=0.05, §P=0.01, significance of the relative hazard ratios.
Our observation that office pulse pressure was a significant predictor of coronary heart disease is in agreement with the Framingham findings. Indeed, Franklin and colleagues demonstrated that in subjects aged <50 years, 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 a median age of 51.1 years, these age-related trends contributed to the prognostic significance of pulse pressure.

The present study must be interpreted within the context of its potential limitations and the choices that we made in our epidemiological and statistical approach. First, at baseline, we did not determine the reproducibility of the APWV measurements. However, only 1 trained observer acquired and read all APWV recordings. Asmar and colleagues reported an intraobserver repeatability of 9.0%. If reproducibility would not have been within state-of-the-art standard limits, this would have weakened rather than strengthened the current estimates of the predictive value of APWV. Second, the number of strokes was too small to include cerebrovascular accidents as a separate end point in our analyses. On the other hand, in contrast to several other reports, our analysis included fatal as well as nonfatal hard cardiovascular outcomes. This is a crucial issue for the external validity of our observations because in this era of high-technology medicine, the case-fatality rate of major cardiovascular complications is declining quickly in developed countries so that solely reporting fatal outcomes is falling short of current clinical practice. Third, we deliberately chose to exclude 129 participants with a previous history of myocardial infarction or stroke or who were taking digoxin or nitrates. The exclusion from analysis of participants with a previous history of cardiovascular disease lends support to the concept that stiffening of the central arteries is already prognostically relevant in relatively healthy subjects. Fourth, whether or not APWV should be standardized for heart rate remains a matter of debate. In the present study, heart rate did not behave as a significant forerunner of a worse cardiovascular outcome. When we standardized APWV to a heart rate of 60 beats per minute, our results were consistent. Finally, we chose to adjust APWV and the office and 24-hour pulse pressures for mean arterial pressure rather than for systolic blood pressure. In keeping with published evidence, we viewed blood pressure as being composed of a steady component (mean arterial pressure) and a pulsatile component (pulse pressure). These measurements are statistically independent from one another. In our data, pulse pressure was more tightly correlated with systolic blood pressure ($r^2=0.50$) than with mean arterial pressure ($r^2=0.29$). For APWV, the $r^2$ values were 0.24, 0.30, and 0.22 for pulse pressure, systolic blood pressure, and mean arterial pressure, respectively.

Our present observations in a population sample without previous cardiovascular complications extend previous reports on the prognostic value of APWV. APWV, a simple and noninvasive measurement obtained over a few heart cycles, significantly refined the risk stratification above and beyond classic risk factors. Even when adjusted for mean arterial pressure determined from 24-hour ambulatory blood pressure recordings, APWV kept its prognostic value in relation to the composite of all cardiovascular events. The present findings highlight the need to develop more sensitive techniques to measure the stiffness of various compartments of the arterial tree, which can be readily applied in routine clinical practice for risk stratification. Moreover, further molecular, clinical, and epidemiological research should clarify the genetic mechanisms, environmental factors, and their interaction that lead to premature stiffening of the arterial wall. Figure 2 suggests that for the same level of mean arterial pressure, APWV might behave as a stronger risk predictor in women than men. Given the age distribution of our study population, this observation might be due to the fact that most of the age-related increase in systolic blood pressure occurs after age 50 years in women, whereas the opposite is true in men. However, when we formally tested the interaction terms between APWV and sex in relation to the 3 outcomes, none reached statistical significance, possibly because of a lack of power.

In conclusion, in a general population of Western European extraction, APWV predicted a composite of cardiovascular outcomes above and beyond 24-hour mean arterial pressure and traditional risk factors. In combination with the previous studies in patients and populations, our present findings support the notion that measurement of arterial stiffness is useful in clinical practice for risk stratification.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Aortic pulse wave velocity is easily acquired at the bedside and reflects central arterial stiffness. Accordingly, we investigated this as a predictor of outcome in 1678 Danes, aged 40 to 70 years, randomly recruited from the population of Copenhagen. Over a median follow-up of 9.4 years, the incidence of fatal and nonfatal cardiovascular end points, cardiovascular mortality, and fatal and nonfatal coronary heart disease amounted to 154, 62, and 101 cases, respectively. We adjusted for sex, age, body mass index, mean arterial pressure measured in the office or by ambulatory monitoring, smoking, and alcohol intake. With these adjustments, aortic pulse wave velocity maintained its prognostic significance in relation to each end point, whereas office and 24-hour pulse pressure lost their predictive value with the exception of office pulse pressure in relation to coronary heart disease. In conclusion, aortic pulse wave velocity acquired in a few seconds predicted cardiovascular outcomes over and beyond 24-hour ambulatory blood pressure and traditional risk factors. These findings highlight the potential of indexes of arterial stiffness in risk stratification and the need to introduce such measurements into clinical practice.
Prognostic Value of Aortic Pulse Wave Velocity as Index of Arterial Stiffness in the General Population
Tine Willum Hansen, Jan A. Staessen, Christian Torp-Pedersen, Susanne Rasmussen, Lutgarde Thijs, Hans Ibsen and Jørgen Jeppesen

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