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

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 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 lacunar infarction than other common subtypes.

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.

*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.
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first stroke, our study eliminates a potential bias common to
evaluation by specialists. By including only patients with
population-based study design limits bias inherent in studies
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 ste-
nosis, 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, lacunae, 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.6,9

Similarly, a comparison of our study and the study of the
black population of metropolitan Cincinnati, Ohio,10
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.8,9,13–15 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.8,13–15

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

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**TABLE 3. Age- and Sex-Adjusted Incidence Rates (95% CIs) per 100 000 Population for Ischemic Stroke Subtypes, 1985–1989**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>All Types</th>
<th>Atherostenosis</th>
<th>Cardioembolic</th>
<th>Lacuna</th>
<th>Unknown</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total†</td>
<td>147 (133–161)</td>
<td>27 (21–33)</td>
<td>40 (33–47)</td>
<td>25 (19–31)</td>
<td>52 (44–60)</td>
<td>4 (2–6)</td>
</tr>
<tr>
<td>Female age-adjusted‡</td>
<td>124 (109–140)</td>
<td>12 (7–17)</td>
<td>37 (29–45)</td>
<td>22 (15–29)</td>
<td>50 (40–59)</td>
<td>4 (1–7)</td>
</tr>
<tr>
<td>Male age-adjusted‡</td>
<td>173 (148–199)</td>
<td>47 (34–61)</td>
<td>42 (30–55)</td>
<td>29 (19–40)</td>
<td>51 (37–64)</td>
<td>3 (0–7)</td>
</tr>
</tbody>
</table>

*Denotes significant sex differences.
†Age- and sex-adjusted to 1990 US population.
‡Age-adjusted to 1990 US population.
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); lacuna, 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 al10 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 different distribution of stroke subtypes in the NINDS Stroke Data Bank.18,19 This study was supported by the National Institute of Neurological Disorders and Stroke (NS06663), Agency for Health Care Policy and Research (282–91-0028), and National Institutes of Health and United States Public Health Service (AR30582).

References
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