Ischemic Stroke Subtypes
A Population-Based Study of Functional Outcome, Survival, and Recurrence

George W. Petty, MD; Robert D. Brown, Jr, MD; Jack P. Whisnant, MD; JoRean D. Sicks, MS; W. Michael O’Fallon, PhD; David O. Wiebers, MD

Background and Purpose—There is scant population-based information on functional outcome, survival, and recurrence for ischemic stroke subtypes.

Methods—We identified all residents of Rochester, Minnesota, with a first ischemic stroke from 1985 through 1989 using the resources of the Rochester Epidemiology Project medical records linkage system. After reviewing medical records and imaging studies, we assigned patients to 4 major ischemic stroke categories based on National Institute of Neurological Diseases and Stroke Data Bank criteria: large-vessel cervical or intracranial atherosclerosis with stenosis (ATH, n = 74), cardioembolic (CE, n = 132), lacunar (LAC, n = 72), and infarct of uncertain cause (IUC, n = 164). We used the Rankin disability score to assess functional outcome and the Kaplan-Meier product-limit method and Cox proportional hazards regression analysis with bootstrap validation to estimate rates and identify predictors of survival and recurrent stroke among these patients.

Results—Rankin disabilities were different across stroke subtypes at the time of stroke and 3 months and 1 year later (P = 0.001). LAC was associated with milder deficits compared with other subtypes. Mean follow-up among the 442 patients in the cohort was 3.2 years. Estimated rates of recurrent stroke at 30 days were significantly different (P < 0.001): ATH, 18.5% (95% CI 9.4% to 27.5%); CE, 5.3% (95% CI 1.2% to 9.6%); LAC, 1.4% (95% CI 0.0% to 4.1%); and IUC, 3.3% (95% CI 0.4% to 6.2%). After adjusting for age, sex, and stroke severity, infarct subtype was an independent determinant of recurrent stroke within 30 days (P = 0.006; eg, risk ratio for ATH compared with CE = 3.3, 95% CI 1.2 to 9.3) but not long term (P = 0.07). Four of 25 recurrent strokes within 30 days were procedure-related, each in patients with ATH. Five-year death rates were significantly different (P < 0.001): ATH, 32.2% (95% CI 21.1% to 43.2%); CE, 80.4% (95% CI 73.1% to 87.6%); LAC, 35.1% (95% CI 23.6% to 46.0%); and IUC, 48.6% (95% CI 40.5% to 56.7%). With adjustment for age, sex, cardiac comorbidity, and stroke severity, the subtype of ischemic stroke was an independent determinant of long-term (P = 0.018; eg, risk ratio for ATH compared with cardioembolic = 0.47, 95% CI 0.29 to 0.77) but not 30-day survival (P = 0.2).

Conclusions—Early recurrence rates for ischemic stroke caused by ATH are higher than those for other subtypes and higher than previous non–population-based studies have reported. Some of the increased risk of early recurrence among patients with ATH may be iatrogenic. Patients with LAC have better poststroke functional status than those with other subtypes. Survival is poorest among those with ischemic stroke with a cardiac source of embolism. (Stroke. 2000;31:1062-1068.)

Key Words: cardioembolic stroke carotid artery diseases cerebral embolism epidemiology lacunar infarction survival thrombosis

Studies of survival and recurrence after stroke have been reported from numerous sites worldwide,1–5 but there is scant population-based information on outcomes for individual subtypes of ischemic stroke. Comparison of functional outcome and survival and recurrence rates for specific ischemic stroke mechanisms could allow clinicians to identify patients who are at higher risk for stroke recurrence and death, assist investigators in designing future clinical trials of tertiary stroke prevention, and permit health care policy investigators to quantify the societal burden attributable to individual pathophysiological mechanisms of ischemic stroke. We undertook a population-based outcomes study of all residents of Rochester, Minnesota, who had a first ischemic stroke from 1985 through 1989 to assess functional
outcome and to estimate and compare rates and identify determinants of recurrence and death for patients with common ischemic stroke subtypes.

Subjects and Methods

Study Population

The Rochester Epidemiology Project medical records linkage system provides resources to identify nearly all new cases of stroke in a community.6 Virtually all medical care in the community is supplied by the Mayo Clinic and its affiliated hospitals or by the Olmsted Medical Group, a smaller group practice, and its hospital. In these institutions, all medical diagnoses made for a resident of the local region are entered into the patient’s medical record, which is then entered into a central computer index. The index includes diagnoses made on region residents at other medical practices in surrounding communities, the University of Minnesota, and the Veterans Administration Hospital in Minneapolis. This index provides access to all inpatient and outpatient data, emergency department visits, nursing home care, and autopsy or death certificate information.

The population of Rochester is 96% white and 51% female. Median age is 31.5 years, compared with 32.9 years in the US population. Education includes 88% high school graduates (75.2%, United States) and 29.5% college graduates (20.3%, United States). The proportion of families with income less than poverty level was 6.9%, compared with 10% for the United States’ Population-based studies of stroke in Rochester are approved by the Mayo Foundation Institutional Review Board.

The medical records of all residents of Rochester who had a diagnosis of stroke or transient ischemic attack or a diagnosis that could be mistaken for stroke or transient ischemic attack during the 5-year period from January 1, 1985, through December 31, 1989, were screened by a neurologist and a trained nurse abstractor to determine whether the case met the criteria for stroke. All identified cases then had verification of residence based on information from city and county directories and earlier medical records. To exclude persons who might have moved to the region to facilitate treatment or diagnosis of an existing disorder, cases were eligible only if the person had been a resident of Rochester for at least 1 year before the stroke. Death certificates and autopsy protocols were also reviewed to identify those with a diagnosis of stroke. The clinical record was then reviewed to determine whether there were any clinical symptoms consistent with stroke. Patients with a clinical diagnosis of stroke or those who had stroke listed as a cause of death on the death certificate who died within 24 hours of symptom onset were excluded if there was no clinical evidence of a focal neurological deficit, no CT or MRI performed, or no autopsy performed.

The type of stroke was determined by using imaging studies and autopsy when available. Definitions of first stroke (hemorrhage or infarction) or those who had stroke listed as a cause of death on the death certificate, no CT or MRI performed, or no autopsy performed. The type of stroke was determined by using imaging studies and autopsy when available. Definitions of first stroke (hemorrhage or infarction) appear elsewhere and are identical to the definitions used in previous studies of stroke incidence, survival, and recurrence in the study region.

A neurologist and a nurse abstractor abstracted the medical record of each patient in this cohort and recorded on standardized forms information regarding stroke risk factors and functional status before or at the time of first cerebral infarction and diagnostic studies, treatment, and dates of last follow-up and death after the stroke but before January 1, 1993. A list and definitions of the stroke risk factors that were recorded have been published elsewhere.8,9 One study neurologist (G.W.P.) reviewed the clinical history, neurological examination, diagnostic studies, and brain imaging studies or neuroradiology reports of all patients and assigned infarct subtype classifications by the use of clinical and radiographic diagnostic rubrics similar to those of the National Institute of Neurological Diseases and Stroke: cardioembolic, large-vessel cerebral or intracranial atherosclerosis with occlusion or stenosis of ≥50%, lacunar, other unusual causes (such as dissection, vasculitis, and so on), and uncertain cause.9,10 Patients with a cardiac source of embolism had ≥1 of the following conditions: (1) congestive heart failure at stroke onset, (2) myocardial infarction within 2 months before stroke onset, (3) hemodynamically significant mitral valve disease, (4) prosthetic mitral or aortic valve, (5) atrial fibrillation or flutter, (6) cardiomyopathy, (7) congenital heart disease, (8) recent systemic arterial emboli, (9) stroke within 48 hours after coronary artery bypass surgery, (10) stroke within 48 hours after left ventricular aneurysm surgery, (11) stroke related to cardiac catheterization or pacemaker installation, (12) left ventricular aneurysm, (13) intracardiac thrombus, (14) valvular vegetations, (15) sick sinus syndrome, (16) autopsy evidence of recent myocardial infarction that could be dated at the time of or before the stroke, (17) autopsy evidence of rheumatic heart disease, (18) autopsy evidence of recent systemic arterial emboli that could be dated at the time of or before the stroke, and (19) autopsy evidence of embolic occlusion of an intracerebral vessel with little or no evidence of cerebral or intracranial atherosclerotic arterial disease. Patients with large-vessel cerebral or intracranial atherosclerosis with occlusion or stenosis had either occlusion or ≥50% stenosis of a cavocephalic artery (carotid, vertebral, basilar, middle cerebral, anterior cerebral, or posterior cerebral) supplying the vascular territory of the stroke documented by ultrasound, transcranial Doppler, oculopneumoplethysmography, cerebral angiography, magnetic resonance angiography, or autopsy.

Patients with lacunar stroke had clinical syndromes consistent with pure motor stroke, pure sensorimotor stroke, pure sensory stroke, ataxic hemiparesis, or clumsy hand dystathria. Brain CT or MRI among patients with lacunar stroke demonstrated either no lesion to explain the syndrome or a deep ischemic stroke in a location consistent with the clinical syndrome ≤15 mm in size. Brain CT, MRI, or autopsy was performed in 92% of residents of the study region with first stroke during the time period of this study,7 and all brain autopsy reports and >98% of brain images were available for review by the study neurologist at the time of infarct subtype classification.8,12

Recurrence stroke was defined as a new neurological deficit fitting the definitions for ischemic or hemorrhagic stroke, occurring after a period of unequivocal neurological stability or improvement lasting ≥24 hours and not attributable to edema, mass effect, brain shift syndrome, or hemorrhagic transformation of the incident cerebral infarction. All recurrences within 30 days were adjudicated by ≥2 study neurologists. Autopsy documentation of recent infarction in a vascular territory different from that of the incident infarction was counted as a recurrence if the date of the recurrent stroke could be estimated.1

The Rankin Disability Scale was used to measure functional status before the stroke, the maximal severity of neurological deficits within the first 7 days after the stroke, and functional outcome after first cerebral infarction 3 months and 1 year after the stroke: grade 1, no significant disability, able to perform all usual duties of daily living; grade 2, slight disability, unable to perform some previous activities but able to look after own affairs without assistance; grade 3, moderate disability, requiring some help but able to walk without assistance; grade 4, moderately severe disability, unable to walk and to attend to own bodily needs without assistance; and grade 5, severe disability, bedridden, incontinent, and requiring constant nursing care and attention.13

Statistical Analysis

Patients with uncommon causes of stroke such as vasculitis, hypercoagulable state as the result of underlying malignancy, and dissection were excluded from the analysis because of the small number of subjects. The χ² test was used to compare Rankin scores and treatments among the subtypes. The Kaplan-Meier product-limit method14 was used to estimate rates of survival and recurrent stroke after first cerebral infarction for the 4 common ischemic stroke subtypes (cerebral or intracranial large-vessel atherosclerosis with stenosis, cardioembolic, lacunar, and ischemic stroke of uncertain cause). Patients were censored at the time of migration from our locale or at the time of last follow-up or at January 1, 1993. The log-rank test was used to compare rate estimates and the Cox proportional hazards model15 was used to estimate the impact in terms of risk ratios of possible determinants of survival and recurrent stroke after first cerebral infarction. Previously published multivari-
able proportional hazards models of survival and recurrence after first ischemic stroke in our community were used as the foundation on which the impact of stroke subtype and Rankin score were assessed. Thus, stroke subtype (4 groups) and maximal deficit Rankin score (3 groups) were "added" to the existing models.

### Results

First ischemic stroke occurred in 454 residents of Rochester during the time period of the study. Three hundred sixty-two (80%) patients were hospitalized and 342 (75%) were evaluated by a neurologist. Transthoracic or transesophageal echocardiography was performed in 227 (50%) patients. Carotid ultrasound, oculopneumoplethysmography, transcranial Doppler ultrasonography, or cerebral angiography was performed in 54.4% of patients.

Each of the ischemic strokes was assigned a subtype: large-vessel cervical or intracranial atherosclerosis with stenosis, 74 (16%); cardioembolic, 132 (29%); lacunar, 72 (16%); uncertain cause, 164 (36%); and other or unusual causes, 12 (3%). Patients with unusual cause of stroke were excluded from the subsequent analysis, leaving 442 patients in the study group. The mean age and frequencies of cardiac and noncardiac risk factors for each subtype in this cohort have been published previously in a study of subtype incidence.

The proportions of patients in the subgroups who received aspirin after incident ischemic stroke were different ($P < 0.001$): atherosclerosis with stenosis, 37 (50.0%); cardioembolic, 31 (23.5%); lacunar, 51 (70.8%); and unknown cause, 79 (48.2%). The proportions of patients in the subgroups who received intravenous heparin after incident ischemic stroke were different ($P < 0.004$): atherosclerosis with stenosis, 36 (48.6%); cardioembolic, 46 (34.8%); lacunar, 29 (40.3%); and unknown cause, 42 (25.6%). The proportions of patients in the subgroups who received warfarin after incident ischemic stroke were different ($P < 0.006$): atherosclerosis with stenosis, 16 (21.6%); cardioembolic, 43 (32.6%); lacunar, 12 (16.7%); and unknown cause, 25 (15.2%).

### Functional Outcome

Table 1 presents the Rankin scores among the 442 patients with common ischemic stroke subtypes before the stroke, at maximal neurological deficit at the time of stroke, and after the stroke. Patients with lacunar ischemic stroke had milder maximal neurological deficits and better poststroke Rankin scores compared with patients with other subtypes. Patients with cardioembolic stroke had poorer prestroke functional status, more severe neurological deficits at the time of stroke, and poorer functional outcome compared with other subtypes.

### Recurrence

During 1425 person-years of follow-up, 110 patients among the 4 common subtypes had recurrent stroke. Seventy-five (68.2%) of these recurrent strokes were of the same subtype as the incident stroke. Table 2 and Figure 1 present the Kaplan-Meier estimates of recurrent stroke for the different subtypes.
subtypes. Twenty-five patients had recurrent stroke within 30 days, 13 of whom had large-vessel atherosclerosis with stenosis as the first stroke subtype. All 30-day recurrent strokes were ischemic. Four 30-day recurrent strokes were procedure related (cerebral angiography in 2, carotid endarterectomy in 1, axillary-axillary bypass in 1 patient with bilateral carotid, and left vertebral artery occlusions in 1), all among patients with large-vessel atherosclerosis with stenosis. Ischemic stroke subtype was a significant predictor of 30-day recurrence both before (log-rank \(P = 0.0001\)) and after \((P = 0.018)\) adjusting for age, atrial fibrillation, congestive heart failure, ischemic heart disease, and stroke severity with the proportional hazards model (Table 5).

### Discussion

The importance of our study is that it reports outcomes for the 4 common subtypes of ischemic stroke among all residents in a community. The population-based nature of our study limits bias inherent to studies derived from patients who were evaluated at tertiary care centers after referral from inside or outside the community or community-based studies of patients who were referred for hospitalization or evaluation by stroke neurologists. No patients were excluded on the basis of race, age, sex, risk factors, prognosis, or whether or not they were hospitalized, enrolled in a prospective study, or evaluated by a neurologist or cerebrovascular specialist. By including only patients with first stroke, our study eliminates a potential bias common to studies that may have included patients who were selected for referral to study centers because they had single or multiple recurrent cerebral ischemic events.

The unique population-based, subtype-specific, 30-day death rates (case-fatality rates) appearing in Table 4 and the previously reported subtype-specific incidence rates derived from this cohort permit estimation of the annual mortality rates in this country attributable to each incident stroke subtype.8,16 Approximately 32 724 Americans die each year of a first stroke with a cardiac source of embolism, 5494 of large-vessel atherosclerosis with stenosis, 1078 of lacunar stroke, and 21 560 of ischemic stroke of unknown cause. These figures underscore the societal importance of research into stroke cause and primary stroke prevention.

Another important result of our study is the quantification of the magnitude of the risk of early recurrence associated with ischemic stroke due to large-vessel atherosclerosis with stenosis. More than 18% of patients with this subtype had a recurrent stroke within 30 days of the first stroke, higher than congestive heart failure, and stroke severity with the proportional hazards model (Table 5). Ischemic stroke subtype was a significant predictor of long-term survival both before (log-rank \(P = 0.0001\)) and after \((P = 0.018)\) adjusting for age, atrial fibrillation, congestive heart failure, ischemic heart disease, and stroke severity with the proportional hazards model (Table 5).

### Survival

Two hundred forty-five patients died during follow-up. Table 4 and Figure 2 present the Kaplan-Meier estimates of rates of death for the different stroke subtypes. Ischemic stroke subtype was a significant predictor of 30-day survival before (log-rank \(P = 0.0001\)) but not after \((P = 0.2)\) adjusting for age, congestive heart failure, and stroke severity with the proportional hazards model (Table 5). Ischemic stroke subtype was a significant independent determinant of 30-day recurrence (Table 3). Ischemic stroke subtype was a significant independent determinant of 30-day recurrence (Table 3). Ischemic stroke subtype was a significant independent determinant of 30-day recurrence (Table 3). Ischemic stroke subtype was a significant independent determinant of 30-day recurrence (Table 3). Ischemic stroke subtype was a significant independent determinant of 30-day recurrence (Table 3).

**Table 3.** Cox Proportional Hazards Models Examining Influence of Ischemic Stroke Subtype on Survival Free of Subsequent Stroke (Recurrence), 1985–1989

<table>
<thead>
<tr>
<th>Variable</th>
<th>30-d Risk Ratio (95% CI)</th>
<th>Long-Term Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 y)</td>
<td>0.86 (0.61–1.20)</td>
<td>1.10 (0.93–1.31)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.87 (0.37–2.06)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rankin 3</td>
<td>0.62 (0.21–1.80)</td>
<td>1.88 (1.25–2.85)</td>
</tr>
<tr>
<td>Rankin 4 or 5</td>
<td>0.73 (0.28–1.91)</td>
<td>0.78 (0.48–1.26)</td>
</tr>
<tr>
<td>Atherosclerosis with stenosis</td>
<td>3.34 (1.20–9.27)</td>
<td>1.86 (0.95–3.02)</td>
</tr>
<tr>
<td>Lacunar*</td>
<td>0.23 (0.03–1.97)</td>
<td>0.74 (0.38–1.43)</td>
</tr>
<tr>
<td>Ischemic stroke of unknown cause*</td>
<td>0.55 (0.16–1.85)</td>
<td>1.12 (0.67–1.89)</td>
</tr>
</tbody>
</table>

*Compared with cardioembolic.
the range of 8% to 14% reported in previous hospital-based studies.\textsuperscript{2,17,18} Our 1-month recurrence rate among patients with this subtype is actually higher than the 3-month recurrence rate of 13% reported recently by Moroney et al.\textsuperscript{17} Although these variations in recurrence rates may be due to differences in age, sex, race,\textsuperscript{19} and risk factors among study subjects, we believe methodological differences between studies are a more likely explanation. In addition to the advantages that a population-based study of incident stroke cases has over hospital-based or referral-based studies that include cases of nonincident stroke, differences in definitions (that is, the degree of stenosis sufficient for classification as ischemic stroke due to large-vessel atherosclerosis) and analysis may account for our higher early recurrence rates for patients with large-vessel atherosclerosis with stenosis. In a Stroke Data Bank study of early recurrence, for example, patients were censored at the time of a recurrence related to a procedure, and recurrent stroke was defined as a new deficit that occurred only in a different anatomic or vascular territory from that of the index stroke.\textsuperscript{18} If a stenotic or occluded artery that has recently given rise to distal embolization or hemodynamic compromise is likely to do so again, as is the assumption behind the rationale for carotid endarterectomy, then excluding recurrences in the same vascular territory as that of the index stroke would guarantee relatively lower recurrence rates for patients with stroke due to large-vessel atherosclerosis with stenosis. Also, if procedure-related recurrences are overrepresented among patients with large-vessel atherosclerosis, as was the case in our cohort, censoring patients at the time of a procedure-related recurrence could also guarantee that recurrence rates for this subtype will be underestimated relative to other subtypes in which procedures such as cerebral angiography and vascular surgery are not likely to be performed. We chose to include procedure-related events as an end point in the recurrence analysis because these procedures are part of a process that clinicians use to select and effect treatment for patients with symptomatic large-vessel atherosclerosis with stenosis. Complications of these procedures, although not a measure of efficacy, are a determinant of effectiveness and thus a potentially important determinant of outcome. Our findings raise the possibility that iatrogenic stroke may not be an insignificant factor contributing to recurrent stroke among patients with large-vessel atherosclerosis with stenosis in the general population, despite the results of the North American Symptomatic Endarterectomy Trial, which demonstrated the efficacy of endarterectomy for stroke prevention among patients with symptomatic carotid bifurcation stenosis.\textsuperscript{20}

Our multivariate model of long-term recurrence did not identify ischemic stroke subtype as a determinant of recurrent stroke (Table 3), in contrast to the referral-based Stroke Data Bank study of Hier et al.\textsuperscript{21} which identified ischemic stroke of unknown cause as a predictor of survival free of recurrent stroke. We believe that the differences between our findings and those of the Stroke Data Bank in this regard again most likely relate to differences in methodology and definitions of recurrent stroke (see above).

Our study also demonstrates significant differences among subtypes not only for maximal neurological deficits at the time of stroke and functional outcome at 3 months and 1 year but also for prestroke functional status (Table 1). Prestroke functional status was best among those destined to have lacunar stroke or ischemic stroke due to large-vessel atherosclerosis with stenosis and worst among those who subsequently had cardioembolic stroke. These differences probably reflect a higher prevalence of heart disease and cardiac-related prestroke disability among those with cardioembolic stroke. Patients with lacunar infarction and stroke due to large-vessel atherosclerosis with stenosis had remarkably
A striking finding of our survival model is that ischemic stroke due to atherosclerosis with stenosis is associated with better long-term survival than cardioembolic stroke, even after adjustment for age, sex, atrial fibrillation, ischemic heart disease, congestive heart failure, and stroke severity (Table 5). This finding is difficult to explain on the basis of generally held concepts about the influence of atherosclerosis and survival and is especially puzzling given the higher 30-day recurrence rates among patients with large-vessel atherosclerosis compared with our previous finding that recurrence is an important independent determinant of death. It suggests that additional unrecognized risk factors, unaccounted for in our model, which may be relatively underrepresented or overrepresented among patients with cardioembolic stroke or patients with large-vessel atherosclerosis with stenosis, could influence survival among these patients.

In summary, early recurrence rates for ischemic stroke due to large-vessel atherosclerosis with stenosis are higher than those for other subtypes and higher than previous non–population-based studies have reported. Some of the increased risk of early recurrence among patients with large-vessel stenosis may be iatrogenic. Patients with cardioembolic stroke have worse prestroke and poststroke functional status than do those with other subtypes. Survival is poorest among those with ischemic stroke with a cardiac source of embolism and best among those with large-vessel atherosclerosis with stenosis, even after adjustment for stroke severity and cardiac comorbidity.

**Acknowledgments**

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