Pure Motor Stroke From Presumed Lacunar Infarct
Long-Term Prognosis for Survival and Risk of Recurrent Stroke

Gert Staaf, MD; Arne Lindgren, MD; Bo Norrving, MD

Background and Purpose—A low risk of recurrent stroke and death after lacunar infarction has previously been reported, but follow-up has been limited to ≤5 years.

Methods—One hundred eighty patients with pure motor stroke, collected between 1983 and 1986 from a hospital-based stroke registry, were followed up until at least 10 years after the index stroke. Two patients were lost to follow-up. Survival status was determined from the official population registry and compared with survival rates of the Swedish population, matched for age and sex. Cox proportional hazards regression analyses were used to identify independent prognostic predictors.

Results—During follow-up 106 (60%) of the 178 patients died, most commonly as a result of coronary heart disease. During the first 5 years after the stroke, survival rates were similar to those of the general population. Beyond this time the risk of death was increased among patients with pure motor stroke, with an excess of 10 to 15 percent units compared with the general population. Independent determinants for death were age (P<0.01), male sex (P<0.01), and nonuse of acetylsalicylic acid (P=0.02). Recurrent stroke occurred in 42 (23.5%) of the patients, corresponding to an annual risk of 2.4%. Hypertension (P=0.025) and diabetes (P=0.024) were independent risk factors for recurrent stroke.

Conclusions—For the first few years after lacunar infarct, the risk of death was similar to that of the general population, but later a clear excess of death was observed. The long-term prognosis in lacunar infarction appears less favorable than previously reported. (Stroke. 2001;32:2592-2596.)

Key Words: cerebral infarction ■ diabetes mellitus ■ hypertension ■ lacunar infarction ■ mortality ■ natural history ■ outcome ■ prognosis ■ risk factors ■ stroke ■ stroke outcome

Lacunar infarcts constitute up to 25% of all ischemic strokes.1-3 The term is used to indicate the small brain lesion resulting from occlusion of a single, small, penetrating artery arising from larger intracerebral arteries, most often from the middle and anterior cerebral arteries and the basilar artery.4 Several clinical aspects of lacunar infarcts have been well studied, eg, risk factors, initial clinical features, and short-term prognosis for survival and stroke recurrence.1-3,5-22 However, the long-term prognosis is less well documented, mainly because the follow-up periods have been limited to ≤5 years, and considerable uncertainty exists about which putative risk factors are independent determinants of survival and recurrent stroke for patients with this subtype of stroke.15,18,22,23

To address these issues, we examined prognostic features and determinants for survival and stroke recurrence in 178 patients with pure motor stroke from presumed lacunar infarct, followed up to 10 years after stroke onset. Epidemiological and clinical features and risk factors of these patients have been described in a previous report.2

Subjects and Methods
Between January 1983 and December 1986, 180 patients with a first-ever pure motor stroke were registered in the prospective, hospital-based stroke data bank at the Department of Neurology, Lund University Hospital. Methods of case ascertainment and clinical definitions have been described previously.2

Follow-up data were collected between 1992 and 1999. All patients were followed up until at least 10 years after the index stroke or until death or recurrent stroke occurred before 10 years. Survival status was determined through the official population registry. Causes of death were assessed by analysis of clinical records, death certificates, and autopsy reports. Patients still alive at 10 years after the index stroke were interviewed by telephone. For patients who had been readmitted to the hospital, relevant clinical records were reviewed.

Statistical Analysis
We used the Kaplan-Meier method to estimate rates of survival, recurrent stroke, and survival free of recurrent stroke. Survival rates for the whole normal Swedish population, matched for age and sex for the actual time period, were calculated and compared with corresponding data for the patient group by means of a computer program (SURV 2 version 2.01) developed for the Finnish Cancer Registry.24 For univariate analysis of putative prognostic factors, we used the χ² test (for ordinal variables) and the Mann-Whitney U test (for continuous data). Prognostic variables and risk factors (as previously defined) included in the analyses were age, sex, hypertension, diabetes mellitus, cardiac risk factors, smoking, severity of stroke, and regular use of acetylsalicylic acid (ASA). To assess the
Results
From the original cohort of 180 patients, we excluded 2 patients who were lost to follow-up because of emigration within the first month after hospital discharge. The present report is thus based on data from 178 patients (106 men and 72 women) with a mean age of 72.5 years (range, 28 to 97 years). Baseline characteristics are further detailed in Table 1. The mean time of follow-up was 77.9 months.

Survival
A total of 106 patients (60%) died during the period of follow-up. A cardiac cause (myocardial infarction or congestive heart failure) was the cause of death in 63 patients, whereas fatal recurrent stroke occurred in 12 patients. Other causes of death were infections (12 patients), uremia (7 patients), pulmonary embolism (6 patients), and cancer (6 patients). An autopsy was performed in 7 patients.

Univariate predictors of death were age (P<0.01) and smoking (P<0.01), whereas treatment with ASA (P<0.01) reduced the risk of death. A Cox regression analysis identified age (P<0.01), male sex (P<0.01), and ASA medication (P=0.02) as independent prognostic factors for survival. The proportion of deaths attributable to a cardiac cause was lower among patients treated with ASA (24.6%) than in those who did not receive this therapy (40.4%; P=0.03).

The probability of survival was 93% at 1 year, 68% at 5 years, and 40% after 10 years (Table 2). During the first 5 years after stroke onset, the survival rates for patients did not differ from those of the general Swedish age- and sex-matched population. However, from 5 years and onward survival among the patients was significantly lower in comparison to estimates of expected survival in the normal population (Figure 1), with an absolute difference of 10 to 15 percent units for each 1-year interval. The excess risk of death compared with the normal population was higher for male patients (difference of approximately 15 to 20 percent units) than female patients (difference of approximately 5 percent units).

Table: Baseline Characteristics of the 178 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>106</td>
<td>59.6</td>
</tr>
<tr>
<td>Female</td>
<td>72</td>
<td>40.4</td>
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<tr>
<td>Hypertension</td>
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<td>52.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27</td>
<td>15.2</td>
</tr>
<tr>
<td>Cardiac risk factors*</td>
<td>26</td>
<td>14.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>50</td>
<td>28.1</td>
</tr>
<tr>
<td>Moderate to severe paresis</td>
<td>66</td>
<td>37.1</td>
</tr>
<tr>
<td>ASA treatment</td>
<td>69</td>
<td>38.8</td>
</tr>
</tbody>
</table>

*Relative cumulative survival = observed cumulative survival/expected cumulative survival.

Recurrent Stroke and Transient Ischemic Attacks During Follow-Up
A total of 42 patients (23.5%) had a subsequent stroke during the follow-up period. The recurrent stroke was lethal in 12 of these patients. Figure 2 presents the Kaplan-Meier estimates of the probability of recurrent stroke. The average annual risk of recurrent stroke during 10 years was 2.4%. However, the risk appeared higher (approximately 5%) during the first few years, whereas the average annual risk from year 5 and onward was <1%.

Univariate variables predicting recurrent stroke were age (P<0.05), hypertension (P<0.05), and diabetes (P<0.05), whereas the difference for smoking did not reach statistical significance (P=0.09). In the Cox proportional hazards analysis, only hypertension (P=0.025) and diabetes (P=0.024) remained as independent predictors.

Because almost all patients with recurrent stroke were readmitted to our hospital, clinical records helping to determine the subtype of recurrent stroke were available. However, CT scan was performed in only 8 of the 42 patients with recurrent stroke, revealing a hematoma in 2 patients, new

Figure 1. Observed percentage of patients surviving (Kaplan-Meier estimates) an incident presumed lacunar infarct. Estimated percentage surviving is based on the age- and sex-specific death rates of the whole Swedish population for the same time period.
single or multiple small deep infarcts in 4 patients, and no new finding in 2 patients. Clinical features of the recurrent stroke (not including the 2 patients with a hematoma) were a lacunar syndrome in 21 patients (pure motor stroke in 19 patients, pure sensory stroke and sensorimotor stroke in 1 patient each; 13 ipsilateral and 8 contralateral relative to the index stroke) and a cortical middle cerebral artery syndrome in 4 patients (2 of whom had a newly recognized cardioembolic source), whereas clinical details were incompletely reported in 15 patients.

During follow-up 69 patients were treated with ASA in doses between 125 and 500 mg per day, whereas 12 patients were treated with anticoagulant medication (because of deep venous thrombosis, pulmonary embolism, or atrial fibrillation). No antiischemic therapy was given to 97 patients. There was no difference in risk of recurrent stroke according to the antiischemic therapy (data not shown). Of the 2 patients with hemorrhagic stroke, 1 was on treatment with ASA and the other with anticoagulant therapy.

New transient ischemic attacks (TIAs) during follow-up were recorded in 7 patients, in all cases with motor symptoms only. Four patients had ipsilateral TIAs, and 3 patients had TIAs contralateral to the hemisphere involved in the index stroke. In none of the patients were the TIAs followed by a major recurrent stroke. In none of the patients were the TIAs followed by a major recurrent stroke.

Recurrent stroke or death occurred in a total of 136 patients during the follow-up period. The probability of survival free of recurrent stroke decreased from 91% at 1 year, 82% at 2 years, 73% at 3 years, to 34% at 10 years.

**Discussion**

**Survival**

Most previous studies have reported that the prognosis for survival (as well as recurrent stroke and functional recovery) in patients with lacunar infarction syndromes is excellent and is more favorable than in patients with other subtypes of stroke. A minimal case fatality at 1 month is a consistent finding, presumably because of the small infarct size and the low rate of secondary complications and cardiac comorbidity. The long-term risk of death is much more variable, ranging from 3.1% to 15% annually, with an average of 2.6% per year in available studies. However, several studies are based on small numbers of patients and have limited statistical precision; only 1 previous study was based on >150 patients. Methodological features may also contribute to differences between studies. Moreover, times of follow-up have been relatively short in most studies. Only 4 previous studies have reported survival rates up to 5 years after the index stroke. Data on survival beyond this time have not been reported previously.

Our study presents the longest reported follow-up period to date of a large number of patients with lacunar infarction syndromes. We can confirm the low case fatality rate at 1 month seen in most previous studies. The death rate at 5 years (32%) in our study is similar to the rates reported in 2 previous community-based studies (25% to 35%) but higher than the rates reported in 2 hospital-based studies (14% to 15.4%). We also confirmed the finding by Sacco et al that survival for the first few years after the stroke was similar to that in an age- and sex-matched general population. However, a novel finding of our study is that from 5 years and onward, patients with lacunar stroke carried an excessive risk of death compared with the general population. Myocardial infarction and cardiac failure accounted for 60% of all deaths, a proportion higher than in previous reports, whereas 11% of deaths were caused by recurrent stroke.

We found age, male sex, and nonuse of ASA to be independent determinants for survival. Previously reported independent risk factors for death after lacunar infarction are age, diabetes, and smoking (in the study by Clavier et al) and age and disability score (in the study by Salgado et al). The high proportion of our patients (54%) not prescribed ASA at discharge from hospital reflects the therapeutic tradition in the mid-1980s, before the wide acceptance of antiplatelet therapy as standard therapy in different thromboembolic disorders. The cause of death was less frequently cardiac among patients who had been prescribed ASA compared with those not given this therapy.

**Recurrent Stroke**

Previously reported data on the risk of recurrent stroke after lacunar infarct syndromes are variable and range from 2.3% to 11.8% within the first year after stroke onset and from 2.4% to 7% per year thereafter (calculated as average risk per year). The risk after the first year averages 5%, which is similar to the rate found in the present study for the first 5 years after the index stroke. Beyond 5 years, surprisingly few strokes occurred in our study, corresponding to a rate of <1% per year. The decline in the stroke rate with time may be real or due to chance. Comparative data beyond 5 years after stroke onset are not available from any other study in lacunar stroke patients. No decline in the rate of recurrent stroke with time has been noted in other long-term studies including all subtypes of stroke, and further studies are needed to explore whether the time pattern of recurrent stroke after lacunar infarcts is different.

A lower rate of recurrent stroke after lacunar infarcts compared with other stroke types has been reported in some studies, whereas no significant difference has been noted in 2 studies. In a recent study by Petty et al, stroke subtype was not an independent predictor of long-term
recurrence before or after adjustment for age, stroke severity, and diabetes mellitus.

In our study hypertension and diabetes were independent predictors for recurrent stroke, in contrast to previous studies in which either no single factor or age only was found. The adequacy of risk factor management and compliance to therapy during follow-up was not addressed in our study. We observed no difference in risk of recurrent stroke according to antithrombotic therapy prescribed, but proper analysis of this issue would require a much larger sample size than in our study.

Assessment of the subtype of recurrent stroke was imprecise in our study. Although approximately half of the recurrent strokes presented as a lacunar syndrome, CT scan was performed in only 20%, and reports on clinical features were incomplete in 36% of the patients. Data on subtype of recurrent stroke in previous studies differ substantially. Sacco et al9 found that only 17% of recurrent strokes were lacunar, in contrast to 84% reported by Boiten and Lodder.14 In the Lausanne Stroke Registry,29 approximately half of second and further recurrent stroke in patients with lacunes were of the same type as the index stroke. A similar heterogeneous pattern has also been reported from a substudy of the Dutch TIA Trial10 and by Samuelsson et al.3 A diverse pathophysiological pattern of recurrent stroke after lacunar infarcts should not be unexpected because the major risk factors that predispose to vascular occlusions in small brain arteries also promote atheroemboli in the coronary arteries, aorta, and cervicocranial arteries.

Other Aspects of Prognosis After Lacunar Stroke
Our study did not address the risk of cognitive decline, dementia, or asymptomatic progression of the underlying vascular process. These are important fields for further studies. Two previous studies have reported that 11% of subjects with lacunar infarcts developed dementia after 2.3 to 3 years,3132 often in conjunction with recurrent strokes. Lesser degrees of cognitive dysfunction are probably much more common.3133 From the few studies available,1934 silent new infarcts have been found to be 2 to 5 times more common than symptomatic infarcts, further emphasizing the need for more effective preventive measures in patients with lacunar infarction.

Conclusions
In conclusion, our study provides new information on the prognosis after presumed lacunar infarction using a longer time of follow-up than in previous prognostic studies of this stroke subtype. Our study shows that the commonly held view of a benign prognosis after lacunar infarcts only holds true for the first few years. In a longer perspective, patients with lacunar infarcts carry an excessive risk of death, mainly attributable to cardiovascular disease, compared with the general population. The continual occurrence of recurrent stroke, development of cognitive dysfunction, and asymptomatic progression of the underlying vascular process in the brain constitute additional long-term risks. There is a need for randomized clinical trials of different therapeutic interventions specifically addressing the lacunar stroke subgroup.

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References


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