Ischemic Stroke Subtypes
A Population-Based Study of Incidence and Risk Factors

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Background and Purpose—There is scant population-based information on incidence and risk factors for ischemic stroke subtypes.

Methods—We identified all 454 residents of Rochester, Minn, with a first ischemic stroke between 1985 and 1989 from the Rochester Epidemiology Project medical records linkage system. We used Stroke Data Bank criteria to assign infarct subtypes after reviewing medical records and brain imaging. We adjusted average annual incidence rates by age and sex to the US 1990 population and compared the age-adjusted frequency of stroke risk factors across ischemic stroke subtypes.

Results—Age- and sex-adjusted incidence rates (per 100,000 population) were as follows: large-vessel cervical or intracranial atherosclerosis with >50% stenosis, 27; cardioembolic, 40; lacuna, 25; uncertain cause, 52; other or uncommon cause, 4. Sex differences in incidence rates were detected only for atherosclerosis with stenosis (47 [95% CI, 34 to 61] for men; 12 [95% CI, 7 to 17] for women). There was no difference in prior transient ischemic attack and hypertension among subtypes, and diabetes was not more common among patients with lacunar infarction than other common subtypes.

Conclusions—The age-adjusted incidence rate of stroke due to stenosis of the large cervicocephalic vessels is nearly 4 times higher for men than for women. There is no association between preceding transient ischemic attack and stroke mechanism. Diabetes and hypertension are not more common among patients with lacunae. Age- and sex-adjusted incidence rates for ischemic stroke subtypes in this population can be compared with similarly determined rates from other populations. (Stroke. 1999;30:2513-2516.)

Key Words: carotid artery diseases ▪ cerebral embolism and thrombosis ▪ cerebral infarction ▪ epidemiology ▪ lacunar infarction

Studies of stroke incidence rates and risk factors have been reported from numerous sites worldwide, but there is scant population-based information on incidence and risk factors of individual subtypes of ischemic stroke. Incidence studies of ischemic stroke subtypes could provide investigators with the opportunity to quantify the societal stroke burden attributable to specific mechanisms of stroke, explore sex and race differences in stroke etiology, and more accurately define the frequency of various stroke risk factors among stroke subtypes. We undertook a population-based study of all residents of Rochester, Minn, who experienced a first ischemic stroke between 1985 and 1989 to determine age- and sex-specific incidence rates and risk factor associations for each subtype of ischemic stroke.

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. Virtually all medical care in the community is supplied by the Mayo Clinic and its 2 affiliated hospitals or the Olmsted Medical Group, a smaller group practice, and its hospital. In these institutions, all medical diagnoses made for a resident of Rochester are entered in the patient’s medical record, which is then entered into a central computer index. The index includes diagnoses made on our 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.

Ninety-six percent of the population of Rochester is white, and 51% is female. Median age is 31.5 years, compared with 32.9 years for the US population. With regard to education, 88% are high school graduates (75.2% for US population), and 29.5% are college graduates (20.3% for US population). The proportion of families with income less than poverty level is 6.9% compared with 10% for the US population. Population-based studies of stroke in our community 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 diagnoses that
could be mistaken for stroke or transient ischemic attack 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 on the basis of information from city and county directories and earlier medical records. To exclude persons who may have moved to Rochester to facilitate treatment or diagnosis of an existing disorder, cases were eligible only if the person had been a resident of the community for at least 1 year before the stroke.

Death certificates and autopsy protocols also were reviewed to identify those with the diagnosis of stroke. The clinical record was 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, or no autopsy performed. The type of stroke was determined with the use of imaging studies and autopsy data when available. Definitions of first stroke (hemorrhage or infarction) appear elsewhere3 and are identical to the definitions used in previous studies of stroke incidence, survival, and recurrence in Rochester.

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 before or at the time of first cerebral infarction and diagnostic studies performed after the stroke. A partial list of coded variables appears in Tables 1 and 2. The definitions used for the variables that were studied have been published elsewhere.4 A study neurologist reviewed the clinical history, neurological examination, diagnostic studies, and brain imaging studies or neuroradiology reports of all patients and assigned infarct subtype classifications using clinical and radiographic diagnostic rubrics of the National Institute of Neurological Disorders and Stroke (NINDS) Data Bank: cardioembolic, large-vessel cervical or intracranial atherosclerosis with stenosis ≥50%, lacuna, other unusual causes, and uncertain cause.4–6 Brain CT, MRI, or autopsy was performed in 92% of residents with first stroke during the period of this study,2 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.3,7

### Statistical Analysis

Average annual incidence rates for subtypes of ischemic stroke were calculated with denominators interpolated from census data and were adjusted by age and sex to the US 1990 population to facilitate comparisons with other studies. Distributions of risk factors and clinical characteristics among patients in the 5 subtypes were compared with the χ² or Fisher exact test. For each risk factor, a logistic regression with age, sex, and 3 or 4 df to separate subtypes was used to test whether the proportions with the factor were the same across the subtypes. Logistic regression was used to model the odds of receiving diagnostic tests to detect large-vessel atherosclerosis with stenosis (ultrasonography, oculopneumoplethysmography, transcranial Doppler ultrasonography, or cerebral angiography) with age and sex. ANOVA was used to compare mean ages of patients in the 5 groups.

### Results

First ischemic stroke occurred in 454 residents during the period of the study. Two hundred seventy (59%) were women. Three hundred sixty-two patients (80%) were hospitalized, and 342 (75%) were evaluated by a neurologist. Transthoracic or transesophageal echocardiography was performed in 227 patients (50%), of which 132 (58.1%) were women. Carotid ultrasonography, oculopneumoplethysmog-

### Table 1. Risk Factors Among 454 Patients With First Ischemic Stroke, 1985–1989

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Atherostenosis (n = 74)</th>
<th>Cardioembolic (n = 132)</th>
<th>Lacuna (n = 72)</th>
<th>Unknown (n = 164)</th>
<th>Other (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>72±11</td>
<td>80±12</td>
<td>73±10</td>
<td>76±14</td>
<td>67±20</td>
<td>0.001</td>
</tr>
<tr>
<td>Age &lt;51 y</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>6 (4)</td>
<td>4 (33)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>50 (68)</td>
<td>44 (33)</td>
<td>31 (43)</td>
<td>55 (34)</td>
<td>4 (33)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>18 (24)</td>
<td>23 (17)</td>
<td>12 (17)</td>
<td>22 (13)</td>
<td>2 (17)</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56 (76)</td>
<td>100 (76)</td>
<td>54 (75)</td>
<td>113 (69)</td>
<td>8 (67)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (16)</td>
<td>31 (23)</td>
<td>16 (22)</td>
<td>35 (21)</td>
<td>0 (0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Smoking</td>
<td>57 (77)</td>
<td>57 (43)</td>
<td>36 (50)</td>
<td>66 (40)</td>
<td>5 (42)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values (except age) are number of patients, with percentage in parentheses.
*Mean (±SD).
†Age- and sex-adjusted.

### Table 2. Cardiac Risk Factors Among Patients With Noncardioembolic First Ischemic Stroke, 1985–1989

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Atherostenosis (n = 74)</th>
<th>Lacuna (n = 72)</th>
<th>Unknown (n = 164)</th>
<th>Other (n = 12)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>8 (11)</td>
<td>2 (3)</td>
<td>17 (10)</td>
<td>1 (8)</td>
<td>0.2</td>
</tr>
<tr>
<td>MI</td>
<td>14 (19)</td>
<td>6 (8)</td>
<td>14 (9)</td>
<td>2 (17)</td>
<td>0.2</td>
</tr>
<tr>
<td>Angina or MI</td>
<td>25 (34)</td>
<td>14 (19)</td>
<td>22 (13)</td>
<td>3 (25)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>7 (9)</td>
<td>4 (6)</td>
<td>10 (6)</td>
<td>2 (17)</td>
<td>0.06</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (15)</td>
<td>4 (6)</td>
<td>9 (5)</td>
<td>4 (33)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are number of patients, with percentage in parentheses.
CHF indicates congestive heart failure; MI, myocardial infarction.
*Age- and sex-adjusted.
raphy, transcranial Doppler ultrasonography, or cerebral angiography was performed in 54.4% of patients. A logistic model demonstrated an interaction between sex and age with respect to the odds of receiving 1 of these tests to detect large-vessel atherosclerosis with stenosis (P = 0.015). The ratio of the odds of a man receiving 1 of these tests to the odds of a woman of the same age receiving 1 of these tests was lower among younger patients with stroke (odds ratio [OR] age 50 = 0.4; 95% CI, 0.14 to 1.33) and higher among elderly patients with stroke (OR age 80 = 1.9; 95% CI, 1.20 to 3.00).

Each of the 454 ischemic strokes was assigned a subtype: large-vessel cervical or intracranial atherosclerosis with stenosis, 74 (16%); cardioembolic, 132 (29%); lacuna, 72 (16%); uncertain cause, 164 (36%); and other, 12 (3%). Age- and sex-adjusted incidence rates are presented in Table 3. Age-adjusted incidence rates of ischemic stroke due to large-vessel cervical or intracranial atherosclerosis with stenosis were nearly 4 times higher (P < 0.0001) for men (47.3 per 100 000) than for women (11.9 per 100 000). No significant sex-related differences in incidence rates were detected for the other subtypes.

The frequencies of noncardiac risk factors for each subtype are presented in Table 1. The subtypes differed by age (P = 0.001), sex (P = 0.001), history of diabetes (P = 0.04), and proportion of current smokers (P = 0.03). There was no difference in the frequency of a preceding diagnosis of hypertension or transient ischemic attack among subtypes. The frequency of diabetes was similar among patients with cardioembolic stroke, lacuna, atherosclerosis with stenosis, and infarcts of uncertain cause. Cigarette smoking was overrepresented among patients with atherosclerosis with stenosis. Because the cardioembolic subtype is defined in part by documentation of certain cardiac risk factors, distributions of cardiovascular risk factors among the 4 noncardioembolic subtypes are presented and compared in Table 2. Atrial fibrillation, ischemic heart disease, and mitral valve disease were each less common among patients with lacunae and infarcts of uncertain cause.

**Discussion**

Our study reports incidence rates and risk factors for ischemic stroke subtypes among all residents in a community. The population-based study design limits bias inherent in studies of patients referred to tertiary care centers for hospitalization or evaluation by specialists. By including only patients with first stroke, our study eliminates a potential bias common to studies that may have included cases because of single or multiple recurrent strokes.

Subtype-specific ischemic stroke incidence rates permit identification of racial and sex differences in stroke etiology. For example, our study documents that men have a 4 times greater age-adjusted incidence rate of ischemic stroke due to large-vessel atherosclerosis than women (47 compared with 12 per 100 000, respectively; Table 3). This biological difference could more than adequately explain why carotid endarterectomy rates in the United States are 30% to 60% higher for men than for women.8-9

Similarly, a comparison of our study and the study of the black population of metropolitan Cincinnati, Ohio,9 demonstrates that although black Americans have higher overall age- and sex-adjusted ischemic stroke incidence (246 per 100 000) compared with whites (147 per 100 000), the incidence of stroke due to large-vessel atherosclerosis with stenosis is significantly greater among whites (27 per 100 000) than blacks (17 per 100 000). This difference cannot be attributed to a disparity in procedure rates because the same proportion (54%) of patients in our study and in the study by Woo et al received diagnostic tests to detect carotid stenosis. Clearly, biological differences in stroke mechanism as well as biological differences in the intracranial and extracranial distribution of atherosclerosis between blacks and whites11,12 could account for a significant portion of the 2- to 3-fold higher carotid endarterectomy rates reported for whites compared with blacks in Massachusetts, California, and the Veterans Affairs Medical Centers.8,13-15

Subtype-specific stroke incidence rates thus permit an informed and objective assessment of various hypotheses that have been proposed to explain race and sex differences in cerebral angiography and carotid endarterectomy rates in the United States.8,9,13-16 Conclusions from studies that use large administrative databases8,9,13-15 must be made in the context of knowledge of race and sex differences in disease biology. Otherwise, it is difficult to assess the importance of other putative explanations for race and sex disparity, such as exclusion from care on “socioeconomic rather than clinical grounds” or even “de facto discrimination” against ethnic or sex groups on the part of physicians, as have been proposed by some.8,13-16

Subtype-specific incidence rates permit estimation of the annual number of first ischemic strokes occurring in the United States for each subtype. The subtype-specific age- and sex-adjusted incidence rates for ischemic stroke among
blacks residing in the metropolitan area of Cincinnati, Ohio, are as follows (per 100,000): atherosclerosis with stenosis, 17 (95% CI, 8 to 26); cardioembolic, 56 (95% CI, 40 to 73); lacunar, 52 (95% CI, 36 to 68); uncertain cause, 103 (95% CI, 80 to 126); and other causes, 17 (95% CI, 9 to 26). With the age- and sex-adjusted subtype-specific incidence rates from our present study of a largely white population of Rochester (Table 3) as estimates for the entire nonblack US population, the incidence rates reported by Woo et al.10 as estimates for the entire black US population, the 1996 estimate of the total US population as 268,000,000, and the 1990 census report of 13% blacks in the US population,5,10,17 it is estimated that the total number of first ischemic strokes occurring in the United States each year is approximately 430,000, of which 69,000 are due to large-vessel atherosclerosis with stenosis, 113,000 are cardioembolic, 76,000 are lacunae, 157,000 are infarcts of unknown or nonobvious cause, and 15,000 are due to uncommon mechanisms.

Our population-based study provides a different perspective on the relative frequency of ischemic stroke subtypes and their risk factors compared with referral-based studies.18 The proportion of patients with cardioembolic stroke in our population was greater than the proportion with either lacunar infarction or atherosclerosis with stenosis, whereas lacunae constituted the single largest subtype of ischemic stroke of identifiable cause in the NINDS Stroke Data Bank.18,19 These differences could be due to race, sex, and age differences between stroke patients in our community and those enrolled in the Stroke Data Bank. Alternatively, selection factors inherent in the referral of patients to tertiary care hospitals that participated in the NINDS Stroke Data Bank and to stroke specialists within those hospitals may account for the different distribution of subtypes in the Stroke Data Bank compared with our study.

Like the Oxfordshire Community Stroke Project,20 we found no association between lacunae and either diabetes or hypertension, in contrast to inferences drawn from nonpopulation-based studies of hospitalized patients.19 In fact, the frequency of hypertension was strikingly similar among patients in our population with stroke due to large-vessel disease, cardioembolic stroke, and lacunae (Table 1). We found no difference in history of prior transient ischemic attack among subtypes in our study, in contrast to referral-based studies.19 The independent association between smoking and ischemic stroke due to large-vessel atherosclerosis with stenosis in our community is consistent with previous observations that smoking is a strong predictor of intracranial and extracranial carotid artery stenosis among patients undergoing arteriography, especially among whites.21–23

In summary, population-based studies of subtype-specific ischemic stroke incidence rates and risk factors provide a means of more accurately quantifying the societal stroke burden attributable to each ischemic stroke mechanism, comparing racial and sex differences in stroke mechanisms, and clarifying risk factor associations for different ischemic stroke subtypes.

Acknowledgments
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References
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