Epidemiology of Ischemic Stroke Subtypes According to TOAST Criteria

Incidence, Recurrence, and Long-Term Survival in Ischemic Stroke Subtypes: A Population-Based Study

Peter L. Kolominsky-Rabas, MD; Margarete Weber, MD; Olaf Gefeller, MSc, PhD; Bernhard Neundoerfer, MD, PhD; Peter U. Heuschmann, MD, MPH

Background and Purpose—The purpose of this study was to determine the incidence, recurrence, and long-term survival rates of ischemic stroke subtypes by a mechanism-based classification scheme (Trial of ORG 10172 in Acute Stroke Treatment, or TOAST).

Methods—We identified all 583 residents of the city of Erlangen, Bavaria, Germany, with a first ischemic stroke between 1994 and 1998. Multiple overlapping sources of information were used to ensure completeness of case ascertainment. The cause of ischemic stroke was classified according to the TOAST criteria. Patients were followed up at 3 months and 1 and 2 years after stroke onset.

Results—The age-standardized incidence rates for the European population (per 100 000) regarding ischemic stroke subtypes were as follows: cardioembolism, 30.2 (95% CI 25.6 to 35.7); small-artery occlusion, 25.8 (95% CI 21.5 to 30.9); and large-artery atherosclerosis, 15.3 (95% CI 12 to 19.3). When age-adjusted to the European population, the incidence rate for large-artery atherosclerosis was more than twice as high for men than for women (23.6/100 000 versus 9.2/100 000). Two years after onset, patients in the small-artery occlusion subgroup were 3 times more likely to be alive than those with cardioembolism. Ischemic stroke subtype according to the TOAST criteria was a significant predictor for long-term survival, whereas subtype was not a significant predictor of long-term recurrence up to 2 years, both before and after adjustment for age and sex.

Conclusions—Epidemiological observational studies that possess wide access to appropriate diagnostic technologies and apply standardized etiologic classifications provide a much better understanding of underlying risk factors for initial stroke, recurrence, and mortality. (Stroke. 2001;32:2735-2740.)

Key Words: epidemiology ■ incidence ■ recurrence ■ stroke classification ■ survival

In stroke epidemiology, routinely collected data including mortality statistics and hospital admission lists are inaccurate, ignore nonadmitted cases, and do not provide reliable details on etiology, subtypes, and long-term prognosis. Only a few of the recent studies of stroke incidence have fulfilled key methodological criteria for a reliable and comparable study to measure overall incidence of stroke as proposed by Malmgren et al in 1987, updated by Bonita in 1992 and by Sudlow and Warlow in 1996, and most recently refined by Warlow. Until recently, observational epidemiological studies of stroke were based mainly on pathological types of stroke. Many of these studies, which adopted near “ideal” methods, had, in general, limited access to both the clinical expertise and the technologies (eg, carotid ultrasound, CT or MR imaging, and echocardiography) to perform a valid etiologic subtype classification. Increasingly, epidemiology is following clinical practice and not only considers all strokes together as the necessary first step but divides them into the 3 pathological types and then into various subtypes as well. Following this approach, we performed a population-based study of all residents of Erlangen, Bavaria, Germany, to determine age- and sex-specific incidence rates, risk factors, recurrence, and survival for each subtype of ischemic stroke.

Subjects and Methods

Study Area and Population
The Erlangen Stroke Project (ESPro) is a prospective community-based stroke register in Bavaria, Germany, which covers a total study population of 100 330 inhabitants (1997 census). Since 1994, ESPro
has been monitoring incidence rates, risk factors, cause, and long-term outcome of stroke. The study population, clinical definitions, methods of assessment, and investigations have been described in detail elsewhere.5,7

Case Ascertainment
From April 1994 to March 1998, all patients with a first-ever stroke from the total study population were identified in a prospective way. To identify patients admitted to hospital, daily checks of hospital discharge records were made in the study area. To ensure inclusion of cases transferred to other institutions outside the community, regular checks were also performed at the regional rehabilitation hospitals and nursing homes outside the study area. As an additional check to detect stroke cases that occurred outside the study area, computerized lists of all patients with a discharge diagnosis of stroke were provided by a record linkage system of a regional health insurance company and matched with our registered patients with ischemic stroke. For determination of the subtype of ischemic stroke, the original TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria were used.18 The TOAST investigators noted that stroke prognosis, risk of recurrence, and choices for management were influenced by ischemic stroke subtype.18 Because of the potential importance of stroke subtype in interpreting the results of this and other acute-intervention trials, they devised a series of definitions to classify patients with ischemic stroke into 5 core etiologic groupings.18 These 5 major categories of the TOAST classification are as follows: large-artery atherosclerosis (LAA), including large-artery thrombosis and artery-to-artery embolism; cardioembolism (CE); small-artery occlusion (SAO); stroke of other determined cause (OC); and stroke of undetermined cause (UND). For strokes of undetermined origin, 1 of 2 explanations was needed: (1) no cause was found despite an extensive evaluation or (2) a most likely cause could not be determined because more than 1 plausible cause was found. The subtype definitions were based on risk factor profiles, clinical features, and results of diagnostic tests. The latter included CT scan, MRI, vascular imaging (carotid duplex, transcranial Doppler), ECG, echocardiography (transesophageal or transthoracic), assessment of prothrombotic syndromes, and postmortem examination. The study neurologists (PLKR, PUH, and MW), who were not involved in the treatment procedures of the patients, reviewed the clinical history, especially information regarding stroke risk factors before or at the time of the first ischemic stroke. Patients were classified when all investigations mandatory for the TOAST classification were completed, 82% before day 7 after the event and 18% later than day 7. Risk factors were defined as follows: hypertension (reported systolic blood pressure ≥160 mm Hg), reported diastolic blood

<table>
<thead>
<tr>
<th>Ischemic Stroke Subtype</th>
<th>Large-Artery Atherosclerosis</th>
<th>Cardioembolism</th>
<th>Small-Artery Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>No. in Population</td>
<td>Rate</td>
<td>95% CI</td>
</tr>
<tr>
<td>&lt;35</td>
<td>0</td>
<td>44 708</td>
<td>2.0</td>
</tr>
<tr>
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<td>0</td>
<td>15 620</td>
<td>2.0</td>
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<tr>
<td>45–54</td>
<td>9</td>
<td>11 952</td>
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<td>20</td>
<td>8943</td>
<td>55.9</td>
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<td>1886</td>
<td>106</td>
</tr>
<tr>
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</tr>
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<td>44</td>
<td>48 631</td>
<td>22.6</td>
</tr>
<tr>
<td>Women</td>
<td>27</td>
<td>51 699</td>
<td>13.1</td>
</tr>
</tbody>
</table>

Standardized to European population

<table>
<thead>
<tr>
<th>Ischemic Stroke Subtype</th>
<th>Large-Artery Atherosclerosis</th>
<th>Cardioembolism</th>
<th>Small-Artery Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>15.3</td>
<td>12–19.3</td>
<td>30.2</td>
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<tr>
<td>Men</td>
<td>23.6</td>
<td>17.1–31.6</td>
<td>29.1</td>
</tr>
<tr>
<td>Women</td>
<td>9.2</td>
<td>6.1–13.4</td>
<td>30.8</td>
</tr>
</tbody>
</table>
pressure ≥95 mm Hg, patient’s self-report of hypertension, or use of antihypertensive drugs), diabetes mellitus (fasting blood glucose level ≥120 mg/dL, patient’s self-report of diabetes, or use of antidiabetic drugs), smoking habit (current smoker, yes or no), and cardiac disease (history of myocardial infarction, coronary artery disease, congestive heart failure, arrhythmia, or valvular heart disease).

Follow-Up
As suggested by the Helsingborg Declaration, all patients were followed up at 28 days, 3 months, and 1 and 2 years after the event.19 If the patient could not be contacted for follow-up, the Population Register of Erlangen was checked for a possible change of address or death.

Recurrence
Recurrent stroke was defined as a new neurological deficit that fit the definitions for ischemic stroke that occurred more than 24 hours after the incident stroke and was not attributable to edema, mass effect, brain shift syndrome, or hemorrhagic transformation. All early recurrences within 21 days were evaluated by the study neurologists (PLKR, PUH, and MW). Procedure-related strokes were not counted as recurrent strokes. During follow-up, we obtained information about stroke recurrence by questioning patients and relatives and by scrutinizing patient charts from previous admissions and general practitioner contacts. If the patient died during follow-up, the general practitioner was contacted to clarify whether the patient had a recurrent stroke since the last follow-up.

Case Fatality
Case fatality rates (CFRs) were reported according to the World Health Organization (WHO) standard20 and as recommended in the Helsingborg Declaration.19

Interobserver Reliability
To control interrater variability in the present study, all participating raters were regularly trained in the use of the TOAST classification. Twenty consecutively admitted patients were randomly classified by the raters. The ratings were performed independently, considering the results of all investigations and the neurological examination. The maximum time interval between the investigations of the raters was 4 hours. For testing interobserver reliability, the κ-statistic was used.

Statistical Analyses
Average annual incidence rates for ischemic stroke subtype were calculated with the denominators from the 1997 census data. Sex-specific stroke subtypes were adjusted to the WHO standard European population.21 The 95% CIs for the incidence rates were calculated by the method of Schoenberg.22 Differences for age were tested by ANOVA within the 5 subgroups. Patients with the TOAST subtype “other cause” were excluded from analyses because of the small number of patients (n=9). For each risk factor, a logistic regression model with age (<65 years, 65 to 74 years, 75 to 84 years, or ≥85 years), sex, and 3 df to separate stroke subtypes was used to test whether the proportions of risk factors were the same among stroke subtypes. The Kaplan-Meier product-limit method was used to estimate rates of survival and recurrence. For “stroke recurrence” as a dependent variable, patients free of recurrent stroke were censored at the time of death. The 95% CIs for the Kaplan-Meier estimates were calculated by Greenwood’s formula. The log-rank test was used to compare rates for recurrence and death. Cox regression was performed to adjust the differences in death and recurrence rates between ischemic subtypes for age and sex. Two-tailed probability values are reported, and a P value <0.05 was considered significant in univariate and multivariate analyses. Statistical analyses were performed with the SAS 8.0 software package.

Ethics
Patients gave their permission for review of medical records pertaining to suspected vascular events that occurred during follow-up. Consent by next of kin or guardian was obtained for patients who were severely ill or unconscious.

Results
In the time period 1994 to 1998, 752 patients with first-ever stroke were included in ESPro. The mean age of all identified patients was 73 years (SD 12.9), and 437 (58%) were female. Five hundred eighty-three patients (78%) had a first ischemic stroke, 100 (13%) had a primary intracerebral hemorrhage, 21 (4%) had a subarachnoid hemorrhage, and 48 (6%) had a
stroke of undefined pathological type because a CT scan could not be performed.

Among the 583 patients with ischemic stroke, the mean age was 73.3 years (SD 12.6), and 331 (57%) were female. Among 52 patients (9%) with ischemic stroke, it was not possible to classify the subtype because the diagnostic procedures required for the TOAST criteria were incomplete. The nonclassified patients were more likely to be older (mean age 76.9 [SD 10.5]; \( P < 0.04 \)) and not hospitalized (\( P < 0.001 \)). These patients were excluded from further analyses.

Among the remaining 531 patients (mean age 72.9 years [SD 12.7]; 299 [56%] female), transthoracic or transesophageal echocardiography was performed in 331 patients (62%), carotid ultrasonography or transcranial Doppler ultrasonography in 475 patients (89%), and cerebral angiography in 82 patients (15%). At the time of the subtype classification, all of the brain images were available and could thus be reviewed by the study neurologist. The overall interrater agreement for the TOAST classification was good, with an \( \kappa \) of 0.65 (95% CI 0.35 to 0.96). The distribution of subtypes was as follows: LAA, 71 (13%); CE, 143 (27%); SAO, 120 (23%); OC, 9 (2%); and UND, 188 (35%). The mean age in the different groups of subtypes was 74.1 years (SD 12.7) for CE, 71.4 years (SD 11.5) for SAO, 70.1 years (SD 12.1) for LAA, 58.1 years (SD 19.2) for OC, and 74.8 years (SD 12.7) for UND, which was significant among subtypes (\( P < 0.01 \)).

Risk Factors
The frequencies of risk factors for each subtype are presented in Table 1. The proportion of hypertension (\( P < 0.01 \)), smoking (\( P < 0.05 \)), and cardiac disease (\( P < 0.001 \)) varied significantly among the different subtypes.

Incidence
Age- and sex-specific annual incidence rates by ischemic stroke subtype are presented in Table 2. The highest overall incidence rate could be found in the CE subtype (30.2/100 000), whereas the lowest was found in the LAA subtype (15.3/100 000). In the LAA subtype, the rate was 2 times higher for men than for women (23.6/100 000 versus 9.2/100 000). In the SAO subtype, a lower incidence was found among women than among men (19.8/100 000 versus 35.3/100 000).

Recurrence
Sixty-one patients had a recurrent stroke during the 2 years of follow-up. Figure 1 presents Kaplan-Meier estimates of recurrence for the different subtypes. After 2 years, the highest recurrence was found in CE (22%; 95% CI 14–30), whereas the lowest recurrence rate was in LAA (10%; 95% CI 2–18). In SAO the recurrence was 11% (95% CI 5–17), in UND 14% (8–20), and for all subtypes 15% (11–18). Ischemic stroke subtype was not a significant predictor of long-term recurrence up to 2 years, either before (\( P = 0.0878 \)) or after (\( P = 0.18 \)) adjustment for age and sex.

Survival
There were 185 deaths during the 2 years of follow-up. Figure 2 presents Kaplan-Meier estimates of rates of survival among the different subtypes up to 2 years. The highest 2-year survival was found in SAO (85%; 95% CI 0.79–0.92) and the lowest in CE (55%; 95% CI 0.47–0.63). The survival in LAA was 58% (95% CI 0.46–0.69), in UND 61% (0.54–0.68), and for all subtypes 64% (0.60–0.69). Subtype was a significant predictor up to 2 years of survival, both before (\( P < 0.0001 \)) and after (\( P < 0.0001 \)) adjustment for age and sex.

Discussion
This prospective study is the first population-based study on incidence, recurrence, and long-term survival of ischemic stroke subtypes with the TOAST criteria used as a mechanism-based subtype classification scheme. The TOAST criteria are a widely used classification scheme of ischemic stroke subtypes that are based on the patient’s neurological signs, the results of brain imaging, and the findings of ancillary diagnostic tests. The present population-based study used widely accepted standardized methods of case ascertainment and provides for the first time basic epidemiological data on causes of ischemic stroke in a European population.
When age adjusted to the European population, the highest incidence rates in the present study were found for CE subtype and the lowest for LAA subtype. Incidence rates for ischemic stroke due to LAA among men were more than twice as high as rates recorded for women (23.6 compared with 9.2 per 100 000, respectively). However, the incidence rate for men was much lower than that reported recently by Petty et al from the Rochester Epidemiology Project, a large epidemiological study in which the incidence of the ischemic stroke subtype with large-vessel cervical or intracranial stenosis with >50% stenosis (atherostenosis) among men was 47 per 100 000. This difference might be due to the fact that the Rochester rates were calculated with a different denominator, the 1990 US population, whereas our results were standardized to the European population. This makes a true comparison difficult. Another possible explanation might be the different distribution of risk factors among populations. The proportion of hypertension, diabetes mellitus, and smoking was lower, whereas the proportion of cardiac disease was much higher in ESPro than in US population-based stroke registries. Different risk factor profiles result in different etiologic stroke subtypes. Thus, the observed heterogeneity in stroke incidence might have been caused by local variations in the distribution of risk factors.

Population-based registries on incidence involve a number of problems, the most important being completeness of case ascertainment. However complete the case-finding methods are considered to be, one can only expect to gain access to those cases presented to the sources surveyed. The Oxfordshire Community Stroke Project found that of those patients whose stroke was preceded by a transient ischemic attack, only about half had sought medical attention for the transient ischemic attack. Similarly, some persons with mild strokes might not ever seek medical attention. This is particularly likely among the elderly, who may attribute symptoms of a stroke to age or an age-associated disease such as osteoarthritis. Although medical care is provided free of charge, and even though it is our policy that all stroke patients should be hospitalized, we cannot exclude the possibility that some older people did not consult their physician. Similarly, fatal strokes that occurred outside the area may have been missed, as well as mild cases, because of cross-boundary medical care. In the present study, the proportion of nonhospitalized strokes was 5%, which is consistent with the findings of the MONICA centers in Denmark, Germany, Sweden, and Finland, where 5% or fewer of nonfatal stroke cases were managed outside the hospital.

In our analyses, the highest recurrence rates were found for CE and the lowest for LAA subtype. The rate of recurrence in LAA differed significantly from the results of other population-based studies. The Rochester study reported a 1-month recurrence rate of 18.5% for the subtype “atherosclerosis with stenosis”; Sacco et al from the Northern Manhattan Stroke Study (NOMASS), another large epidemiological study reporting subtypes of ischemic stroke, recorded a recurrence rate of 14.4%, whereas our rate was 1%. The 1- and 2-year recurrence rate in the present study was 10%, which is lower than that reported by Petty et al (1 year 24.4%, 2 years 29.3%) and Sacco et al (1 year 26.5%). Methodological differences between the studies might be one explanation for these results. In the present study and in the Rochester and NOMASS cohorts, recurrence was defined as a stroke that occurred more than 24 hours after the incident stroke. However, in the Rochester study, procedure-related strokes were included, whereas in the present study, they were excluded, thus representing a limitation of our study. The proportion of procedure-related strokes in the Rochester study was nearly 31% of all recurrent strokes that occurred within 30 days in the subgroup “atherosclerosis with stenosis.” This methodological difference might have biased our analysis toward underestimating both the early and long-term recurrence rates in the LAA subtype. Additionally, some of the variations in recurrence rates in LAA might be attributable to differences in risk factor profiles in the observed populations. A higher proportion of hypertension was found in the Rochester cohort and in the NOMASS cohort than in the present study. This might be of particular interest, because hypertension could be identified as an independent predictor of stroke recurrence. Another potential factor might represent an improvement in early secondary stroke prevention in the last decade after both US studies, which were performed in 1985 to 1989 and in 1983 to 1988.

In the present analyses, the highest CFRs were found for CE and LAA and the lowest for SAO. Our CFRs in CE were very similar to those reported from the NOMASS cohort, contrasted, however, to the results recently published by the Rochester Epidemiology Project. In the Rochester study, the CFRs at 1 month (30.3%), 1 year (53%), and 2 years (61.4%) were higher than in the present study. Several studies identified older age as one of the main predictors for mortality after ischemic stroke. Therefore, the most likely explanation for the worse survival among Rochester patients with CE stroke is that they were older (mean age 80 years) than those in ESPro (mean age 74 years).

In summary, the present study has demonstrated that epidemiological observational studies that possess wide access to appropriate diagnostic technologies and apply a standardized etiologic classification scheme such as the TOAST criteria provide a much better understanding of the distribution of underlying risk factors for initial stroke, recurrence, and mortality. The estimation of incidence rates for pathological or anatomic stroke subtypes together with consideration of underlying risk factors may, for the first time, allow a valid and reliable comparison between incidence rates in different populations. In the present study, substantial differences between etiologic subtypes were revealed for long-term survival and recurrence. Therefore, our results suggest that in epidemiological stroke research, ischemic stroke should not be regarded as a homogeneous disease condition. This information is mandatory for the focused planning and implementation of primary and secondary prevention programs and represents the first step toward monitoring the effectiveness of public health strategies to reduce the burden of stroke imposed on different societies.

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References


†Deceased.
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