Predictive Value of Repeated Systolic Blood Pressure Measurements for Stroke Risk
The Zutphen Study
Sirving Keli, MD; Bennie Bloemberg, MSc; and Daan Kromhout PhD, MPH

Background and Purpose: The strength of the association between blood pressure and stroke incidence is dependent on the number of blood pressure measurements. Different summary variables of repeated blood pressure measurements taken during 10 years were evaluated in relation to the long-term risk of stroke in the Zutphen Study.

Methods: During the period 1960–1970 repeated blood pressure measures were taken yearly in 603 men aged 50–69 years in 1970 in the town of Zutphen, The Netherlands. The individual average systolic blood pressure between 1960 and 1970, the predicted systolic blood pressure for 1970 (based on regression of blood pressure readings on time), and the single observed systolic blood pressure in 1970 were used as systolic blood pressure estimates. Their strength in predicting the 15-year stroke incidence was assessed using Cox proportional hazards models. Adjustment was made for the confounding effects of age, cigarette smoking, and serum total cholesterol.

Results: The average systolic blood pressure between 1960 and 1970 was the strongest predictor of 15-year stroke incidence. The strength of the association was underestimated by 55% when a casual systolic blood pressure measurement was used instead of 11 yearly measurements.

Conclusions: It can be concluded that a casual blood pressure measurement leads to a substantial underestimation of the long-term stroke risk of an individual.

KEY WORDS • blood pressure • cerebrovascular disorders • incidence

Cohort studies have shown that casual blood pressure measurements have a strong predictive power for stroke incidence and mortality.1–8 This has also been reported for The Netherlands.9–11 Randomized clinical trials on the effect of treatment of hypertension have shown that lowering blood pressure by drug treatment is an effective measure to decrease stroke incidence and mortality within a few years.12–17 Blood pressure can therefore be considered an important independent predictor of stroke.

Most studies on the relation of blood pressure and stroke are based on a single baseline blood pressure measurement and subsequent follow-up of the study subjects.1–11 However, blood pressure has a large intra-individual variation and is also subject to measurement errors.18–22 Single blood pressure measurements, therefore, do not reflect the true blood pressure level of an individual and do not take into account changes in blood pressure level during follow-up. Summary variables of several blood pressure readings have been proposed as better risk indicators than a single blood pressure measurement.18–22 In most studies, periods of 4–5 years at a maximum were used to summarize the blood pressure readings. However, it is of great interest to study the effect of blood pressure on stroke incidence based on blood pressure measurements during a longer period before the baseline measurement to get a better estimate of the true blood pressure. This was done in the Zutphen Study. The predictive power of three blood pressure estimates on the stroke incidence during the subsequent 15 years was studied in univariate and multivariate analyses. The results of these analyses are reported here.

Subjects and Methods
Since 1960, a longitudinal investigation of risk factors for chronic diseases has been carried out among middle-aged men from the town of Zutphen in The Netherlands. The Zutphen Study is the Dutch contribution to the Seven Countries Study.23–25 In 1960 a random sample of 1,088 men born between 1900 and 1919 was drawn from a total of 24,500. A cohort of 878 men aged 40–59 years was eventually medically examined.

Blood pressure was measured with an ordinary mercury sphygmomanometer at the end of the physical examination on the right arm with the men in supine position, according to the protocol of the Seven Countries Study.23 Only the result of the last of two measurements was recorded. Between 1960 and 1970 blood pressure was measured yearly. The average systolic blood pressure was calculated as the sum of the systolic blood pressure readings from 1960 to 1970 divided by the number of measurements, provided that the subject
had a total of at least four readings during this period. At least one of these readings should have been taken in the last 5 years before or during 1970. To include trends in systolic blood pressure during the period 1960-1970, the predicted systolic pressure was calculated from the linear regression equation of the systolic pressure readings from 1960 to 1970 on time.

Information on cigarette smoking was collected in a standardized manner. Exposure to smoke was operationalized by calculating the variable pack-years of cigarette smoking. Serum cholesterol determinations were carried out according to the method of Abell-Kendall in the period 1960-1965 and the method of Zlatkis in the period 1966-1970, which provided values equivalent to those obtained with the Abell-Kendall method. The average total serum cholesterol level over the period 1960-1970 was calculated in the same way as the average systolic blood pressure.

During follow-up, the men were medically examined yearly between 1960 and 1973, in 1977/1978, and in 1985. Questionnaires about their health status were entered as a continuous variable in these models. The average diastolic blood pressure values. Therefore, only the results for systolic blood pressure were used in further analyses.

Of the 755 men who were alive and free of stroke in 1970, 143 were excluded either because of missing blood pressure readings in 1970 or because of having more than seven missing values during the period 1960-1970. Nine of the remaining 612 persons were excluded because of having more than seven missing values during the period 1960-1970. Nine of the remaining 612 persons were excluded because of having more than seven missing values during the period 1960-1970.

Nine of the remaining 612 persons were excluded because of missing data needed to correct for confounders, leaving 603 men for the final analyses.

Statistical analyses were performed using the SPSS/PC+ and BMDP package programs. Stroke risk was assessed by survival analysis using the Kaplan-Meier product limit estimator and the Cox proportional hazards model. Correction for confounding by age, cigarette smoking, and serum total cholesterol was performed in multivariate Cox models. The following cutoff points were used for the single observed systolic blood pressure in 1970: < 130 mm Hg (lowest quartile), 130-155 mm Hg (two middle quartiles), and ≥ 156 mm Hg (highest quartile). These categories will be referred to as low, middle, and high systolic blood pressure. The same cutoff points were used for the other systolic blood pressure estimates.

Regression dilution bias is defined as the percent decrement in risk when a single measurement of a potential risk factor is used to study the association with a disease. This bias is due to intraindividual variation and measurement variability, causing regression toward the mean. Regression dilution bias was assessed by calculation of the percent underestimation of the regression coefficient for systolic blood pressure in the Cox model when the single observed systolic blood pressure is used instead of the average systolic blood pressure between 1960 and 1970 or the predicted systolic blood pressure estimates.

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Results

Between 1970 and 1985, 46 of the 603 men aged 50-69 years in 1970 had a first stroke. Fourteen of these men died because of stroke. The overall stroke incidence rate was 6.2 per 1,000 person-years. The 46 men who developed a stroke were older but did not have significantly higher single observed diastolic and systolic blood pressures in 1970 compared with nonstroke cases (Table 1). The predicted systolic blood pressure for 1970 and the average systolic blood pressure between 1960 and 1970 were significantly higher in the stroke cases. This was not the case for the predicted and average diastolic blood pressure values. Therefore, only the results for systolic blood pressure were used in further analyses.

The highest relative risk for stroke was observed for the average systolic blood pressure between 1960 and 1970. Men with high systolic blood pressure levels had a 4.01 times higher 15-year stroke incidence than those with low systolic blood pressure levels (Table 2). When adjustment was made for age, cigarette smoking, and average serum total cholesterol between 1960 and 1970, the stroke incidence was 3.11 times higher. For the predicted systolic blood pressure in 1970, a stroke

### Table 1. Systolic Blood Pressure Estimates and Other Risk Factors in 603 Men Aged 50–69 in 1970 in Relation to 15-year Stroke Incidence in the Zutphen Study

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No stroke (n=557)</th>
<th>Stroke (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.4±5.3</td>
<td>62.0±5.4*</td>
</tr>
<tr>
<td>Observed SBP 1970 (mm Hg)</td>
<td>145.7±19.9</td>
<td>152.4±25.4</td>
</tr>
<tr>
<td>Observed DBP 1970 (mm Hg)</td>
<td>88.6±11.4</td>
<td>90.4±13.2</td>
</tr>
<tr>
<td>Predicted SBP 1970 (mm Hg)</td>
<td>147.6±18.4</td>
<td>156.0±25.2t</td>
</tr>
<tr>
<td>Predicted DBP 1970 (mm Hg)</td>
<td>89.3±10.3</td>
<td>91±11.9</td>
</tr>
<tr>
<td>Average SBP 1960–1970 (mm Hg)</td>
<td>141.9±14.1</td>
<td>148.3±19.2t</td>
</tr>
<tr>
<td>Average DBP 1960–1970 (mm Hg)</td>
<td>86.9±7.7</td>
<td>88.8±8.9</td>
</tr>
<tr>
<td>Cigarettes/day · years before 1970</td>
<td>443.8±325.3</td>
<td>457.2±329.0</td>
</tr>
<tr>
<td>Average serum cholesterol 1960–1970 (mg/dl)</td>
<td>237.5±36.4</td>
<td>235.7±37.9</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure. *p<0.01, tp<0.05.

<table>
<thead>
<tr>
<th>Systolic blood pressure (mm Hg)</th>
<th>Observed 1970</th>
<th>Predicted systolic pressure 1970</th>
<th>Average systolic pressure 1960–1970</th>
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<tbody>
<tr>
<td></td>
<td>Crude HR 95% CL</td>
<td>Adjusted HR 95% CL</td>
<td></td>
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<tr>
<td>Observations 1970</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
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<tr>
<td>130–155</td>
<td>0.55</td>
<td>0.74</td>
<td>1.29</td>
</tr>
<tr>
<td>≥156</td>
<td>1.99</td>
<td>2.52</td>
<td>4.01</td>
</tr>
<tr>
<td></td>
<td>0.24–1.27</td>
<td>0.29–1.88</td>
<td>0.53–3.13</td>
</tr>
<tr>
<td></td>
<td>0.92–4.31</td>
<td>1.03–6.17</td>
<td>1.54–10.45</td>
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<tr>
<td>Predicted systolic pressure 1970</td>
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<td>&lt;130</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>130–155</td>
<td>0.74</td>
<td>0.76</td>
<td>1.26</td>
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<tr>
<td>≥156</td>
<td>2.52</td>
<td>2.34</td>
<td>3.11</td>
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<tr>
<td></td>
<td>1.03–6.17</td>
<td>0.95–5.76</td>
<td>1.17–8.24</td>
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HR, hazard ratio, calculated from Cox proportional hazards model; 95% CL, 95% confidence limits of hazard ratio; Adjusted, adjusted for age in 1970, average serum total cholesterol between 1960 and 1970, and cigarette smoking; χ², chi-square test for linear trend.

Discussion

The results of the present study showed that the average systolic blood pressure of 11 yearly readings was more strongly related to stroke incidence than a single systolic blood pressure measurement. Other studies reported a better assessment of stroke risk by a cumulative measure of blood pressure over a prolonged period instead of a single observed blood pressure measurement. Although the estimates of the true blood pressure used in these studies are somewhat different, the findings are consistent with those observed in the present study.

Yearly blood pressure values were strongly correlated (r>0.6). This means that in hypertensive patients the blood pressure is correlated with the duration of hypertension. This was especially the case in the 1960s, because at that time only very high blood pressure levels were treated. However, the effect of the duration of hypertension should not be overstated, because hypertensive patients are still prone to variability in blood pressure and measurement errors, which cause regression dilution bias. MacMahon and coworkers reported an increase of 60% in the strength of the association between diastolic blood pressure and stroke risk when bias due to regression dilution was taken into account. They adjusted for regression dilution bias by using repeated diastolic blood pressure measurements in a subsample of the examined populations. Our estimate of a 55% increase in the strength of the association was based on 11 yearly blood pressure measurements before 1970. Although different methods were used to take regression dilution bias into account, similar results were obtained in both studies.

The stroke risk rose sharply above systolic blood pressure values of 156 mm Hg, suggesting a possible threshold effect around this cutoff point (Table 2, Figure 1).
1). This effect was stronger for the average systolic blood pressure than for the single observed or predicted blood pressure for 1970. This cutoff point is in accordance with the commonly used cutoff point of 160 mm Hg for systolic hypertension.36 In the guidelines for the management of hypertension prepared by the guidelines subcommittee of the World Health Organization/International Society of Hypertension Mild Hypertension Liaison Committee, diastolic blood pressure was used to diagnose hypertension.37 However, the findings of the present study and several other epidemiological studies suggest that systolic hypertension is a stronger predictor for stroke risk than diastolic hypertension.8,21,32,38

The findings of the present study clearly showed that a casual systolic blood pressure measurement is not sufficient to predict stroke risk. The average systolic blood pressure measured over a long period of time provides a much better estimate of the true pressure. When considering treatment most clinicians do not rely on a single blood pressure reading.3,24 The best estimate of the long-term stroke risk of a patient in clinical practice is achieved when the average systolic blood pressure over a period of several years is taken into account.

Acknowledgments

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