The Relation Between Pulse Pressure and Cardiovascular Mortality in 12 763 Middle-aged Men From Various Parts of the World

A 25-Year Follow-up of the Seven Countries Study

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Background: Hypertension is a dominant characteristic in the prediction of cardiovascular diseases (CVDs). We aimed to evaluate the association of blood pressure measurements with CVD mortality among different populations of the world.

Methods: A total of 12 763 men, aged 40 to 59 years, from 7 countries (United States, Japan, Italy, Greece, former Yugoslavia, Finland, and the Netherlands) were surveyed from 1958 to 1964. Follow-up for vital status and causes of death was carried out over 25 years.

Results: All baseline blood pressure measurements were the best predictors of CVD mortality, compared with age, physical activity, total serum cholesterol level, body mass index or height, and smoking. Moreover, pulse pressure and diastolic and systolic blood pressures were the best predictors for CVD death, followed by mean and mid blood pressures. The age-adjusted hazard ratio per 10–mm Hg increase in pulse pressure varied among cohorts from 1.19 in the United States (P = .04) to 1.29 in southern Europe (P = .01). Differences among cohorts were not significant. In the pooled cohorts, pulse pressure measurements were also a significant predictor for coronary heart disease (hazard ratio per 10–mm Hg increase, 1.15; P = .04) as well as stroke death (hazard ratio per 10–mm Hg increase, 1.32; P = .01).

Conclusions: Pulse pressure followed by diastolic and systolic blood pressures were the best predictors for CVD mortality among other blood pressures, as well as age, physical activity, total serum cholesterol level, anthropometric indexes, and smoking habits. No significant differences were observed among the different populations studied.

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their similarities in culture into the following 4 populations: United States, northern Europe (eastern and western Finland and Zuphen), southern Europe (Montegiorgio, Crete, Corfu, Dalmatia, Rome, Crevalcore, Slavonia, Belgrade, Zrenjanin, and Velika Krsna), and Japan (Tanushimaru and Ushibuka). The 4 populations are homogeneous. The United States and northern and southern Europe populations consisted of white people in the late 1950s when the baseline survey was carried out. The Japanese populations, both from the Island of Kyushu, were homogeneous as well.

**FOLLOW-UP**

From the early 1960s, periodic visits every 5 years were made to check the vital status and to define the causes and dates (day, month, and year) of deaths. The causes of death were obtained from the previous clinical records, by necroscopy records (when available), or by information from family or hospital physicians or any other witnesses.11-14

**END POINTS**

Defined criteria, using the International Classification of Diseases, Eighth Revision (World Health Organization), were applied to determine causes of death. In the presence of multiple causes, a hierarchical preference was adopted with violence, cancer in advanced stages, coronary heart disease, and stroke, in that order. The end points of this analysis were coronary heart disease (myocardial infarction; angina pectoris; and other identified forms of ischemia, sudden coronary death, heart failure, and chronic arrhythmias), stroke, and cardiovascular mortality (ie, the previous causes, plus hypertensive and peripheral artery disease).

**MEASUREMENTS**

The following entry information were considered: age, physical activity, systolic and diastolic BP, pulse pressure (systolic minus diastolic), mean (physiologic) BP as the sum of diastolic plus one third of pulse pressure, mid BP as the average between systolic and diastolic BP, self-reported daily cigarette smoking, total serum cholesterol level, and body mass index (calculated as weight in kilograms divided by the square of height in meters). Two measurements of BP were taken 1 minute apart, and the average was used for the analysis. Classification of physical activity was based on the responses to questions about the occupation and usual activities, including part-time jobs and notable nonoccupational exercise. Further details regarding the procedures applied in the study have been presented in detail elsewhere.11-14

**STATISTICAL ANALYSIS**

Continuous variables are presented as mean±SD, while categorical variables are presented as absolute and relative frequencies. Death rates were calculated using the observed person-time, in years. For each population, the 25-year mortality rates from cardiovascular mortality, adjusted for age, total cholesterol level, smoking, and body mass index, were computed per quartile of pulse pressure. Comparisons of continuous variables between regions were performed using analysis of variance. Survival analysis was performed using the Cox model. The continuous factors were entered linearly, while age was tested exponentially in the model. The associations between the investigated factors and the fatal events are presented as exponentials (hazard ratios [HRs]) of the estimated coefficients. The goodness-of-fit test was based on comparing observed survival probability with the expected probability under the assumption of proportional hazards. To examine whether HRs to die from CVD differ in the 4 populations, we created an ordinal variable from 1 to 4 that indicated each population (1 represented the population with the lowest age-standardized mortality due to CVD, and 4, the populations with the highest mortality). We subsequently tested for a significant interaction between this ordinal population variable and the pulse pressure variable. P<.05 indicated statistical significance. For statistical analysis, SPSS version 11.0 (SPSS Inc, Chicago, III) software was used.

**RESULTS**

Compared with men alive at follow-up, those who died had higher baseline systolic and diastolic BP and pulse pressure measurements, as well as greater frequency of smoking (Table 1). Moreover, Japanese cohorts had the lowest systolic and diastolic BP and the highest pulse pressure measurements (Table 2; P<.001). Pulse pressure...
measurements varied from 9 to 156 mm Hg, while the interquartile range was 17 mm Hg. Less than 10% of the population studied had systolic BP values higher than 167 mm Hg and diastolic BP values higher than 100 mm Hg.

Correlations among BP components were $r=0.82$ for pulse pressure and systolic BP, $r=0.73$ for systolic and diastolic BP, and $r=0.22$ for pulse pressure and diastolic BP. These correlations were similar in all cohorts. However, Japanese cohorts had the lowest height compared with southern Europe, northern Europe, and US cohorts (169 ± 7 cm vs 170 ± 7 cm vs 171 ± 7 cm vs 174 ± 7 cm; $P=.01$). Therefore all the analyses followed up on were also adjusted for height and body mass index.

The mean follow-up time was 20.3 years. During this time, 5340 deaths occurred (45.8%). Overall, 2445 deaths (20.9%) were due to CVDs. Of those deaths, 1565 (13.4%) were due to coronary heart disease and 708 (6.1%) were due to stroke. The annual incidence rate was 10 cardiovascular deaths per 1000 men (6 deaths per 1000 men were due to coronary heart disease and 2.7 deaths per 1000 men were due to stroke). The regional cardiovascular mortality rates were 8 per 1000 men in Japan (n=169 deaths), 9 per 1000 men in southern Europe (n=1171 deaths), 11 per 1000 men in the United States (n=635 deaths), and 13 per 1000 men in northern Europe (n=787 deaths) (P value between regions, <.001). Specifically, stroke mortality rates were 11 per 1000 men in Japan, 7 per 1000 men in northern Europe, 6 per 1000 men in southern Europe, and 4 per 1000 men in the United States (P<.001). The number of the observed deaths was adequate for the regional comparisons followed up on (at $\alpha=5\%$ and statistical power $>80\%$).

### PREDICTION OF CARDIOVASCULAR DEATH THROUGH BP MEASUREMENTS

All BP measurements were significant predictors of cardiovascular mortality, after adjusting for age and baseline physical activity, total serum cholesterol level, body mass index or height, and smoking. In the pool of all cohorts, for every 10–mm Hg increase in pulse pressure we observed a 22% increase in the HR of cardiovascular death; for every 5–mm Hg increase in diastolic BP we observed a 16% increase in the HR; while for every 10–mm Hg increase in systolic, mean, and mid BP measurements, we observed a 22% (P= .01), 42% (P=.009), and 38% (P=.006) increase in the HRs, respectively.

When we stratified the analysis by cause of death, pulse pressure was a significant predictor for coronary heart disease (HR per 10 mm Hg, 1.15; 95% confidence interval [CI], 1.08-1.18) and for stroke death (HR per 10 mm Hg, 1.32; 95% CI, 1.02-1.69).

Furthermore, all BP measurements were the best predictors for CVD death among the other investigated cofactors (because they had the highest likelihood ratio). In addition, pulse pressure measurements had the most significant contribution, based on the maximum log-likelihood difference (−2 log-likelihood, 15 978; $P<.001$) in the prediction of cardiovascular death compared with systolic (−2 log-likelihood, 15 874; $P<.001$), diastolic (−2 log-likelihood, 15 923; $P<.001$), mid (−2 log-likelihood, 15 640; $P<.001$), and mean (−2 log-likelihood, 15 642; $P<.001$) BP. To reinforce the previous findings, we estimated a survival model with systolic and diastolic BP as well as a model with mean blood and pulse pressure together. Both diastolic and systolic BP were significantly associated with cardiovascular mortality (−2 log-likelihood, 15 639; $P<.001$). Moreover, pulse and mean BP measurements were also significant predictors of cardiovascular death, while they were found to have the same predictive ability compared with the previous model (−2 log-likelihood, 15 639; $P<.001$).

We then classified the participants according to their baseline BP measurements, that is, optimal (n=2985), prehypertension (ie, systolic/diastolic BP, 120/80 to 140/90 mm Hg [n=4554]), and hypertension (n=5224). The previous findings regarding pulse pressure and cardiovascular risk were also recognizable in the optimal (HR for every 10 mm Hg, 1.07; 95% CI, 1.01-1.15), prehypertension (HR for every 10 mm Hg,1.06; 95% CI, 0.99-1.13), and hypertension groups (HR for every 10 mm Hg, 1.18; 95% CI, 1.15-1.22) (Table 3).

### RELATIONSHIP BETWEEN PULSE PRESSURE AND CARDIOVASCULAR DEATH IN VARIOUS POPULATIONS

We further explored the association of BP with CVD mortality in relation to region. The relationship between pulse pressure and hazard of cardiovascular death was positive and significant in all cohorts. Specifically, the adjusted HR varied from 1.19 in the United States (P<.001), to 1.25 in Japanese and northern Europe cohorts (P<.001) and to 1.29 in southern Europe cohorts, per 10–mm Hg increase in pulse pressure. Moreover, in spite of the large differences in 25-year incidence rates for CVD mortality, the HRs for pulse pressure in relation to CVD death did not differ among the populations (P= .07 for the interaction

### Table 2. Baseline Levels of Blood Pressure Components in Different Regions of the Seven Countries Study*

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>United States (n = 2571)</th>
<th>Northern Europe (n = 2555)</th>
<th>Southern Europe (n = 6627)</th>
<th>Japan (n = 1010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>139 ± 21</td>
<td>141 ± 20</td>
<td>139 ± 20</td>
<td>135 ± 25</td>
</tr>
<tr>
<td>Diastolic</td>
<td>86 ± 12</td>
<td>84 ± 12</td>
<td>85 ± 12</td>
<td>76 ± 14</td>
</tr>
<tr>
<td>Pulse</td>
<td>53 ± 14</td>
<td>57 ± 14</td>
<td>54 ± 14</td>
<td>59 ± 18</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD millimeters of mercury.
between the pulse pressure and the ordinal population variable). Similar results were observed when we evaluated the other BP measurements (data not shown in text or tables).

We then calculated the mortality rates per tertile of pulse pressure level (first tertile up to 48 mm Hg, second tertile up to 59 mm Hg, and third tertile greater than 60 mm Hg). Overall, the adjusted survival in men who were in the upper tertile at entry examination was less than 70% (Figure), whereas the survival in men who had a pulse pressure less than 59 mm Hg was roughly 80% (P = .007). Compared with the lowest tertile of pulse pressure, southern European men in the upper tertile had 78% higher risk for CVD death (P < .001, men from the United States had 84% higher risk (P < .001), and men from northern Europe and Japanese cohorts had 96% higher risk (P < .001), after adjusting for age (P value for regional differences, .15). Moreover, the highest death rates in the upper tertile of pulse pressure were observed in northern Europe and US cohorts, whereas the lowest death rates were observed in Japanese and southern Europe cohorts (Table 4, P value for the interaction between tertile of pulse pressure and the ordinal variable that described the region, .21).

### Table 3. Age-Adjusted Estimates From a Backward Step-Wise Cox Proportional Hazards Model Predicting 25-Year Cardiovascular Mortality as a Function of Baseline Risk Factor Levels

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse pressure (per 10 mm Hg)</td>
<td>1.22 (1.10-1.34)</td>
</tr>
<tr>
<td>Diastolic blood pressure (per 5 mm Hg)</td>
<td>1.16 (1.05-1.27)</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mm Hg)</td>
<td>1.22 (1.10-1.35)</td>
</tr>
<tr>
<td>Mean blood pressure (per 10 mm Hg)</td>
<td>1.42 (1.38-1.47)</td>
</tr>
<tr>
<td>Mid blood pressure (per 10 mm Hg)</td>
<td>1.38 (1.30-1.41)</td>
</tr>
</tbody>
</table>

*Variables also included in all models were age, body mass index or height, total serum cholesterol level, smoking habits, and physical activity status. All the aforementioned covariates were statistically significant predictors of cardiovascular events at P < .001.

We observed that the 25-year risk of CVD death among 12,763 middle-aged men was strongly associated with various BP measurements. Furthermore, pulse pressure was the best predictor of death, followed by diastolic, systolic, mid, and mean BP measurements, as well as among all the other investigated factors (age, smoking habits, anthropometric indexes, and total serum cholesterol levels). In addition, although mortality rates differed among populations, no significant interaction was observed between BP levels and the region of study on CVD mortality. The latter finding may imply that the relation between pulse pressure and the risk of death over the long term did not differ among populations in which the absolute risk of death from CVD varied considerably. This lack of population differences in HRs was similar to that observed earlier in the same study.4,15,16

### ARTERIAL BP AND CVD

We observed that every 10–mm Hg increase in pulse pressure levels corresponds to a 22% increase in the risk for cardiovascular death. In addition, for every 10– and 5–mm Hg increase in systolic and diastolic BP, respectively, we observed a 22% and 16% increase in the risk of death. The effect of pulse pressure on cardiovascular death was more prominent among those with hypertension compared with normotensive individuals. The aforementioned HRs for pulse pressure values were similar to those reported by Franklin et al1 from the 20-year follow-up in both men and women of the Framingham Heart Study. Moreover, Benetos9 reported that pulse pressure was a significant predictor of coronary mortality but not cerebrovascular mortality. On the contrary, in our study the effect of pulse pressure on stroke mortality was significant and stronger compared with the effect of pulse pressure on coronary death.

It is well known that high BP levels are the dominant characteristic in the prediction of cardiovascular death.1,2 In the 25-year follow-up the Seven Countries Study investigators reported that systolic BP was associated with coronary mortality at given levels of diastolic BP, but diastolic BP was not predictive of mortality at given levels of systolic BP.4 Moreover, Menotti et al16 observed that increases in BP were associated with subsequent excess of stroke deaths only in those who started from high levels (>140 mm Hg), whereas diastolic BP was not associated with stroke risk. In several classes of diastolic BP, increasing systolic BP was associated with increasing death rates, whereas this was not present for increasing diastolic BP as systolic BP increased. It should also be highlighted that in the present work pulse pressure was the best predictor of cardiovascular mortality among all arterial BPs. This is in accord with the results from the Framingham Heart Study, which underlined that nei-
Table 4. Mortality Rates of Cardiovascular Diseases per Quartile Tertile of Pulse Pressure

<table>
<thead>
<tr>
<th>Pulse Pressure, mm Hg</th>
<th>United States</th>
<th>Northern Europe</th>
<th>Southern Europe</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;48</td>
<td>8/1000</td>
<td>10/1000</td>
<td>7/1000</td>
<td>5/1000</td>
</tr>
<tr>
<td>49-59</td>
<td>11/1000</td>
<td>12/1000</td>
<td>8/1000</td>
<td>8/1000</td>
</tr>
<tr>
<td>&gt;59</td>
<td>17/1000</td>
<td>19/1000</td>
<td>13/1000</td>
<td>12/1000</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Blood pressure measurements were significant long-term predictors of CVD death, and despite the high correlation of pulse pressure with systolic BP, pulse pressure predominates in predicting cardiovascular death in middle-aged men. Moreover, the relative increase in long-term mortality due to CVD for a given increase in pulse pressure was similar in various populations, whereas the absolute risk at the same level of pulse pressure varied substantially.

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LIMITATIONS

Although the collection of mortality data and causes of death for the subsequent 25 years was almost 100%, the exact cause of death was difficult to determine in some cases. However, CVD mortality is considered a robust category, so misclassification is probably not severe. An additional limitation of the study is that it was conducted only among men. Thus, generalizing the findings to women should be made with caution. Another limitation is that in the analysis we did not take into account risk factor changes over the follow-up period. Also, a limitation is the use of a single measurement in relation to long-term prediction of death, which may hide inherent variability of the estimates. There were also several problems due to the standardization of BP measurement among field conditions. Keys reported that there is no way to assure that BP measurements by a physician examining men in one cohort were absolutely comparable with those made by their colleagues in another cohort. Finally, the lack of information about serum creatinine and sodium intake is another limitation of this study.

It has been shown that diastolic and systolic BPs are positively associated with cardiovascular risk. However, most of these studies were mainly based on young individuals, in whom systolic and diastolic BPs tend to track together. Thus, the effect of pulse pressure may be underestimated. We know that after the fifth decade of life, systolic BP rises more than diastolic BP, resulting in elevation of pulse pressure. Thus, diastolic BP rises with increased peripheral arterial resistance and falls with increased central artery stiffness; the relative contributions of these 2 opposing forces determine diastolic BP and ultimately pulse pressure. Moreover, pulse pressure and systolic BP are highly correlated because both BP components rise with increases in vascular resistance and large artery stiffness. Franklin et al reported that when the components of BP are assessed individually, increments in pulse pressure at a fixed systolic BP are associated with a greater risk for CVD compared with increments in systolic BP at a fixed pulse pressure. Subsequently, Franklin et al hypothesized that cardiovascular risk was related more to the pulsatile stress caused by large-artery stiffness during systole than to the steady state stress due to small-vessel resistance during diastole. Moreover, Benetos suggested that since arterial stiffening causes an increase in systolic BP and a decrease in diastolic BP, the gap between the two (ie, pulse pressure) might be the best predictor of coronary events. This hypothesis is confirmed by our findings. Furthermore, compelling evidence has emerged that pulse pressure is a strong indicator of stroke risk even among normotensive individuals. This was also revealed by the present work. In addition, we observed no differences regarding the effect of BP measurements on CVD mortality between different populations of the world.

However, there are also opposing results. Recently, the MRFIT study investigators, studying a sample of about 340,000 middle-aged men, reported that systolic and diastolic BP measurements were more strongly related to cardiovascular mortality compared with pulse pressure. In addition, a recent meta-analysis from the Prospective Studies Collaboration reported that pulse pressure provides much less “informativeness,” compared with other BPs, in predicting overall and cardiovascular mortality.

LIMITATIONS

Although the collection of mortality data and causes of death for the subsequent 25 years was almost 100%, the
REFERENCES


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n this issue of ARCHIVES, we publish a letter from Rice et al1 concerning the article by Panagiotakos and colleagues titled “The Relation Between Pulse Pressure and Cardiovascular Mortality in 12 763 Middle-aged Men From Various Parts of the World: A 25-Year Follow-up of the Seven Countries Study” (Arch Intern Med. 2005;165:2142-2147).

The letter was received shortly after publication of the article by Panagiotakos et al, and it reports errors in the statistical calculations and interpretation of the analyses presented in that article. Following additional thorough review of the article by the editors, along with considerable consultation with the authors, all authors agreed that the contents of the letter were correct and that the findings of the article were invalid as originally presented. The editors and the authors have agreed to retract the article.

The editors regret the publication of this article, which contained incorrect statistical analyses. We deeply regret that these errors were not detected in the course of prepublication review, but we are grateful to Rice and colleagues for bringing this matter to our attention during postpublication peer review. The editors and authors regret the error and apologize for any inconvenience this matter may have caused to our readers.

Philip Greenland, MD
Editor

Analytic Errors Undermine Conclusions of Cardiovascular Study

In their study of hypertension as a predictor of cardiovascular mortality, we believe that Panagiotakos and colleagues1 have made serious analytic errors, undermining their reported conclusions.

We question two specific sets of results. First, the authors report inferences based on “log-likelihood differences.” These are usually represented by χ² statistics, as produced by the authors’ software (version 11.0; SPSS Inc, Chicago, Ill). However, they report values ranging from 15 640 to 15 978, which are inconceivable χ² values given the sample size. More straightforwardly, these “−2 log-likelihood” values are really minus two times the optimized values of the log-likelihood for each model. Hence, the lowest reported value, using mid blood pressure, is actually the best fitting model considered, making mid blood pressure the best predictor. Pulse pressure is the worst of the single predictors, the opposite of the authors’ stated conclusions. Further evidence comes from Table 31(p2145); converting the stated confidence intervals into z values, the pulse pressure effect accords with z = 4, while mid pressure gives z ~ 14, which is far more statistically significant.

Second, the authors implement two further models, with “systolic and diastolic BP [blood pressure] as well as...mean blood and pulse pressure together,” and “found” them to have the same predictive ability. They are exactly the same model. Linearly transforming covariates makes no difference to a model’s fit, nor to estimates of covariate effects, likelihood ratio tests and so on. Thus, this section does little to “reinforce the previous findings.”

In summary, the analysis directly contradicts the reported results.

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