Risk Factors, Outcome, and Treatment in Subtypes of Ischemic Stroke

The German Stroke Data Bank

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Background and Purpose—Data on risk factors for etiologic subtypes of ischemic stroke are still scant. The aim of this study was to characterize stroke subtypes regarding risk factor profile, outcome, and current treatment strategies.

Methods—We analyzed data from 5017 patients with acute ischemic stroke (42.4% women, aged 65.9±14.1 years) who were enrolled in a large multicenter hospital–based stroke data bank. Standardized data assessment and stroke subtype classification were used by all centers.

Results—Sex and age distribution, major risk factors and comorbidities, recurrent stroke, treatment strategies, and outcome were all unevenly distributed among stroke subtypes (P<0.001, respectively). Cardioembolism, the most frequent etiology of stroke (25.6%), was particularly common in the elderly (those aged >70 years) and associated with an adverse outcome, a low rate of early stroke recurrence, and frequent use of thrombolytic therapy and intravenous anticoagulation. Large-artery atherosclerosis (20.9%), the most common cause of stroke in middle-aged patients (those aged 45 to 70 years), showed the highest male preponderance, highest rate of early stroke recurrence, and highest prevalence of previous transient ischemic attack, current smoking, and daily alcohol consumption among all subtypes. The highest prevalence of hypertension, diabetes mellitus, hypercholesterolemia, and obesity was found in small-vessel disease (20.5%), which, in turn, was associated with the lowest stroke severity and mortality.

Conclusions—Our results foster the concept of ischemic stroke as a polyetiologic disease with marked differences between subtypes regarding risk factors and outcome. Therefore, studies involving risk factors of ischemic stroke should differentiate between etiologic stroke subtypes. (Stroke. 2001;32:2559-2566.)

Key Words: outcome ■ risk factors ■ stroke classification ■ stroke, ischemic

It is unanimously accepted that different diseases can cause ischemic stroke. The most important etiologies of ischemic stroke include large-artery atherosclerosis (macroangiopathy), cardioembolism, and cerebral small-vessel disease (microangiopathy). Less common causes of stroke are cervical artery dissection, cerebral vasculitis, coagulopathies, hematologic disorders, and others. A considerable minority of ischemic stroke cases remains etiologically undefined even after complete diagnostic workup. It is presently an important challenge to tailor acute therapy and secondary prevention according to the cause of stroke in individual patients. However, there is still scant information on the role of risk factors and the clinical course in etiologic stroke subtypes.1,2

The Stroke Data Bank of the German Stroke Foundation (Stiftung Deutsche Schlaganfall-Hilfe) is a multicenter hospital–based stroke registry that was initiated in 1997 to obtain data on stroke etiology, management, and outcome, as well as on the quality of clinical stroke care in Germany. It was one of the prespecified aims of this data bank to collect a patient sample that would be large enough to allow for proper characterization of different stroke subtypes regarding associated risk factors and comorbidities, stroke severity, mortality, clinical complications, early stroke recurrence, and current treatment strategies.

Based on previous studies and observations during the treatment of stroke patients, the following hypotheses were developed that guided the data analysis in the present study: (1) Stroke due to large-artery atherosclerosis and stroke due to small-vessel disease show the highest prevalence of hypertension and diabetes mellitus. (2) Macroangiopathic stroke...
is characterized by a strong prevalence of current smoking, coronary heart disease, and peripheral arterial disease. (3) Cardioembolic stroke is associated with the highest stroke severity and stroke due to small-vessel disease with the lowest stroke severity. (4) The diagnosis of different stroke etiologies guides decisions regarding early- and long-term secondary prevention in current practice.

Subjects and Methods

Twenty-three neurology departments from all geographic parts of Germany participated in data acquisition for the German Stroke Data Bank, which took part between January 1998 and December 1999. All hospitals are equipped with an acute-stroke unit and, in most cases, also with a neurological intensive care unit. They serve catchment areas of 100,000 to 1 million inhabitants and are the main care providers for stroke patients in these regions. Almost all stroke patients with acute stroke in these centers received a cranial CT or MRI, intracranial and transcranial Doppler sonography and/or an angiographic evaluation of brain-supplying arteries (including CT or magnetic resonance angiography), an ECG and/or ECG monitoring, basic blood tests, and additional laboratory investigations as required. The majority of patients were examined by transthoracic or transesophageal echocardiography. The protocol of the Stroke Registry was approved by the responsible Institutional Review Boards. All patients gave informed consent if their personal data (name, address, and telephone number) were to be transferred to the data management center. If no informed consent could be obtained from the patient, only the anonymous medical data were transferred to the data management center.

Prospective data collection was performed by using a standardized questionnaire based on an extensive manual. It included age, sex, time of ischemia and admission to hospital, vascular risk factors and prior diseases, previous medication, results from technical examinations (eg, Doppler ultrasound), infarct localization, acute-stroke therapy, complications, medication for secondary prevention, and severity of the clinical deficit; the National Institutes of Health Stroke Scale (NIH-SS), the Barthel index, and the modified Rankin Scale (mRS) were used at admission and discharge. Assessment of the NIH-SS was based on video training. Information on risk factors, previous diseases, and medication was primarily obtained from the patient, and additional information was collected from relatives and general practitioners. The definitions of risk factors follow.

Risk Factors

Arterial Hypertension

Arterial hypertension was defined as history of elevated blood pressure >160/90 mm Hg at 2 independent readings before stroke or on antihypertensive medication.

Diabetes Mellitus

Diabetes mellitus was defined as history of elevated blood glucose at 2 independent readings before stroke or elevated hemoglobin A1c at admission or on antidiabetic medication.

Hypercholesterolemia

Hypercholesterolemia was defined as history of elevated total cholesterol >220 mg/dL at 2 independent readings before stroke or lipid-lowering medication. Complications were assessed until the day of discharge from the documenting hospital, but for this analysis, only such complications that occurred within the first week after admission were considered.

Follow-up evaluations after 3 months assessed recurrent stroke and functional dependency by Barthel index and mRS. If the patient did not consent in submission of his personal data, the participating center performed the follow-up interview at site. Otherwise, the follow-up was performed by trained telephone interviewers at the University of Essen or the Stiftung Deutsche Schlaganfall-Hilfe. If a patient could not be reached by telephone or via his general practitioner, a follow-up letter was sent. If still no information on the patient’s outcome could be obtained, a query at the citizen registry was made to check for current address or death.

The NIH stroke criteria for acute ischemic stroke were used in the current analysis. In this analysis, only patients with ischemic stroke, defined as a clinical deficit lasting >24 hours, were included. Patients with TIA or cerebral hemorrhage were excluded. For assessment of etiologic stroke subtypes, we used the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) investigators. We included, as a slight modification, an additional category for patients with ≥2 possible etiologies (concurrent etiology, see below). The diagnoses are based on clinical features and ancillary tests, such as brain imaging, Doppler ultrasound studies, cardiological examinations, and laboratory investigations. The classification in the present study was performed by the local neurologists after completion of ancillary studies and was based on the criteria that follow.

Stroke Criteria

Macroangiopathy (Large-Artery Atherosclerosis)

Macroangiopathy is defined as the presence of an occlusion or a stenosis with ≥50% diameter reduction of a brain-supplying artery corresponding to clinical symptoms and with location and morphology typical of atherosclerosis on Doppler ultrasound or angiography. Diagnostic studies had to exclude potential sources of cardiogenic embolism.

Cardioembolism

Cardioembolism is defined as the presence of a high- or medium-risk source of cardiac embolism. Potential large-artery atherosclerotic sources of thrombosis or embolism had to be absent.

Microangiopathy (Small-Vessel Disease)

Microangiopathy is defined as the presence of one of the traditional lacunar syndromes (eg, pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and dysarthria-clumsy hand syndrome), infarction(s) <1.5 cm of diameter or normal CT/MRI examination, and absence of acute cerebral cortical dysfunction. Potential cardiac sources for embolism should be absent, and evaluation of the large extracranial arteries should not demonstrate a stenosis of >50% in an ipsilateral artery.

Other Determined Etiologies

The questionnaire specifically mentioned spontaneous dissection, traumatic dissection, vasculitis, hematologic disorders, coagulopathies, or other not-further-specified diseases. These diagnoses had to be revealed by diagnostic studies, such as angiography or blood tests. Cardiac sources of embolism and large-artery atherosclerosis had to be excluded by other studies.

Undetermined Etiology

This category included patients in whom a likely etiology could not be determined despite an extensive evaluation or in whom the treating physician felt that not all necessary investigations had been performed.

Concurrent Etiology

This category was included as an independent entity for the frequent situation in which a patient had ≥2 probable stroke etiologies, and it could not be determined which of them was causative.

In the present analysis, we only included patients from those centers who registered ≥75% (range 76% to 98%) of all acute-stroke patients hospitalized during the period in which the respective center participated. Thus, we included data from 14 centers who participated for 10 to 24 months during the biannual registration period and registered a total of 5105 patients with acute ischemic stroke. The centers, 8 university hospitals and 6 municipal and local hospitals, are situated in North (Bielefeld, Minden, and Rostock), East (Leipzig, Berlin, Magdeburg, and Jena), West (Essen, Frechen, and Hamburg), and South (Stuttgart, Ulm, München-Harlaching, and Salzhausen) Germany. Of these centers, 6 centers with a registration rate ≥95% and a total of 2797 patients were compared with the other.
TABLE 1. Demographic Data in Etiologic Subgroups of Ischemic Stroke

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Macroangiopathy</th>
<th>Cardioembolism</th>
<th>Microangiopathy</th>
<th>Other Etiologies</th>
<th>Concurrent Etiologies</th>
<th>Unknown Etiology</th>
<th>Total Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group, n (%)</td>
<td>1047 (20.9)</td>
<td>1286 (25.6)</td>
<td>1028 (20.5)</td>
<td>175 (3.5)</td>
<td>344 (6.9)</td>
<td>1137 (22.7)</td>
<td>5017 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>354 (33.8)</td>
<td>644 (50.1)</td>
<td>411 (40.0)</td>
<td>77 (44.0)</td>
<td>125 (36.3)</td>
<td>516 (45.4)</td>
<td>2127 (42.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>693 (66.2)</td>
<td>642 (49.9)</td>
<td>617 (60.0)</td>
<td>98 (56.0)</td>
<td>219 (63.7)</td>
<td>621 (54.6)</td>
<td>2890 (57.6)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>65.7±11.5</td>
<td>69.6±12.3</td>
<td>68.7±10.7</td>
<td>50.0±15.6</td>
<td>69.4±11.2</td>
<td>66.2±14.3</td>
<td>65.9±14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, y</td>
<td>67.7±12.7</td>
<td>72.0±12.3</td>
<td>72.4±10.5</td>
<td>49.7±17.0</td>
<td>71.5±11.3</td>
<td>69.0±14.7</td>
<td>69.8±13.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, y</td>
<td>64.7±10.8</td>
<td>67.1±11.9</td>
<td>66.3±10.1</td>
<td>50.3±14.5</td>
<td>68.2±10.9</td>
<td>63.3±13.1</td>
<td>65.1±12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &lt;45 y, n (%)</td>
<td>47 (4.5)</td>
<td>58 (4.5)</td>
<td>18 (1.8)</td>
<td>61 (34.9)</td>
<td>12 (3.5)</td>
<td>89 (7.8)</td>
<td>285 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Age 45–70 y, n (%)</td>
<td>618 (59.0)</td>
<td>551 (42.8)</td>
<td>541 (52.6)</td>
<td>95 (54.3)</td>
<td>142 (41.3)</td>
<td>588 (51.8)</td>
<td>2535 (50.5)</td>
<td></td>
</tr>
<tr>
<td>Age &gt;70 y, n (%)</td>
<td>382 (36.5)</td>
<td>677 (52.6)</td>
<td>469 (45.6)</td>
<td>19 (10.9)</td>
<td>190 (55.2)</td>
<td>459 (40.4)</td>
<td>2196 (43.8)</td>
<td></td>
</tr>
</tbody>
</table>

The data depict numbers of patients in each group. Numbers in parentheses give percentages that add to 100 in each subgroup. Age is given as mean±SD.

**Data Evaluation and Statistics**

After a final consistency check with the source data at the site, questionnaires were sent to the data management centers at the University of Essen and the German Stroke Foundation. They were rechecked by 2 physicians for completeness and plausibility and were entered in duplicate into the database by trained personnel. Missing or implausible data (in particular, contradictions between clinical and ancillary test results and subtype classification) were referred to the treating clinician. Data quality was furthermore ensured by monthly reports and clinical site visits. The final decisions of the local centers on subtype diagnosis were accepted, and patients were not excluded from our analyses for possible misclassification. Missing data were not considered in the analyses.

Continuous variables are presented as mean±SD or as median and first and third quartile and were compared by ANOVA between groups of stroke subtypes. Categorical variables are presented as percentages. Comparisons of categorical variables between all subtypes were performed with the χ² test according to Pearson with 5 df. Therefore, significance levels refer to differences between all groups. Separate comparisons between single groups were limited to those etiologic subgroups and parameters for which separate hypotheses had been formulated to avoid multiple testing. We used binary logistic regression analysis with forward selection and adjustment for age (as a linear variable) and sex to test for significant differences in risk factor distribution and treatment strategies between stroke subtypes with macroangiopathy as the reference category. Statistical analyses were performed by using the program package SPSS version 9.0.

**Results**

A total of 5017 patients with ischemic stroke, 2127 women and 2890 men aged 65.9±14.1 (mean±SD) years, were included in the present study. Cardioembolism was the most common cause of stroke (n=1286, 25.6%), followed by large-artery atherosclerosis (n=1047, 20.9%) and microangiopathy (n=1028, 20.5%) (Table 1). Patients with stroke from large-artery atherosclerosis had territorial (n=936) or extraterritorial infarcts of presumed hemodynamic origin (n=111). Combined other etiologies (n=175, 3.5%) involved patients with spontaneous (n=68, 1.3%) or traumatic (n=12, 0.2%)

cervical artery dissection, vasculitis (n=13, 0.3%), coagulation disorders (n=35, 0.7%), other hematologic diseases (n=10, 0.2%), or nonspecified etiologies (n=37, 0.7%). In 1137 patients (22.7%), the etiology remained undefined because of incomplete investigations (n=255, 5.1%) or despite complete workup (n=882, 17.5%), and in 344 patients (6.9%), >1 potential cause of stroke could be found.

The diagnosis of etiologic subgroups was based on frequently used ancillary tests. All patients received cerebral imaging, either cranial CT scan (4859 patients, 96.9%) or cranial MRI (1460 patients, 29.1%); 4177 patients (83.3%) were examined by extracranial Doppler sonography; 3846 (76.7%), by duplex sonography; 4517 (90.0%), by transcranial Doppler; 1022 (20.4%), by CT, magnetic resonance, or digital subtraction angiography; and 3170 (63.2%), by thoracic or transesophageal echocardiography.

**Risk Factors**

Sex distribution differed significantly between etiologic subtypes; the highest male preponderance was in the macroangiopathic stroke category (66.2%), and the lowest proportion of men was in the cardioembolic stroke category (49.9%). Cardioembolism, concurrent etiologies, and microangiopathy were associated with the highest mean age, and combined other etiologies were associated with the lowest mean age. The relative contribution of various etiologies differed among age strata. Combined other etiologies clearly dominated among young patients (aged <45 years), macroangiopathy was the most common cause in the middle-age stratum (aged 45 to 70 years), and cardioembolism was the most common cause among the elderly (aged ≥70 years) (Table 1).

The prevalence of modifiable risk factors and associated diseases was significantly different among various stroke subgroups (Table 2). A history of previous stroke was most common in patients with concurrent etiologies (29.1%), least frequently encountered in patients with combined other etiologies (10.5%), and of similar prevalence in patients with macroangiopathy (22.8%), cardioembolism (22.3%), and microangiopathy (25.1%). In contrast, a history of previous TIA was most prevalent in large-artery atherosclerosis (20.0%) and least frequent in cardioembolism (8.1%). Arterial hypertension was highly prevalent in all groups except combined centers with a lower registration rate to test for a potential selection bias.
other etiologies (35.1%). Despite a generally high level, hypertension was significantly more common in microangiopathy (79.4%) than in macroangiopathy (70.0%, P<0.001) and also more common in macroangiopathic than in cardioembolic stroke (62.5%, P<0.001). Diabetes mellitus was more prevalent in microangiopathy (35.5%) than in stroke due to large-artery atherosclerosis (29.0%, P=0.002) or cardioembolism (28.1%, P<0.001) and relatively uncommon in patients with combined other etiologies (9.4%). Hypercholesterolemia was particularly common in both microangiopathic stroke (44.0%) and macroangiopathic stroke (41.4%) and least frequent in cardioembolism (27.8%) and combined other etiologies (21.9%). Patients with stroke due to large-artery atherosclerosis most often affirmed current smoking (37.6%) and smoked more often than did patients with microangiopathy (25.9%, P<0.001). Current smoking was also common in combined other stroke etiologies (34.7%) but infrequent in cardioembolism (17.6%) (Table 2).

Patients with large-artery atherosclerosis most often reported daily alcohol consumption (14.7%) and least often reported complete alcohol abstinence (40.6%), whereas a reverse pattern was found in patients with cardioembolism. A normal body mass index (<25) was most often present in patients with combined other etiologies (50.3%) and least frequent in patients with cerebral microangiopathy (36.5%). Instead, stroke due to microangiopathy was most often associated with severe obesity (body mass index >30, 17.7%). Coronary heart disease was particularly prevalent in patients with concurrent etiologies (36.4%), whereas the rate was similar in macroangiopathic (23.3%), cardioembolic (29.5%), and microangiopathic (21.5%) stroke. Patients with concurrent etiologies (12.4%) and those with large-artery atherosclerosis (10.3%) most often had a concomitant diagnosis of peripheral arterial disease.

**Stroke Severity, Complications, Mortality, and Treatment Strategies**

The neurological deficit on admission was most severe in cardioembolism, least pronounced in microangiopathic stroke, and of medium severity and similar distribution in the other etiologies. Within the first week, recurrent cerebral ischemic events occurred in 216 (4.3%) patients. Recurrent ischemic stroke or TIA was most common in patients with large-artery atherosclerosis (8.1%) and also occurred frequently in patients with concurrent etiologies (5.2%) and least often in patients with cardioembolic stroke (2.8%). Secondary parenchymal hemorrhage was most prevalent in stroke of unknown origin (2.6%) and in cardioembolic stroke (2.7%). A similar proportion of patients with concurrent etiologies, cardioembolism, and large-artery atherosclerosis required treatment for severe hypertension (>200/110 mm Hg). Epileptic seizures were uncommon in all subgroups and least common in microangiopathic stroke (Table 3).

Mortality within 90 days amounted to 14.7% of all patients with available follow-up assessment (n=3529, 70.3% of all patients). Mortality was highest in cardioembolic stroke (22.6%) and lowest in microangiopathy (3.3%) and combined other etiologies (9.3%). Similarly, good outcome (mRS 0 to 2) was most frequently reached by patients with microangiopathic stroke and stroke due to other etiologies, whereas a poor outcome (mRS 4 to 5) was most common in patients with cardioembolism, followed by those with macroangiopathy and concurrent mechanisms (Table 3).

Almost the same proportions of patients with cardioembolic stroke (31.1%), macroangiopathic stroke (29.3%), and
microangiopathic stroke (29.0%) and a slightly higher proportion of patients with concurrent etiologies (36.0%) had been treated with aspirin before ictus. Previous anticoagulation was particularly common in patients with cardioembolism (8.0%) and in those with \textit{H11022}/1 probable etiology (7.0%). Systemic thrombolysis was most often used in cardioembolic stroke (6.5%) and only rarely in patients with a final diagnosis of microangiopathy. Intra-venous anticoagulation with heparin was most frequently administered in patients with combined other etiologies (36.0%) and in patients with cardioembolism (55.7%) but only rarely in microangiopathy (18.8%). Similarly, oral anticoagulants for long-term secondary prevention were most often administered in patients with combined other etiologies (50.6%) and in patients with cardioembolism (44.8%). In contrast, almost all patients with microangiopathy (96.2%) and the vast majority of patients with macroangiopathic stroke (73.7%) were treated with platelet inhibitors for secondary prevention (Table 4). A separate analysis including only the 6 centers with \textit{H11350}/95\% registration completeness did not show any relevant differences regarding stroke subtypes, age, sex, risk factors, previous treatment, and stroke severity among subtypes compared with the above analyses.

**Discussion**

The present study from a large multicenter hospital–based stroke data bank investigates the distribution of risk factors,
in-hospital complications, outcome, and treatment strategies in different subtypes of ischemic stroke. Despite including patients from both university and municipal hospitals in all parts of Germany, the present study is not population-based; therefore, certain limitations apply when interpreting its results. However, precise and unselected clinical data of an equally high number of patients can be obtained neither from a population-based register nor from a clinical study.

According to an ongoing population-based stroke registry in the city of Erlangen (Germany), almost 95% of all stroke patients in Germany are admitted to the hospital for acute treatment, and even in the elderly (aged >75 years), the admission rate is >90%. Mean age in the present study was 69.8 years for women and 65.1 years for men and was thus somewhat lower than in the Erlangen study (mean age 75.3 years for women and 69.7 years for men). Thus, our patients are probably representative of all stroke patients except for the oldest age groups. It is a shortcoming of the present study that participating centers did not include all consecutive patients into the data bank. Reasons given for not including a patient were forgetfulness or lack of time of the treating physicians, loss of questionnaires, early referrals, or misdiagnoses. Because 6 centers with a near complete inclusion rate (>95%) showed only minor differences regarding stroke subtypes, age, sex, and risk factor distribution, the patients included in the present study most likely represent a random sample of all patients hospitalized in German neurology departments with acute-stroke units. There is no reason to believe that the ascertainment of risk factors differed between stroke subtypes; therefore, the data bank lends itself to investigate the association of risk factors with different stroke subtypes, which was a main focus of the present study. Despite many advantages, population-based stroke registries have often lacked the power to detect differences between stroke subtypes because of small sample size, a problem that is overcome by the large number of patients in our hospital-based data bank.

The TOAST criteria are a reliable tool to determine etiologic subtypes of ischemic stroke. Using the TOAST criteria, interphysician agreement was shown to be high for stroke subtypes because of small sample size, but the rate of unclassified stroke was still 23% in the largest sample size so far, support this concept by indicating that hypertension and diabetes mellitus are more closely associated with microangiopathic stroke being most often and cardioembolic stroke being least frequently preceded by TIA. In contrast, the rate of stroke caused by large-artery atherosclerosis was the most prevalent etiology in middle-aged patients (aged 45 to 70 years). Despite the frequent use of ancillary tests, the rate of unclassified stroke was still 23%, a proportion that is smaller than in some studies but comparable to many other studies.

The present study shows a strong male preponderance in stroke due to large-artery atherosclerosis and a less pronounced dominance of men in the other stroke subtypes, with the striking exception of cardioembolic stroke, for which slightly >50% of the patients were women, which can be explained by the higher age in this subgroup. Unlike a previous study but similar to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) Stroke Data Bank, we found strong differences in prior TIA rates among stroke subtypes, with macroangiopathic stroke being most often and cardioembolic stroke being least frequently preceded by TIA. In contrast, the rate of previous stroke was similar in macroangiopathic and cardioembolic stroke. This is compatible with the hypothesis that cardiac emboli particularly often lead to persistent vessel occlusion and definite infarction.

Arterial hypertension, the single most frequent stroke risk factor, showed a high prevalence in all stroke subtypes, except for combined other etiologies. The results confirm the hypothesis that hypertension and diabetes mellitus are more common in macroangiopathic stroke than in cardioembolism. Our hypothesis that their prevalence is also higher in stroke due to large-artery atherosclerosis is confirmed only for hypertension but not for diabetes mellitus. In the NINCDS Stroke Data Bank, hypertension and diabetes mellitus were more common in lacunar and atherothrombotic stroke than in cardioembolic stroke. In the Rochester Study, the prevalence of hypertension was not different among stroke subtypes, and diabetes mellitus was less common in atherothrombotic than in lacunar and cardioembolic stroke. The Oxfordshire Community Stroke Project found no differences between lacunar and cardioembolic stroke regarding hypertension or diabetes mellitus. Fisher originally suggested that lacunar stroke was almost exclusively caused by small-vessel disease related to hypertension. Our results, based on the largest sample size so far, support this concept by indicating that hypertension and diabetes mellitus are more closely associated with microangiopathic stroke than with other stroke subtypes, although causality between risk factors and stroke subtype cannot be inferred from our data. We cannot exclude that the simultaneous presence of hypertension and diabetes mellitus may have influenced physicians toward a diagnosis of cerebral microangiopathy in some patients with doubtful etiology. However, with the TOAST criteria applied, it appears unlikely that such ascertainment bias could account for the whole effect detected.

Results for hypercholesterolemia as a stroke risk factor are contradictory, and previous studies on stroke subtypes did not include this risk factor. Our results indicate that hypercholesterolemia plays a role in some but not in other stroke etiologies. The high prevalence in atherothrombotic stroke is in line with a previous study that identified hypercholesterolemia as a risk factor for stroke due to large-artery atherosclerosis. Furthermore, our results allow us to generate the
hypothesis that hypercholesterolemia is associated with stroke due to cerebral microangiopathy. To the best of our knowledge, such an association has not been reported so far, and further studies are required to specifically investigate this issue. In accordance with a recent Japanese study that identified obesity as a risk factor for lacunar infarction in women,22 we found a particularly high prevalence of obesity in patients with microangiopathy.

The prevalence of current smoking was rather low among our patients but comparable to that found in previous studies in Germany.18,23 Our finding that smoking is mainly associated with stroke due to large-artery atherosclerosis is in accordance with our own hypothesis and with previous results.2,24,25 Smoking may furthermore contribute to uncommon etiologies in younger patients (eg, coagulopathy in female smokers taking oral contraceptives) but appears to be less important in other stroke subtypes. Smoking was not unanimously identified as a risk factor for stroke by large prospective studies.26,27 The different impact of smoking on various subtypes of stroke may partly account for these varying results. Several studies indicated a J- or U-shaped association between alcohol consumption and carotid atherosclerosis, with light drinkers facing a lower risk than either heavy drinkers or abstainers.28,29 In the present study, daily alcohol consumption was most often reported by patients with atherothrombotic stroke, supporting the hypothesis that high intake of alcohol may be associated with atherogenesis. Daily alcohol consumption was relatively infrequent in cardioembolic stroke, which may partly be explained by the higher age of this subgroup.

Similar to studies that focused on atrial fibrillation,15,30,31 we found that cardioembolic stroke was associated with the highest mortality and worst functional outcome after 90 days and the most severe acute neurological deficit. Consequently, thrombolytic therapy was most often administered in cardioembolism. The poor prognosis in cardioembolic stroke was mainly caused by the index stroke, whereas early stroke recurrence was low in these patients. In line with previous studies, early stroke recurrence was most common in macroangiopathic stroke.2,17,32 The reason for this difference is poorly understood. It could be argued that the frequent use of anticoagulants may prevent further cardioembolic events, whereas rapidly effective measures may not be available for arterial embolism. However, results from recent studies do not support this hypothesis.17 Instead, stroke due to large-artery atherosclerosis is particularly prone to procedure-related cerebral ischemia, which may partly account for the higher risk of recurrent ischemia in this subtype. As expected, patients with lacunar stroke had the mildest deficits and the best prognosis among all subtypes.33,34

One aim of modern stroke therapy is to tailor treatment and secondary prevention to stroke etiology and individual conditions of the patient to optimize the risk-benefit ratio. The results support our initial hypothesis that early and permanent secondary prevention are adjusted to stroke etiology; eg, only a few patients with a final diagnosis of microangiopathy received intravenous and oral anticoagulants, whereas such therapy was frequently used in patients with cardioembolism or combined other etiologies. Despite the frequent use of heparin early after stroke, the rate of secondary parenchymal hemorrhage was rather low (1.7%), suggesting that physicians take into account contraindications and associated risks of this therapy.

In conclusion, our results foster the concept of ischemic stroke as a polyetiologic disease with profound differences between subtypes regarding age and sex distribution, risk factors, outcome, and current treatment strategies. Our findings support the hypotheses that both smoking and high alcohol intake are associated mainly with stroke due to large-artery atherosclerosis and suggest a particular link between stroke from small-vessel disease, obesity, and hypercholesterolemia. However, to confirm any causality, our findings require investigation in prospective studies. Therefore, future studies on risk factors of ischemic stroke should differentiate between stroke etiologies to unmask the role of particular risk factors (eg, smoking and hypercholesterolemia) for single subtypes.

## Appendix

### Participating Centers and Investigators of the German Stroke Data Bank

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### Acknowledgments

We thank the Stiftung Deutsche Schlaganfall-Hilfe as well as the following sponsors: Bayer, Bristol-Myers-Squib, Boehringer Ingelheim, Glaxo-Wellcome, Heinz-Nixdorf-Stiftung, Janssen-Cilag, Knoll, Sanofi-Synthelabo, and Schering. This sponsorship was not performed to identify patients for randomized trials.

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Risk Factors, Outcome, and Treatment in Subtypes of Ischemic Stroke: The German Stroke Data Bank
Armin J. Grau, Christian Weimar, Florian Buggle, Alexander Heinrich, Michael Goertler, Stefan Neumaier, Joerg Glahn, Tobias Brandt, Werner Hacke and Hans-Christoph Diener
on behalf of the German Stroke Data Bank Collaborators

Stroke. 2001;32:2559-2566
doi: 10.1161/hs1101.098524

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/11/2559

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