Blood Pressure Control and Risk of Stroke
A Population-Based Prospective Cohort Study

Cairu Li, MD, PhD; Gunnar Engström, MD, PhD; Bo Hedblad, MD, PhD; Göran Berglund, MD, PhD; Lars Janson, MD, PhD

Background and Purpose—Adequate control of blood pressure (BP) is a cornerstone in stroke prevention. This study explored the risk of stroke in relation to the quality of BP control in a population-based cohort and whether control of hypertension was related to background characteristics of patients.

Methods—A total of 27 936 subjects (10 953 men and 16 983 women), 45 to 73 years old, living in Malmö, Sweden participated in the study. Incidence of stroke was followed-up for a mean period of 6 years. Controlled BP was defined as BP $<140/90$ mm Hg in subjects with pharmacological treatment for hypertension.

Results—In the whole cohort, 16 648 subjects (60%) had hypertension (BP $\geq 140/90$ mm Hg) and 23% of them received treatment. Among treated hypertensives, 88.2% had BP levels $\leq 140/90$ mm Hg and 49.5% had BP levels $\geq 160/100$ mm Hg. During the follow-up, 137 strokes occurred among treated hypertensive subjects. The crude incidence of stroke was 289/100 000 person-year in controlled hypertensive subjects and 705/100 000 person-year in treated hypertensive subjects with BP $\geq 140/90$ mm Hg. It was estimated that $\approx 45\%$ of all strokes among subjects with treatment for hypertension might be attributed to uncontrolled BP. In treated hypertensives, the risk of stroke increased significantly with advancing age, current smoking, high level of diastolic BP, and diabetes. In hypertensive subjects without treatment ($n=12 819$), incidence of stroke was 363/100 000 person-year.

Conclusion—Uncontrolled BP is highly prevalent in patients with pharmacological treatment for hypertension. More than 90% of stroke in this group occurred in those with uncontrolled BP. Adequate hypertension control may prevent a substantial proportion of first-ever stroke among treated hypertensives. (Stroke. 2005;36:725-730.)

Key Words: blood pressure ■ hypertension ■ stroke

Hypertension is generally considered to be the most important risk factor for stroke in the general population. Clinical trials have demonstrated the beneficial effect of pharmacological antihypertensive intervention on lowering the incidence of stroke. However, the management of hypertension is still far from the goal treatment levels in the general population.

The “rule of halves” was described by Wilber and Barrow in 1972 to delineate the prevalence of hypertension and its treatment, ie, half of the hypertensive subjects are detected and half of them are treated, of which only half achieve adequate blood pressure (BP) control. Over 3 decades, the “rule of halves” is still valid in most European countries and in the US, even though many new pharmacological medications have been developed.

In Malmö, the third largest city of Sweden, $\approx 800$ citizens experience a first-ever stroke each year. The annual incidence of stroke increased from 1989 to 1998 in men and women. Because hypertension is regarded as the most important risk factor for stroke, its increasing incidence may be attributed to inadequate hypertension control. Few population-based studies have studied the incidence of stroke in relation to the quality of hypertension treatment.

The aim of the present population-based study is to evaluate the relationship between the incidence of first-ever stroke and the quality of BP control in Swedish men and women with treatment for hypertension. An attempt was also made to explore whether the quality of BP control was related to the patient’s socio-demographic characteristics, lifestyle, and health-related problems.

Materials and Methods

Study Population
From 1991 to 1996, all men and women, born between 1923 to 1950 and living in the Malmö area in the southern part of Sweden, were recruited into the Malmö Diet and Cancer (MDC) study. The detailed information of the MDC study has been reported elsewhere. Briefly, the participants were offered a health assessment program, including a self-administered questionnaire in combination with clinical examinations at the screening center. All participants were followed-up from the time of baseline examination until death or until December 31, 1999.
The final cohort consisted of 28,449 subjects (11,246 men and 17,203 women) from the eligible population of ∼74,000 individuals. Those who had a history of stroke before the examination (according to self-report or hospital register) (n=467) and those who had a missing value of BP (n=46) were excluded from the analysis.

Stroke Registration
The records of patients with stroke were retrieved by data linkage to the Stroke Register in Malmö (STROMA). Since 1989, all Malmö residents who have had a stroke, whether hospitalized or nonhospitalized, have been registered in STROMA. Stroke cases that have moved from Malmö have been retrieved by data linkage with the National Hospital Discharge Register.

Stroke was defined as rapidly developed clinical signs of local or global loss of cerebral function that lasted for >24 hours or led to death within 24 hours. Subtypes of stroke were classified as cerebral infarction (ischemic), intracerebral hemorrhage, and subarachnoid hemorrhage. Patients with transient ischemic attacks were excluded.

The diagnosis of stroke was verified by computed tomography scan, lumbar puncture, or necropsy. Stroke cases without verification by computed tomography, lumbar puncture, or necropsy were considered to be undetermined cases of stroke.

BP Definitions and Categories
By using mercury sphygmomanometer, BP was measured once in the right arm after 5 minutes of rest at the screening center. Hypertension was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg or use of antihypertensive medication. Pharmaceutical treatment for hypertension was defined as use of BP-lowering treatment in subjects who reported that they were treated for hypertension. The subjects filled in the name of the drug and the indication for treatment in a questionnaire at home before the examination. Control of blood pressure was defined as BP <140/90 mm Hg in subjects with medical treatment for hypertension.

To evaluate the relationship between incident stroke and quality of BP control, the levels of BP achieved by treatment were grouped into 4 categories in accordance with the 1997 Joint National Committee (JNC) recommendation, ie, normal BP (<130/85 mm Hg), high-normal BP (130 to 139 and/or 85 to 89 mm Hg), mild hypertension (140 to 159 and/or 90 to 99 mm Hg), moderate or severe hypertension (≥160 and/or 100 mm Hg).

Baseline Characteristics
Information concerning the baseline characteristics of participants was collected from the self-reported questionnaire, including marital status (married or unmarried), educational level (≤8 years, 9 to 12 years, and college/university degrees), occupational status (manual work, nonmanual work, and other occupations), and lifestyle factors (smoking status, alcohol consumption, and physical activity during leisure time). Previous hospitalization coronary heart disease (CHD), eg, myocardial infarction or angina pectoris, and diabetes mellitus were assessed in the self-reported data from questionnaire. Current use of lipid-lowering medication (statins) was reported in the questionnaire.

Body weight, height, and waist and hip circumferences were measured at the baseline examination. Waist was measured as the circumference at the umbilicus, and hip circumference was measured as the largest circumference between waist and thighs. The calculation of body mass index and waist-to-hip ratio were subsequently performed.

Statistical Analyses
Logistic regression was used to analyze the impact of baseline characteristics on BP control with adjustments for age and sex. Cox regression model was applied to assess the relationship between the incidence of stroke and levels of BP, with adjustment for potential confounders. Furthermore, a backward stepwise Cox regression was used to estimate the impact of baseline variables on the incidence of stroke among the patients who received antihypertensive treatment. Variables with P>0.10 were removed from the stepwise model.

The Kaplan–Meier method was adopted to compare stroke-free survival in relation to the levels of treated BP. Population-attributable fraction was calculated to estimate the proportion of stroke attributable to uncontrolled BP or untreated hypertension in this population.

All comparisons were 2-sided and a 5% level of significance was used. The statistical analyses were conducted by the computer software SPSS (11.5).

Results
The prevalence of hypertension (≥140/90 mm Hg and/or use of BP-lowering medication) was 60% (66% in men, 54% in women). Pharmacological treatment was used by 23% of hypertensive subjects (n=3829) for control of hypertension. Among treated hypertensive subjects, 88.2% had BP levels ≥140/90 mm Hg and 49.5% ≥160/100 mm Hg.

Patients With Pharmacological Treatment for Hypertension
A total of 1720 men and 2109 women received medical treatment for hypertension.

The most commonly used antihypertensive agents were β-blockers (57%), diuretics (34%), calcium antagonists (27%), and angiotensin-converting enzyme inhibitors (18%). The mean duration of treatment was 10±8 years.

Of the patients who did not reach the level of 140/90 mm Hg, 67% had single-drug regimens, 30% used 2 drugs, and 3% used 3 or more drugs.

Table 1 describes the baseline characteristics among treated hypertensive patients with controlled and uncontrolled BP. Logistic regression analyses showed that older age (61 years or older) and male gender were significantly associated with uncontrolled BP. Current smoking, use of lipid-lowering drugs (statins), and history of CHD was inversely associated with uncontrolled BP.

Incidence of Stroke in Treated Hypertensive Subjects
A total of 137 strokes occurred among subjects with treatment for hypertension. 89 (65%) were classified as ischemic infarction, 15 (11%) as intracerebral hemorrhage, and 6 (4%) as subarachnoid hemorrhage. The remaining 27 (20%) cases were considered as unspecified stroke.

The degree of BP control and incidence of stroke is presented in Table 2. Among the stroke cases with treatment for hypertension, 5% (crude rate: 289/100,000 person-year) occurred in controlled hypertensive subjects, 95% (705/100,000 person-year) in those with BP levels ≥140/90 mm Hg, and 63% (845/100,000 person-year) in those with BP levels ≥160/100 mm Hg.

Furthermore, the population-attributable risk indicates that 45% (use of age- and sex-adjusted relative risk (RR) in formula) or 52% (use of unadjusted RR) of strokes in subjects with treatment for hypertension might be attributed to uncontrolled BP.

Most stroke patients (88% to 100%), irrespective of subtypes, had uncontrolled BP (Figure 1). The differences in stroke-free survival were small during the first years of observation, but the differences increased continuously over
time between controlled and uncontrolled BP categories (Figure 2).

**Risk Factors for Stroke in Patients With Treatment for Hypertension**

Age, smoking, diastolic BP, and diabetes were significantly associated with stroke in a backward stepwise Cox regression of patients with antihypertensive treatment (Table 3). Several covariates were removed from the stepwise model, including gender, marital status, educational level, occupation, alcohol consumption, physical activity, systolic BP, body mass index, waist-to-hip ratio, type of therapy, duration of treatment, use of lipids-lowering drugs, and history of CHD.

**Hypertensive Subjects Without Treatment and Subjects Treated for Other Indications**

In the cohort, 5605 men and 72 14 women had high BP (BP ≥140/90 mm Hg) and were without BP-lowering medication. Of them, 265 patients had a stroke (crude rate: 363/100 000 person-year). In comparison to the subjects with normal BP

### TABLE 1. Baseline Characteristics Among Treated Hypertensive Patients With Controlled BP (<140/90 mm Hg) and Uncontrolled BP (≥140/90 mm Hg)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controlled, BP &lt;140/90 (n=450)</th>
<th>Uncontrolled, BP ≥140/90 (n=3379)</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 y, %</td>
<td>15.8</td>
<td>9.6</td>
<td>1.0</td>
</tr>
<tr>
<td>50–60 y, %</td>
<td>35.4</td>
<td>26.1</td>
<td>1.13 (0.83–1.55)</td>
</tr>
<tr>
<td>≥61 y, %</td>
<td>48.8</td>
<td>64.2</td>
<td>2.02 (1.51–2.72)</td>
</tr>
<tr>
<td>Gender, male, %</td>
<td>37.1</td>
<td>46.0</td>
<td>1.37 (1.12–1.69)</td>
</tr>
<tr>
<td>Marital status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>65.9</td>
<td>66.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Not married</td>
<td>34.1</td>
<td>33.2</td>
<td>0.99 (0.80–1.22)</td>
</tr>
<tr>
<td>Education level, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low, ≤8 y</td>
<td>42.8</td>
<td>49.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate, 9–12 y</td>
<td>38.6</td>
<td>33.0</td>
<td>0.81 (0.65–1.02)</td>
</tr>
<tr>
<td>High, college/university</td>
<td>18.6</td>
<td>17.4</td>
<td>0.90 (0.67–1.18)</td>
</tr>
<tr>
<td>Occupation condition, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual work</td>
<td>63.8</td>
<td>65.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Nonmanual work</td>
<td>30.6</td>
<td>29.9</td>
<td>0.91 (0.72–1.14)</td>
</tr>
<tr>
<td>Others</td>
<td>5.6</td>
<td>5.1</td>
<td>0.76 (0.49–1.19)</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>44.5</td>
<td>42.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Past smoker</td>
<td>29.2</td>
<td>42.3</td>
<td>1.51 (0.80–2.80)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>26.3</td>
<td>15.2</td>
<td>0.60 (0.32–0.97)*</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gram/day ±SD§</td>
<td>0.86 ±0.51</td>
<td>0.88 ±0.53</td>
<td>1.02 (0.82–1.29)‡</td>
</tr>
<tr>
<td>BMI, mean ±SD</td>
<td>27.3 ±4.2</td>
<td>27.7 ±4.3</td>
<td>1.08 (0.99–1.18)‡</td>
</tr>
<tr>
<td>WHR, mean ±SD</td>
<td>0.86 ±0.09</td>
<td>0.88 ±0.10</td>
<td>1.12 (0.98–1.29)‡</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>5.6</td>
<td>8.2</td>
<td>1.39 (0.91–2.13)</td>
</tr>
<tr>
<td>History of coronary heart disease, %</td>
<td>8.7</td>
<td>4.4</td>
<td>0.36 (0.24–0.51)⩓</td>
</tr>
<tr>
<td>Use of lipid-lowering drugs, %</td>
<td>9.3</td>
<td>5.5</td>
<td>0.48 (0.34–0.70)⩓</td>
</tr>
<tr>
<td>Pattern of antihypertensive therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy, %</td>
<td>65.0</td>
<td>66.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Combined therapy, %</td>
<td>35.0</td>
<td>33.3</td>
<td>1.13 (0.97–1.30)</td>
</tr>
</tbody>
</table>

*P<0.05 compared with reference.
†Odds ratio (OR) was adjusted for age and sex, excepting age (sex-adjusted) and sex (age-adjusted).
‡ORs for BMI and WHR were presented as increase per SD.
§Mean values were log-transformed because of skewed distributions.
⩓P<0.001.

BMI indicates body mass index; CI, confidence interval; SD, standard deviation; WHR, waist-to-hip ratio.
(n=11 288), the age- and sex-adjusted RR in untreated hypertension group was 2.55 (95% confidence interval, 1.93 to 3.37), in treated uncontrolled group it was 4.30 (95% confidence interval, 3.16 to 5.85), and in treated controlled group it was 2.21 (95% confidence interval, 1.01 to 4.82). On the basis of the whole population, it could be estimated that 28% of stroke was attributable to untreated hypertension, 9.2% to treated uncontrolled hypertension, and 0.9% to treated controlled hypertension.

In addition, 414 men and 584 women used BP-lowering drugs for reasons other than hypertension, such as heart failure, angina, edema, migraine, etc. In this group, the prevalence of high BP (≥140/90 mm Hg) was 56.7%. The incidence of stroke was 586/100 000 person-years.

**Discussion**

The relationship between hypertension control and the incidence of stroke was evaluated among middle-aged and older Swedish men and women. The incidence of first-ever stroke was strongly related to poor BP control. Among the treated patients who later had strokes, only 5% of cases had BP levels <140/90 mm Hg. It was estimated that ≈45% to 52% of incident strokes among pharmacological-treated patients were attributable to uncontrolled blood pressure. Those observations are consistent with other publications.2,6,14 The findings of this study indicate that the traditional “rule of halves” is still valid. This may be one reason why the incidence of stroke in Sweden has remained unaltered or tended to increase.4,15

Poor hypertension control is a long-standing and problematic clinical issue. There is more than one explanation, such as the attitude of the patient toward treatment, the clinician’s notion and behavior, patient–doctor relations, drug intolerance, resistant hypertension, etc.16–18 Furthermore, lack of appropriate treatment (less intensive regimen or low doses) is also identified as one important barrier to hypertension control. In this study, this is illustrated by the fact that

<table>
<thead>
<tr>
<th>Categories of BP, mm Hg</th>
<th>Subjects, No.</th>
<th>Stroke Cases, No.</th>
<th>Stroke/100 000 Person-Years</th>
<th>Age- and Sex-Adjusted RR (95% CI)</th>
<th>Multiple Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;130/85</td>
<td>149</td>
<td>1</td>
<td>128 (123–379)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>130–139/85–89</td>
<td>301</td>
<td>6</td>
<td>366 (73–659)</td>
<td>2.89 (0.35–23.98)</td>
<td>2.84 (0.34–23.60)</td>
</tr>
<tr>
<td>140–159/90–99</td>
<td>1482</td>
<td>44</td>
<td>532 (375–689)</td>
<td>3.76 (0.52–27.32)</td>
<td>3.90 (0.54–28.34)</td>
</tr>
<tr>
<td>≥160/100</td>
<td>1897</td>
<td>86</td>
<td>845 (666–1024)</td>
<td>5.36 (0.75–38.51)</td>
<td>5.43 (0.75–39.11)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, smoking, BMI, use of lipid-lowering drugs, history of diabetes, and coronary heart disease.

Table 2. Relative Risk of First-Ever Stroke According to Categories of BP Control in Patients Using Antihypertensive Treatment

![Figure 1. Proportion (%) of stroke subtypes in relation to BP control among hypertensive patients using BP-lowering medication.](http://stroke.ahajournals.org/)

![Figure 2. Stroke-free survival in relation to BP control among hypertensive patients using BP-lowering medication. Note categories of BP control: BP I, <130/85 mm Hg; BP II, 130 to 139/85 to 89 mm Hg; BP III, 140 to 159/90 to 99 mm Hg; BP IV, ≥160/100 mm Hg.](http://stroke.ahajournals.org/)
two-thirds of hypertensive subjects with uncontrolled BP were treated by single-line drugs only.

Apart from these common reasons for poor BP control, the patient’s background characteristics in the present cohort appeared to affect the degree of BP control. We found that besides high level of diastolic BP and advanced age, current smoking and a history of diabetes independently increased the risk of first-ever stroke in treated hypertensive subjects.

Advancing age exhibited a strong increasing risk for poor BP control as well as for stroke incidence, despite ongoing medical treatment. In older patients, adequate treatment may still not be fully accepted in routine practice, which could contribute to the increased risk. One of the reasons may be the physician’s traditional notion that diastolic BP was regarded as principal determinant of cardiovascular disease risk. Consequently, patients with isolated systolic hypertension may be poorly treated.

In treated hypertensive subjects, 2 cardiovascular disease risk factors increased the risk of first-ever stroke significantly, ie, smoking and diabetes. This implies that pharmacological antihypertensive treatment could lower blood pressure but does not offset the risks caused by other factors. It has been documented that the patients with cardiovascular disease risk factors may have a higher prevalence of target organ damage at cardiac, macrovascular, and microvascular level, and be prone to true refractory hypertension.

In this cohort, smoking, use of statins and history of CHD were linked to a better BP control. Contrary to the relationship of smoking and risk of stroke, the hypertensive subjects who were current smokers had a higher proportion of controlled BP compared with nonsmokers. This finding is consistent with longitudinal results, in which BP levels were lower in smokers in comparison to nonsmokers and the incidence of hypertension tended to increase after the cessation of smoking. However, the mechanism beyond the effect of smoking on BP is uncertain.

The association between history of CHD and better BP control may be attributed to more intensive antihypertensive treatment administered to the patients who encountered CHD because the risk of re-infarction is positively correlated to BP levels. In addition, left ventricular damage might occur after myocardial infarction, which results in low cardiac output and a low BP.

Of all hypertensive subjects, 77% were without treatment. Even though some individuals in this group probably would have been normotensive after several repeated measurements, this group still had 2.6× higher risk than normotensives. It was estimated that ~28% of incident stroke in the whole population was attributable to untreated hypertension, which indicates a substantial potential for prevention in this group.

Many participants used BP-lowering drugs for other indications than hypertension. Even though hypertension was not mentioned as an indication for treatment, it is likely that some of them were treated also because of high BP. The proportion with uncontrolled BP and incidence of stroke were similarly high in this group, indicating that many stroke are preventable in this group too.

Several limitations of this study deserve to be mentioned. During the years when the study was designed, the regional guideline defined hypertension as BP ≥160/95 mm Hg. This may partly explain the low rates of intervention and well-controlled treatment.

Recently, even lower BP goals have been recommended for diabetic subjects (BP <130/80 mm Hg). In this study, 375 patients had diabetes. If this new level had been used for the diabetic subjects, the proportion of controlled BP and the population-attributable risk attributable to uncontrolled BP had been nearly the same.

Like other population-based surveys, findings in this study were based on 1 BP reading at a single visit. This may lead to an overestimation of the proportion of high BP. However, reduced misclassification of the BP levels would also increase the RR associated with high BP. It is therefore likely that the effects on the population-attributable risk would be small. In addition, evaluation of hypertension control in the whole cohort was performed only on entering the study, and there was no information during the period of follow-up. It is possible that some with poorly controlled hypertension at the baseline achieved better treatment control later. This would, however, reduce the differences between the groups and bias the results toward null findings instead of increasing differences over time.

Conclusion

In patients with ongoing pharmacological treatment for hypertension, uncontrolled BP is highly prevalent. More than 90% of stroke in this group occurred in those with uncontrolled BP. Achieving adequate hypertension control may prevent a substantial proportion of first-ever stroke among treated hypertensive subjects.

Acknowledgments

This study was supported by grants from the Swedish Council for Working Life and Social Research and the Segerfalk Fund. We thank Swedish Cancer Society, Swedish Society for Hypertension, Swedish Medical Research Council, and Scania Regional Government.

References


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Stroke. 2005;36:725-730; originally published online March 3, 2005;
doi: 10.1161/01.STR.0000158925.12740.87
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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