Predictors of Severe Stroke
Influence of Preexisting Dementia and Cardiac Disorders

Peter Appelros, MD; Ingegerd Nydevik, MD, PhD; Åke Seiger, MD, PhD; Andreas Terént, MD, PhD

Background and Purpose—There is little research into the impact of prestroke dementia on stroke severity and short-term mortality. We included prestroke dementia, along with other risk factors, to determine independent predictors of stroke severity and early death in a community-based stroke study.

Methods—All patients (n=377) with a first-ever stroke were evaluated in terms of risk factors. Registration took place over a 12-month period. Stroke severity was evaluated with the National Institutes of Health Stroke Scale. Predictors of severe stroke and early death were analyzed in logistic regression models. The following independent variables were used: age, sex, living alone, arterial hypertension, ischemic heart disease, heart failure, atrial fibrillation, diabetes mellitus, transient ischemic attack, cigarette smoking, peripheral atherosclerosis, and dementia.

Results—Risk factors for stroke were found in 82% of the patients. Heart failure, atrial fibrillation, and dementia were associated with more severe strokes. Dementia, atrial fibrillation, heart failure, and living alone were associated with death within 28 days of the event.

Conclusions—These results raise the question of whether certain high-risk patients, ie, patients with atrial fibrillation, heart failure, and dementia, can benefit from more aggressive primary and secondary stroke prevention measures. (Stroke. 2002;33:2357-2362.)

Key Words: atrial fibrillation ■ cognitive disorders ■ heart failure ■ prognosis ■ stroke

The major risk factors for stroke are age,1 male sex,1 arterial hypertension,2 cigarette smoking,3 diabetes mellitus,4 atrial fibrillation (AF),5 and other cardiac disorders.6 In addition, some of the risk factors, eg, AF7–9 and heart failure,10–12 are predictors of case fatality. In recent years, the association between cognitive disorders and stroke has come into focus. Currently, there is evidence that dementia is a risk factor for stroke13,14 and that dementia after stroke has a negative impact on long-term survival.15 There has, however, been little research into the impact of prestroke dementia on stroke severity and short-term mortality. We therefore included prestroke dementia, along with other risk factors for stroke, in a multivariate analysis to evaluate its impact on stroke severity and early death. This was accomplished within the frames of a community-based stroke study. All patients with brain infarction (BI), intracerebral hemorrhage (ICH), and undetermined pathological type (UND) were examined for relevant medical history, and stroke severity was defined for each patient.

Subjects and Methods
The study population included all inhabitants of the municipality of Örebro, Sweden, during the 12-month study period, 123 503 as of December 31, 1999 (48.4% men, 51.6% women). Details regarding the case ascertainment have been described elsewhere.16 The study was population based; ie, subjects were traced outside and inside the hospital. World Health Organization diagnostic criteria were used.17 The data collection was prospective, and subjects were identified in several overlapping ways by use of the “hot pursuit” technique; ie, subjects were pursued as they occurred.

A single study doctor (geriatrician with 20 years of experience) examined all suspected cases, whether detected by us directly or reported to us by our clinical collaborators. A neurological examination was performed, and stroke severity was defined according to the National Institutes of Health Stroke Scale (NIHSS).18 The medical examination was performed 24 to 48 hours after the event, except if a patient’s general health was rapidly declining, in which case the examination had to be done within the first 24 hours. The NIHSS score was estimated from information in patient records in 19 cases when patients were discovered retrospectively.19 A CT scan was performed in 84% of the patients. Patients were divided into the following main types of stroke: BI, ICH, UND, and subarachnoid hemorrhage (SAH). For the purposes of this study, patients with a BI were further classified according to the Oxford Community Stroke Project20 into those with lacunar infarcts and those with other infarcts. Patients with SAH were not included in the present study because of the different origin.

The evaluation of risk factors was done at the time of stroke diagnosis. A structured interview was performed by the main author (P.A.) to map the relevant medical history of each patient. Next of kin was interviewed when a patient was unconscious or disoriented. This was necessary in 35% of the patients. Previous hospital medical records and, when relevant, primary care records were reviewed. First-hand information on cardiovascular diseases was gained from

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TABLE 1. Medical History According to Stroke Subtypes

<table>
<thead>
<tr>
<th></th>
<th>ICH (n=44)</th>
<th>All (n=274)</th>
<th>Lacunar (n=76)</th>
<th>Other (n=198)</th>
<th>UND (n=59)</th>
<th>All (n=377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (SD), y</td>
<td>73</td>
<td>75</td>
<td>72</td>
<td>77</td>
<td>85</td>
<td>77 (11)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>25 (57)</td>
<td>125 (46)</td>
<td>38 (49)</td>
<td>87 (44)</td>
<td>19 (32)</td>
<td>169 (45)</td>
</tr>
<tr>
<td>Living alone, % (95% CI)</td>
<td>48</td>
<td>49</td>
<td>50</td>
<td>48</td>
<td>80</td>
<td>53 (47–58)</td>
</tr>
<tr>
<td>Arterial hypertension, % (95% CI)</td>
<td>32</td>
<td>38</td>
<td>40</td>
<td>37</td>
<td>26</td>
<td>36 (31–41)</td>
</tr>
<tr>
<td>Ischemic heart disease, % (95% CI)</td>
<td>25</td>
<td>32</td>
<td>18</td>
<td>37</td>
<td>24</td>
<td>30 (25–35)</td>
</tr>
<tr>
<td>With myocardial infarction</td>
<td>18</td>
<td>17</td>
<td>5</td>
<td>21</td>
<td>19</td>
<td>17 (14–21)</td>
</tr>
<tr>
<td>Heart failure, % (95% CI)</td>
<td>14</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>20</td>
<td>14 (10–17)</td>
</tr>
<tr>
<td>Atrial fibrillation, % (95% CI)</td>
<td>16</td>
<td>24</td>
<td>12</td>
<td>29</td>
<td>31</td>
<td>24 (20–29)</td>
</tr>
<tr>
<td>Diabetes mellitus, % (95% CI)</td>
<td>9</td>
<td>19</td>
<td>27</td>
<td>15</td>
<td>24</td>
<td>18 (14–23)</td>
</tr>
<tr>
<td>TIA, % (95% CI)</td>
<td>7</td>
<td>17</td>
<td>9</td>
<td>20</td>
<td>12</td>
<td>15 (11–19)</td>
</tr>
<tr>
<td>Cigarette smoking, % (95% CI)</td>
<td>21</td>
<td>25</td>
<td>37</td>
<td>19</td>
<td>7</td>
<td>22 (18–27)</td>
</tr>
<tr>
<td>Peripheral atherosclerosis, %</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Dementia, % (95% CI)</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>10</td>
<td>34</td>
<td>12 (9–16)</td>
</tr>
</tbody>
</table>

Medical records in 75% of patients. The reverse was true regarding cigarette smoking and dementia, which was not always documented in medical records.

Arterial hypertension was diagnosed when its presence was documented in medical records. Alternatively, it was diagnosed when ≥2 readings of blood pressure were ≥160 mm Hg (systolic) or ≥95 mm Hg (diastolic) before the onset of stroke. Ischemic heart disease was diagnosed when there was a history of angina pectoris or myocardial infarction. The diagnosis of heart failure was established if this condition was documented in medical records and the patient was still on medical treatment at the time of stroke. AF was diagnosed either when there was a documented history of paroxysmal AF or if AF was present at the time of stroke. Diabetes mellitus was diagnosed if the patient gave a history of diabetes that was confirmed by their medical records or was taking insulin or an oral hypoglycemic agent. Prestroke transient ischemic attack (TIA) was diagnosed if it was documented in medical records or from the patient’s own report that all symptoms resolved within 24 hours. A patient was defined as a smoker if there had been a history of cigarette smoking during the last 5 years. Peripheral atherosclerosis was diagnosed when a patient had a history of calf pain induced by exercise or if the patient had been subjected to positive angiography or vascular surgery. Assessment of prestroke dementia was based on interviews with the patient and a knowledgeable informant. We required the presence of memory impairment and deficits in other cognitive abilities according to the International Classification of Diseases, 10th Revision.21 The presence of prestroke dementia was established if these disabilities had been so severe as to interfere with everyday activities for at least 6 months or if there had been a confirmed diagnosis of dementia according to medical records. In addition to medical risk factors, age, sex, and living alone were recorded. Population statistics were used to ascertain whether a patient was still alive 28 days after the stroke event.

Ethics
Before entering the study, patients were asked orally for consent. They also received an information letter. If a patient’s ability to communicate was restricted, consent from next of kin was obtained. The Human Ethics Committee of the Örebro County Council and the local Data Inspection Board approved the study.

Statistical Analysis
Assuming the binomial distribution, confidence intervals (CIs) for proportions were calculated with the STATA software package, version 7.0. Multiple logistic regression was calculated with the SPSS package, version 11.0.

The logistic regression was performed as follows. All variables except age were dichotomized. The outcome variable was dichotomized to either mild stroke (NIHSS score <6, n=185), or severe stroke (NIHSS score ≥6, n=192). This level was chosen to divide the cohort into equal halves. Age was categorized into 4 groups (<72, 72 to 77, 78 to 84, and >84 years) so that the categories were of approximately uniform size. The 12 explanatory variables were first tested 1 by 1 against the dependent variable for the presence of significant association (P<0.05). Variables for which no significant association was found were removed from the model. Thereafter, the remaining variables were cross tabulated to assess for multicollinearity. In no case were variables correlated at >0.32, which was acceptable for the subsequent analysis. The logistic regression analysis (forward stepwise method) was then performed. Finally, the model was examined for goodness of fit. Deviance values were calculated to analyze how well the model fit each case. The relative influence of individual observations was analyzed by Cook’s influence statistic. In both cases, it was concluded that model fit was adequate, and experimental removal of outliers did not violate the model.

Results
Between February 1, 1999, and January 31, 2000, 377 patients were found to have had a first-ever-in-a-lifetime stroke (non-SAH). Nineteen were included retrospectively when hospital discharge records and death certificates were scrutinized. Of the 377 patients, 208 were women, and 169 were men. The mean age for all patients was 76.6 years (for women, 78.9 years; for men, 73.9 years). The distribution of stroke types was as follows: BI, 73% (95% CI, 68 to 77); ICH, 12% (95% CI, 9 to 15); and UND, 15% (95% CI, 12 to 20). No patients were lost during follow-up.

Medical History
A history of risk factors for stroke (arterial hypertension, ischemic heart disease, heart failure, diabetes mellitus, TIA, cigarette smoking, atherosclerosis of peripheral arteries, AF, or dementia) was obtained in 82% of the patients. The frequencies according to stroke subtypes are given in Table 1.
Only 6 of 90 patients (7%) with AF were on warfarin before the event.

**Stroke Severity**

At the examination, 59% of the patients had no impairment of consciousness, whereas 48% were conscious and oriented, according to the NIHSS. Thirty-four percent of patients had some degree of visual field disturbance, and 83% had some degree of motor deficit. Ataxia was present in 12%, sensory disturbance in 37%, aphasia in 31%, dysarthria in 42%, and extinction or inattention in 14%. The median NIHSS score was 6 (range, 0 to 38; interquartile range, 3 to 12), and the mean value was 9.2, which indicates a skewed distribution. For individual subtypes of stroke, the median scores were as follows: ICH, 9 (range, 1 to 38; interquartile range, 4 to 15.5); nonlacunar type of BI, 6 (range, 0 to 38; interquartile range, 2 to 11); lacunar type of BI, 3 (range, 1 to 14; interquartile range, 3 to 5); and UND, 13.5 (range, 2 to 38; interquartile range, 7 to 25).

**Risk Factors for a Severe Stroke and 28-Day Case Fatality**

To evaluate whether any risk factors were independent predictors of stroke severity or 28-day case fatality, we analyzed the data in 2 logistic regression models. The results of the NIHSS assessment and the 28-day case fatality were used as dependent variables. The following explanatory variables were used: (1) age, (2) sex, (3) living alone, (4) arterial hypertension, (5) ischemic heart disease, (6) heart failure, (7) AF, (8) diabetes mellitus, (9) previous TIA, (10) cigarette smoking, (11) peripheral atherosclerosis, and (12) dementia. Because of obvious covariation between dementia and the items 1b and 1c in the NIHSS (Questions and Commands), these items were excluded from analysis. Eleven patients (3%) were not included in the logistic regression because of missing data regarding risk factors.

These 11 patients did not differ from the others with respect to age and sex but more often had a UND stroke (55%), more often were demented (45%), and had a 28-day case fatality of 90%.

The results of analyses (with 95% CIs and probability values) are shown in Table 2. Age, heart failure, AF, and dementia were included in the multivariate analysis for stroke severity because of significant association in the univariate analysis. The following combination was identified as the best predictor variables for severe stroke: heart failure, AF, and dementia. The model was also tested with other NIHSS cutoff levels for the severe stroke criterion. When this level was set to 10 (≤10, n = 286; >10, n = 91), there was only 1 significant explanatory variable left: AF. When the NIHSS cutoff level was set to 15 (≤15, n = 315; >15, n = 62), the only significant explanatory variable was dementia. To further explore the association between the age variable and dementia, we tested the model with the age variable dichotomized. The cutoff value was set to 84 years, which was the mean age of patients with dementia. Dementia then still remained a significant independent variable.

In the logistic regression model for 28-day case fatality, the variables sex, ischemic heart disease, diabetes mellitus, TIA, and peripheral atherosclerosis were removed because of lack of significant association in the univariate analysis. The following variables were identified as the best predictors of death within 28 days: dementia, AF, heart failure, living alone, and arterial hypertension.

We also performed an analysis in which stroke severity (dichotomized as above, NIHSS ≤6 or ≥6) was introduced as an independent variable for case fatality, in addition to the above-mentioned variables. Logistic regression then showed only 2 variables that were independent predictors of case fatality: stroke severity (odds ratio [OR], 24.41; 95% CI, 8.5 to 89.7) and dementia (OR, 2.35; 95% CI, 1.1 to 5.0). Heart failure, AF, and living alone were nonsignificant.
**Discussion**

This study has shown that certain prestroke risk factors have an impact on neurological symptoms and case fatality in the acute phase. These risk factors are dementia, AF, heart failure, and living alone. The most challenging of them is prestroke dementia.

Stroke is strongly associated with dementia. The identification of poststroke dementia may be affected by brain damage after the stroke event itself; therefore, its presence has limited value as a risk factor for stroke. We evaluated prestroke dementia in a manner similar to that of Pohjasvaara and coworkers. They found prestroke dementia in 9.2% of their study group, which comprised patients 55 to 85 years of age. Hénon and coworkers and Barba and coworkers used a questionnaire. They found that 16% and 15%, respectively, of their patients were demented before stroke. These studies were hospital based and included recurrent stroke, which may limit comparison with our study. The higher prevalence of prestroke dementia found in the latter 2 studies may also reflect a higher sensitivity of a questionnaire for milder dementia.

It has previously been reported that clinically stroke-free individuals with severe cognitive impairment are at an elevated risk of first stroke. Dementia after stroke also has a negative impact on long-term survival, and stroke patients with dementia are at an elevated risk of long-term stroke recurrence compared with nondemented stroke patients. To the best of our knowledge, it has not been shown previously in multivariate analysis that prestroke dementia is a risk factor for stroke severity and early death. However, Hénon and coworkers found in bivariate analysis that in-hospital mortality, functional outcome at discharge, and 6-month mortality were worse in patients with prestroke dementia. They failed, however, to show an effect on short-term outcome in multivariate analysis. The discrepancy between their study and ours in this respect may be explained by 3 factors. First, their study was hospital based and included recurrent stroke, which may limit comparison with our study. The higher prevalence of prestroke dementia found in the latter 2 studies may also reflect a higher sensitivity of a questionnaire for milder dementia.

A question arises as to how stroke and dementia are associated. One suggestion, although purely conjectural, may be that apolipoprotein E plays a role. The isoform apolipoprotein E4 (apoE4) is strongly linked to both sporadic and late-onset Alzheimer’s disease, as well as to dementia with stroke. It has been shown that in terms of a neurological severity score, transgenic mice expressing human apoE4 are more susceptible to adverse outcome after closed-head injury than those expressing apoE3. Therefore, a possible explanation for our results is that the patients who had prestroke dementia also to a greater degree represented the apoE4 genotype, thereby being more vulnerable to a vascular insult such as stroke.

The well-documented impact of AF on the prognosis of first-ever stroke is confirmed in this investigation. Heart failure was also a significant predictor of stroke severity and case fatality. From earlier studies, it is known that patients with signs of cardiac failure have worse short time survival. It is also known that patients with dilated cardiomyopathy have a high incidence of left ventricular thrombus formation and are at increased risk of embolic complications. There is less information regarding the risk of systemic emboli in patients with decreased ventricular function from coronary artery disease, although in the Framingham study, heart failure was ranked second in cardiogenic stroke risk, with a 2- to 3-fold relative risk. Some promising results exist regarding the use of warfarin in patients with heart failure. At present, there are proposals for 2 new studies, Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) and Warfarin Versus Aspirin in Reduced Cardiac Ejection (WARCEF), to compare warfarin and antiplatelet agents in patients with low ejection fraction. The pooled data will provide sufficient power to determine whether warfarin reduces stroke risk in patients with low ejection fraction.

Age was not a significant predictor of stroke severity or short-term survival, which is in line with previous studies showing that age is not an independent risk factor for early death after stroke. The impact of age on mortality seems to rise after a year. To the best of our knowledge, it has not been shown before that living alone is a risk factor for short-term mortality. One previous study found an association between marital status and 1-month survival in univariate but not multivariate analysis. A recently published study showed that if patients had negative attitudes toward their illness, they did not survive as long as other patients. Although that study and others evaluating psychological measures often aim at long-term survival, it is possible that the same factors, ie, fatalism and helplessness or hopelessness, which were significant predictors in the before-mentioned study, also influence short-term survival.

A history of arterial hypertension was found in 36% of our patients. Our figure is somewhat lower than the registries used for comparison, which may be due to regional or secular trends, different diagnostic criteria, or different case finding procedures. Prestroke hypertension did not involve a worse prognosis; rather, the contrary is true when it comes to case fatality, although the significance is borderline. Although this relationship has to be confirmed, patients with hypertension may benefit in some way from their higher blood pressure in the acute phase. This, we think, stresses the importance of avoiding decreases in blood pressure in the acute phase, eg, through liberal administration of intravenous fluids. In previous studies, prestroke hypertension has not had any significant beneficial influence on short-term mortality. In some studies, high blood pressure on admission has even been shown to be an adverse factor. This suggests that high blood pressure on admission does not need to reflect a prestroke hypertension or vice versa.

Because measuring the level of blood lipids is not a part of routine medical examination at health centers in Örebro, the impact of prestroke cholesterol levels could not be studied. We do not think that this has had a significant effect on the results. The effect of cholesterol on stroke prognosis seems
small. Although 1 retrospective study has shown that higher serum cholesterol concentrations were associated with reduced long-term mortality after stroke,38 other studies have shown no effect.

The outcome of a multivariate analysis is strongly affected by the independent variables used. They should be clinically and intuitively relevant.39 Although statistics cannot tell whether something is a confounder or an intervening variable, the ability of multivariate analysis to simultaneously assess the independent contribution of a number of risk factors is particularly important when there are confounders. Whether a variable is a confounder or just intervening is a decision that has to be made on the basis of prior research and biological plausibility.40 We have shown that there is significant correlation between heart failure, AF, and prestroke dementia on one side and stroke severity on the other. Therefore, when we assess risk factors for case fatality, it is questionable whether prestroke risk factors and different manifestations of stroke severity should be included in the same analysis, because these 2 groups of factors reflect different phases in the disease development. In spite of this, we performed such an analysis to show the effect. As expected, this analysis showed that the impact of the most powerful predictors of stroke severity (heart failure and AF) were out-leveled, whereas dementia, which had less impact on stroke severity, was still significant. Evaluation of the prestroke risk factors was done at the time of the stroke diagnosis, not prospectively. That may have led to some underestimation of the prevalence of risk factors rather than the contrary. We do not think that this jeopardizes the validity of the study, because most likely milder forms of risk factor conditions that have escaped prestroke discovery are in question. The only way to achieve prospective data collection for purposes like our study is through large longitudinal cohort studies, which are time consuming and costly but would certainly be desirable to confirm our results.

With a community-based stroke incidence study design, this investigation has shown that AF, heart failure, and prestroke dementia are risk factors for having a severe stroke, as well as for death within 1 month of a stroke event. Living alone was also a risk factor for early death after stroke. If confirmed by other studies, this knowledge may be translated into primary and secondary prevention measures. There may be great potential in finding and giving primary prophylaxis to certain high-risk groups of patients such as patients with AF or heart failure.

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