A Multifactorial Analysis of Risk Factors for Recurrence of Ischemic Stroke

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Background and Purpose  Risk factors for stroke recurrence have usually been evaluated as single variables. This study is a multivariate analysis of five risk factors (hypertension, myocardial infarction, cardiac arrhythmia, diabetes mellitus, and transient ischemic attacks) for second stroke after an initial ischemic stroke.

Methods  Six hundred twenty-one patients with an acute ischemic stroke were followed prospectively first at 4 months after onset and then at approximately 6-month intervals until death, recurrence of stroke, or the end of the study. The five risk factors were measured at each visit. A Cox multifactorial regression analysis was conducted using the risk factor status at enrollment and adjusted for age and sex.

Results  Follow-up averaged 24 months (range, 1 to 48 months). Men comprised 52% of the cohort and were slightly older; 97% of the cohort was white, and 57% had multiple risk factors. Hypertension occurred in 59%, cardiac arrhythmia in 47% (of which 16% had atrial fibrillation), diabetes mellitus in 30%, myocardial infarction in 25%, and transient ischemic attacks in 18%. Only history of hypertension and atrial fibrillation by electrocardiogram were associated with increased risk of second stroke independently and significantly (P<0.01 and P<0.04, respectively).

Conclusions  Among the five factors analyzed, control of hypertension and atrial fibrillation appear to offer the greatest chance of reducing risk of stroke recurrence after an ischemic stroke. (Stroke. 1994;25:958-962.)

Key Words  • atrial fibrillation  • diabetes mellitus  • hypertension  • risk factors

Ischemic stroke has a significant adverse impact on public health because of its high prevalence and associated disability. In a national survey approximately one in four hospital admissions for stroke was attributable to recurrent stroke. As the proportion of elderly people in the population increases, the number with initial stroke as well as those with stroke recurrence may be expected to increase. The reported rates of stroke recurrence after an initial stroke vary widely from 3% to 22% in 1 year to 10% to 53% in 5 years in different studies. These wide variations in recurrence rates may be related to methodological differences or differences in age, sex, or coexistent morbidities among the cohorts studied.

Compared with the data for risk factors on an initial stroke, data on risk factors for recurrent stroke are meager, and no consensus yet exists in regard to their relative contribution even for widely recognized risk factors. For example, an increased risk for stroke recurrence in men was observed in the Framingham Study but not in other studies. Hypertension (HTN) was found to be associated with a higher risk of stroke recurrence in the Framingham Study and in the Lehigh Valley Study but not in medical centers in Chicago, Maryland, and Boston using the Stroke Data Bank in Sweden using a hospital series or in Rochester, Minn, using data from the population-based Rochester Epidemiology Project. Similarly, patients with diabetes mellitus (DM) had an increased risk of stroke recurrence in several stroke cohorts studied by Hier et al, Alter et al, and Olsson et al but not by Viitanen et al or Broderick et al. One of the explanations for these inconsistent findings is that only one risk factor or at most two or three were taken into account in determining the effect on risk of stroke recurrence. Furthermore, when considering the potential risk factors, interactions among them were rarely investigated. In the present study we reexamined the effect of widely accepted stroke risk factors on recurrent stroke rate using data from the Lehigh Valley. We focused on patients with first-ever ischemic infarction.

Subjects and Methods

The Lehigh Valley Recurrent Stroke Study (LVRSS) was designed to ascertain prospectively the frequency of a second stroke after an initial stroke considering five selected risk factors and their controls. These factors included history of HTN, history of DM, electrocardiographic (ECG) evidence of myocardial infarction (MI), ECG evidence of cardiac arrhythmia (other than atrial fibrillation [AF]), and history of transient ischemic attack (TIA). If a patient, a surrogate, or the medical chart reported a history of HTN, the patient was considered hypertensive at enrollment. A patient was considered diabetic if the hospital record indicated or the patient reported this diagnosis or if the patient was on insulin, oral hypoglycemic medication, or a diabetic diet. MI, ARR, and AF were diagnosed using the patient's in-hospital ECG(s).

All ECGs were reviewed and interpreted by a study cardiologist according to standard criteria. History of TIA was obtained from the patients and from the hospital record. Further details on criteria used to define each of these risk factors are described elsewhere.

The study cohort was recruited between July 1, 1987, and August 1, 1989. Patients with stroke or TIA (or conditions
inferred to be stroke or TIA) and admitted to any of the eight acute-care hospitals in the Lehigh Valley were identified by screening all admissions. Approximately 4000 patients were screened. Of these, 684 patients were eligible for the LVSS. To be accepted into this study the patient had to fulfill the following criteria: (1) clinical history and findings consistent with initial stroke and a computed tomographic (CT) scan of the brain during hospitalization for the acute stroke indicating no evidence of prior stroke, and (2) admission to the hospital within 3 weeks of the onset of symptoms, with a CT scan performed within 1 week of hospital admission. Reasons for screened patients being excluded from this study have been described elsewhere.17 Of these 684 eligible patients, 22 died in the hospital without a diagnosis of recurrent stroke. The remaining 662 who were discharged alive constituted the cohort for the present study. Forty-one of these patients had an initial intracerebral hemorrhage and were excluded, leaving 621 patients with an initial ischemic infarction for analysis in the present study. The diagnosis of initial stroke was based on criteria similar to those of the Stroke Data Bank18 and was verified clinically by two neurologists (G.F. and M.A.).

Each patient received a follow-up visit at approximately 4 months and then approximately every 6 months thereafter. The assessment at baseline and at each follow-up included personal interviews with the patient or a surrogate, review of interim medical records, measurement of blood pressure, and an ECG. In addition, if the patient was diabetic or suspected of being diabetic, a glycosylated HbAlC assay was obtained at each follow-up visit. All patients were followed until they had a second stroke, died, were lost to follow-up, or until the end of the study. Additional details of the study design are given in another report.17

Because the potential risk factors can interactively affect the risk of stroke recurrence, the degree of comorbidity in this ischemic stroke cohort with respect to the five selected risk factors was analyzed for the subset of 621 patients with an ischemic stroke. The overall differences in distribution of the five selected risk factors by age (≤65, 66 to 75, and >75 years) and by sex were tested for statistical significance by x². Fisher’s exact test was used when appropriate.

To ascertain the effect of the risk factors on the likelihood of stroke recurrence and also to take into account varying lengths of follow-up, survival analysis was used. The survival time for those who had a second stroke was considered as the time from the date of the initial stroke to the date of the second stroke. If death occurred after a recurrent stroke, the patient was listed as having a second stroke and not as a death. The survival time was considered as the interval from date of stroke onset to date of the last visit for those patients who were still actively followed when the study ended, those patients who refused to be followed, and those who moved out of the study area. Those who died of causes other than second stroke were considered to be censored from the time of their death.

Cumulative risk of stroke recurrence over time was calculated using the Kaplan-Meier method for specific age groups, sex, and five selected risk factors. These factors were coded as present or absent. The log-rank statistic was used to test the effect of each factor on the distribution of cumulative risk of stroke recurrence over time.

A multivariate analysis using the Cox proportional hazards model19 was used to analyze the joint effect of the risk factors and the interactions among the selected risk factors on risk of stroke recurrence. The risk factors included in the multivariate analysis were HTN, DM, MI, AF, ARR, and TIA. Age and sex were treated as covariates in the analysis. Stepwise forward selection was used first to identify the statistically significant risk factor(s) associated with risk of a recurrent stroke. The likelihood ratio statistic was used to test the statistical significance for an added factor compared with the model without that factor. Risk ratio for patients with a specific factor in developing a recurrent stroke was then estimated by adjusting for age, sex, and other identified statistically significant risk factors in the final model. Because recurrent stroke was the outcome event of interest, those who died of other causes were considered censored in this analysis.

Results

A total of 621 patients with an initial ischemic stroke were identified during the period of July 1, 1987, through August 1, 1989. Among these patients, the average age at stroke onset was 70±10.6 years for men and 74±11.1 years for women (P<.0001). Three hundred twenty-two (52%) case subjects in this cohort were male. The 621 patients were followed prospectively for an average of 24 months (range, 1 to 48 months). By the end of the study, 77 (12%) of the patients had a second stroke, 132 (21%) died, 24 (4%) moved out of the study areas, and 64 (10%) refused to be followed.

The profile of the five selected risk factors at enrollment for these 621 stroke patients was analyzed. Only 73 (11.8%) patients had none of the above five risk factors. Of the remaining, 192 (30.9%) patients had only one risk factor, 191 (30.8%) had two risk factors, 121 (19.5%) had three risk factors, 35 (5.6%) had four risk factors, and 9 (1.4%) had all five risk factors. Of the patients with a single risk factor, HTN (12.9%) was the most common. Of the patients with two risk factors, HTN and ARR together were the most commonly occurring comorbidities (10.3%). Of the patients with three risk factors, HTN, DM, and ARR was the most common risk factor combination (5.5%). Other combinations occurred with less than 5% frequency.

The distributions of five selected risk factors are shown by age in Table 1 and by sex in Table 2. In this cohort, patients aged older than 75 years had a significantly higher proportion of ECG evidence of an ARR (P<.001) and in particular ECG evidence of AF (P<.001). A higher proportion of women were found to...
have a history of HTN (P= .001) and DM (P= .081) compared with men. On the other hand, more men were found to have MI on ECG (P= .041).

The Kaplan-Meier estimates of the cumulative stroke recurrence rates in this ischemic stroke cohort were 9% in the first, 13% in the second, 15% in the third, and 19% in the fourth year. Each selected risk factor was tested individually for its influence on the likelihood of stroke recurrence over time. Among the risk factors tested, only HTN (P= .01) and ECG evidence of AF (P= .03) had a statistically significant impact on risk of a second stroke (Figs 1 and 2, respectively). For example, the cumulative stroke recurrence rates for those patients with a history of HTN compared with those without a history of HTN were 11% versus 6% at 1 year, 16% versus 9% at 2 years, 18% versus 9% at 3 years, and 24% versus 9% at 4 years (Fig 1). No difference in the cumulative stroke recurrence rates was found in patients with a history of DM compared with patients without a history of DM. However, when the treatment of DM was considered, diabetic patients treated with insulin had higher cumulative stroke recurrence rates than diabetic patients with other noninsulin treatments or nondiabetic patients (Fig 3). MI, ARR, and TIA were not associated with an increased risk of second stroke.

The results from the stepwise Cox proportional hazards model are shown in Table 3. Only HTN and ECG evidence of AF had a statistically significant increased risk of stroke recurrence (P= .01 and P= .03, respectively). No statistically significant effect of interaction between AF and HTN on risk of stroke recurrence was found. The risk ratios of stroke recurrence for patients with AF and/or HTN were reestimated by adjusting for age and sex. Ischemic stroke patients with AF had a 1.8-fold (95% confidence interval [CI] = 1.04 to 3.06) higher risk of stroke recurrence compared with patients of the same age and sex without AF at baseline. Patients with a history of HTN at the time of initial stroke had a 1.9-fold (95% CI = 1.18 to 3.24) higher risk of subsequent stroke compared with those who were the same age and sex and had no history of HTN. A patient with both AF and HTN at baseline had a 3.5-fold higher risk of recurrent stroke compared with patients of the same age and sex without AF and HTN at baseline. Thus, when considering multiple factors and their interaction, HTN and cardiac arrhythmia (particularly AF) significantly affected risk of stroke recurrence in this cohort even when adjusting for age and sex.

**Discussion**

A 13% stroke recurrence rate over an average 24 months of follow-up was observed in our study; a rate of 14% was observed for the same period using the Stroke Data Bank cohort. In Rochester, Minn, the recurrence rate was 10% in the first year compared with 9% in our study and 20% by the fifth year compared with 19% in 4 years in our series. Thus, our data agree very well with the results of these studies. It should be noted that the results from Rochester, Minn, are approximately 20 years old, implying that recent innovations in control of hypertension have not changed risk of stroke recurrence much. However, among hypertensive subjects success-
fully treated, risk of stroke recurrence can be reduced, as we have shown elsewhere (M. Alter, G. Friday, S.M. Lai, E. Sobel, J. O'Connell, unpublished data, 1994).

The effect of individual selected risk factors on stroke recurrence was examined in several previous studies. Few studies considered the effect of more than three risk factors in their cohorts. The Framingham Study only considered HTN, congestive heart failure, and coronary heart disease. The study from Mayo Clinic by Broderick et al considered HTN, DM, and various heart diseases (angina, MI, AF or flutter, left ventricular hypertrophy, congestive heart failure, and cardiac valve diseases). In our study we analyzed five selected risk factors: HTN, MI, DM, ARR (and AF), and TIA. The Stroke Data Bank reports and Swedish studies analyzed more risk factors, but the analyses were not restricted to those with an initial stroke: 28% of patients in the Swedish cohort and 26% in the Stroke Data Bank had a previous stroke. In our study only patients with an initial stroke were included. Furthermore, the apparent effect of a given risk factor on stroke recurrence is also influenced by comorbidities. When a large proportion of stroke patients have more than one selected risk factor (57.3% in our cohort), interaction must be taken into account in determining the effect of the risk factors on frequency of recurrent stroke.

Olsson et al. studied the risk of stroke recurrence in diabetic and nondiabetic patients. Diabetic patients were found to have an increased risk of recurrent stroke. In the data analysis of Olsson et al, no interaction between potential risk factors was investigated. Therefore, whether DM was a significant, independent risk factor for stroke recurrence remains a question. Similarly, after including a large number of risk factors in their multivariate analysis, Hier et al. concluded that history of DM, initial diastolic HTN, and history of stroke were independently associated with higher risk of stroke recurrence, but they did not take into account the potential interaction(s) among risk factors. DM in our study was not shown to be a significant predictor of stroke recurrence. However, we found that diabetic patients on insulin had a higher risk of stroke recurrence compared with patients without DM or diabetic patients not on insulin (Fig 3). These variations in risk of stroke recurrence among diabetic patients treated with or without insulin can certainly be attributed to the potentially different vascular pathophysiology in insulin-dependent DM or non-insulin-dependent DM.

In the present study as well as in a previous stroke study in the Lehigh Valley based on a population-based stroke register that included all stroke, HTN emerged as a significant risk factor in the analytic models. In the Framingham Study, Sacco et al. also confirmed an increased risk of stroke recurrence in patients with HTN. They also analyzed risk factor interaction and found that HTN and cardiac comorbidity, consisting of congestive heart failure and coronary heart disease, were major determinants of stroke recurrence. We also studied the risk of second stroke due to interactions between HTN and MI, as well as between HTN and AF and between HTN and ARR. However, no statistically significant difference was found.

In the Framingham Study, congestive heart failure and coronary heart disease as cardiac comorbidities were combined. In the Mayo Clinic study various cardiac diseases (eg, angina, congestive heart failure, and MI) were considered as separate variables in the analysis. In their study 16% of patients were found to have AF or flutter, and 16% of patients were found to have MI. We considered MI, ARR, and AF separately. In our study 16% of the patients had ECG evidence of AF, and 25.1% of the patients had ECG evidence of MI. The proportion of patients with AF in our study was similar to that of the Mayo Clinic study. On the other hand, the proportion of patients with MI was higher in the Mayo Clinic study compared with that of the LVRSS. The cardiac conditions in the Mayo Clinic were diagnosed by clinical or ECG evidence or both. Depending on the time the initial stroke was diagnosed, only 67% to 88% of their patients with a cerebral infarction had an ECG when evaluated for stroke. In our study almost 100% of patients had at least one ECG obtained at the time of stroke onset.

In the LVRSS Cox modeling analysis, of those cardiac conditions studied, only AF emerged as a significant predictor for stroke recurrence. Of the 16% of patients with AF, 55% also had HTN, but no statistically significant interaction of HTN and AF on frequency of recurrent stroke was found. However, patients with both HTN and AF did have a higher risk of stroke recurrence than patients with either HTN alone or AF alone. Broderick et al. found that AF/flutter was not associated with an increased risk of stroke recurrence, but congestive heart failure did increase stroke recurrence.

There are some differences in the methodologies between our study and the study from the Mayo Clinic. For example, all of our patients had a CT scan of the brain, but not all of their patients did. In our study only those patients who survived the initial hospitalization were included in the analysis, whereas they included patients with at least 7 days' survival. The differences in inclusion criteria for studying risk of stroke recurrence may also account in part for the discrepancy in findings. However, we reanalyzed the risk of stroke recurrence

### Table 3. Significant Risk Factors for Stroke Recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient*</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension</td>
<td>.672</td>
<td>1.96</td>
<td>1.18-3.24</td>
<td>.01</td>
</tr>
<tr>
<td>Atrial fibrillation (by ECG)</td>
<td>.579</td>
<td>1.78</td>
<td>1.04-3.06</td>
<td>.04</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; ECG, electrocardiogram.

*Coefficient and hazard ratio were estimated by adjusting for covariates, age, sex, and other significant risk factor(s) using the Cox proportional hazards model. Other insignificant factors included myocardial infarction by ECG, diabetes mellitus, transient ischemic attack, and cardiac arrhythmias other than atrial fibrillation.
including the entire cohort of 684 patients without excluding those who died in hospitals. Also, HTN and ECG evidence of AF remained the significant risk factors for stroke recurrence.

We only monitored five risk factors for stroke in the present study, but our approach could be used to examine additional factors such as lipid profile, insulin concentration, and smoking for their effect on risk of stroke recurrence. Control of risk factors also needs to be evaluated for an effect in reducing risk. In an example of one such report based on our cohort, control of HTN reduced risk of stroke recurrence in hypertensive subjects to a level close to that of nonhypertensive subjects (M. Alter, G. Friday, S.M. Lai, E. Sobel, J. O'Connell, unpublished data, 1994). Only analyses similar to ours, which include patients with initial ischemic stroke and take into account multiple risk factors and their interactions, can provide the most accurate assessment of the relation between risk factors and risk of stroke recurrence.

References

A multifactorial analysis of risk factors for recurrence of ischemic stroke.
S M Lai, M Alter, G Friday and E Sobel

Stroke. 1994;25:958-962
doi: 10.1161/01.STR.25.5.958

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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