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# Stroke Recurrence within 2 Years after Ischemic Infarction

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# Original Contributions

# Stroke Recurrence Within 2 Years After Ischemic Infarction

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**We prospectively studied stroke recurrence in 1,273 patients with ischemic stroke who were entered into the Stroke Data Bank. Median follow-up was 13 months. The 2-year cumulative recurrence rate among these patients was 14.1%. Age, sex, race, history of hypertension, atrial fibrillation, or transient ischemic attacks, and stroke location were not associated with a higher risk of stroke recurrence. Patients with an elevated blood pressure, an abnormal initial computed tomogram, or a history of diabetes mellitus were at a higher risk of stroke recurrence. In contrast, patients with an infarct of unknown cause were at a lower risk of stroke recurrence than patients with a defined stroke mechanism, such as lacune, embolism, or atherosclerosis. A multivariate model suggests that patients at the lowest risk for stroke recurrence have a low diastolic blood pressure, no history of stroke, no history of diabetes mellitus, and an infarct of unknown cause. (*Stroke* 1991;22:155–161)**

Although recurrence after ischemic stroke is frequent, with an annual incidence of 4–14%,[1–3] the risk factors for stroke recurrence have not been firmly established. The risk factors for an initial cerebral infarction are well studied and include increasing age, hypertension,[4] diabetes mellitus,[5] cardiac disease, atrial fibrillation,[6,7] coronary heart disease,[8] congestive heart failure,[8] carotid bruit,[9] transient ischemic attack (TIA), and cigarette smoking.[10] We prospectively followed 1,273 ischemic stroke patients in the Stroke Data Bank to determine whether prognostic indicators of stroke recurrence could be identified. We also compared our findings with those of previous work restricted to early recurrence of cerebral infarction.[11]

## Subjects and Methods

We entered a total of 1,805 cases of stroke into the Stroke Data Bank between July 1983 and June 1986. This report examines stroke recurrence in a subset of 1,273 patients with an index stroke diagnosed as cerebral infarction. The index strokes were predominantly (508, 40%) infarcts of unknown cause (IUC); 337 (27%) were lacunar strokes, 246 (19%) were embolic strokes from a cardiac source, 117 (9%) were infarctions due to atherosclerosis, and 65 (5%) were infarctions with tandem arterial pathology. Besides detailed records of the acute hospitalization, we obtained follow-up information by direct contact, telephone contact, or mail contact at approximately 3, 6, 12, and 24 months after the index stroke. Information obtained at follow-up included possible stroke recurrences.

We defined a recurrent stroke as a cerebrovascular event subsequent to the index stroke that met one of the following criteria: 1) the event produced a neurologic deficit different from that of the index stroke, 2) the event occurred in an anatomic site or vascular territory different from that of the index stroke (by contrast, in the Stroke Data Bank events occurring ≤21 days after the index stroke in the same anatomic site or vascular territory were considered to be evolving strokes and not recurrent strokes), or 3) the event was of a stroke subtype different from that of the index stroke. Exclusionary criteria were deteriorations associated with cerebral edema, hypoperfusion, metabolic disturbance, toxemia, fever, epilepsy, or postictal states and those strokes related to surgery, angiography, or anticoagulant treatment. Further details concerning the Stroke Data Bank are published elsewhere.[12] Median follow-up (time from onset of index

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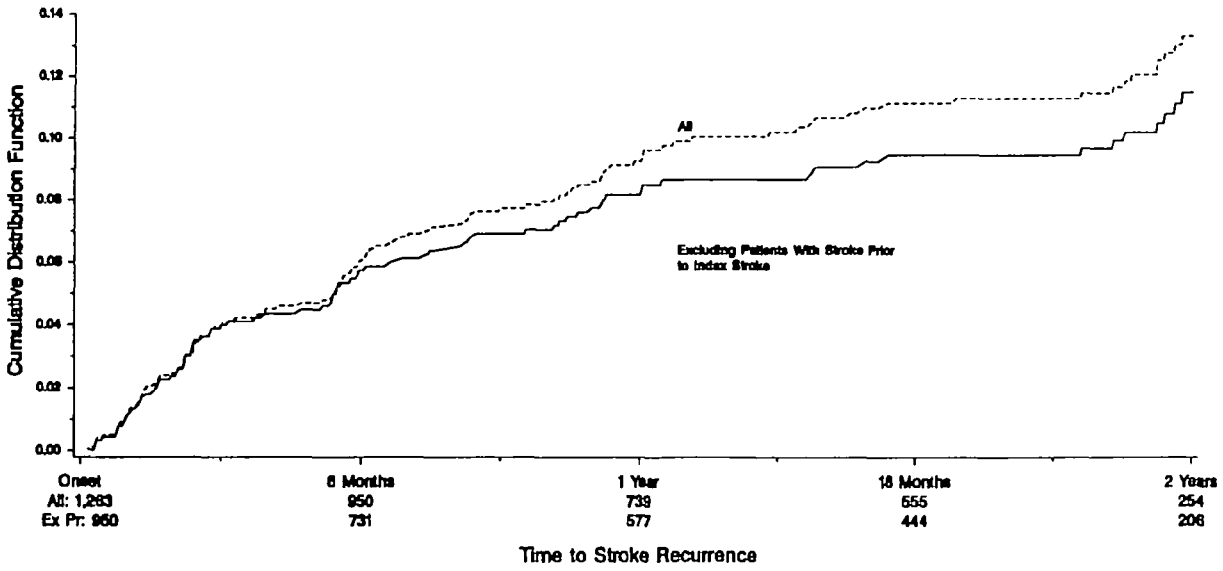


FIGURE 1. *Stroke recurrence within 2 years by prior stroke status. Numbers below horizontal axis are patients remaining in risk group at end of each interval.*

stroke to recurrence, death, or last follow-up) was 13 months, with a range from 2 to 1,093 days.

Life table methods, including the Kaplan-Meier product-limit method and proportional hazards regression,[13] were used to estimate the recurrence-free survival function (cumulative probability of remaining free from recurrence at a given time after onset of the index stroke) and hazards (interval-specific risk of a recurrence after the index stroke). If death and a possible recurrent stroke were recorded as occurring simultaneously, only the death was considered as a censoring event in this analysis because it would be difficult in that instance to document the stroke recurrence.

We studied the univariate influence of a variety of factors on the probability of stroke recurrence. These factors were divided into the groups demographics, medical history, neurological history, initial examination, stroke diagnosis, laboratory examinations, and discharge medications. Missing data affected our ability to detect significant differences; for example, stroke subtype was recorded in all patients, but findings on Holter monitoring were not. Factors found to be significant prognostic indicators of stroke recurrence in a univariate analysis were then entered into a proportional hazards model that used backward elimination stepwise regression to select a parsimonious subset of prognostic factors. For the multivariate analysis, patients who had missing data for any prognostic indicator were excluded.

## Results

Of the 1,273 patients, 129 (10.1%) had a recurrent stroke during follow-up. The recurrence-free survival function was estimated by the product-limit method (Figure 1). Of the patients censored (i.e., no recurrent stroke by last follow-up), only 16% (183 of 1,144) were censored due to death. The estimated 2-year cumulative recurrence rate for all patients was 14.1%.

Of the 1,273 patients, 734 were black, 438 were white, and 101 were of another racial group. There were 76 recurrences among the blacks, 42 among the whites, and 11 among the patients of other racial groups. Using life table methods that account for the duration of follow-up, the estimated 2-year recurrence rate for blacks was 13.7%, that for whites was 13.9%, and that for other racial groups was 16.2% (Table 1). No demographic factor (age, race, and sex) was associated with stroke recurrence.

Among the medical history factors, history of diabetes was significantly associated with stroke recurrence; history of atrial fibrillation, myocardial infarction, congestive heart failure, and angina were not. A history of stroke was associated with recurrence while a history of TIA was not. By contrast, when Sacco et al[11] investigated early (≤30 days after the index stroke) recurrences in the same cohort, diabetes and hypertension were the only significant medical history factors.

Blood pressure at time of the initial examination was predictive of stroke recurrence (Table 2). A similar relation between the initial blood pressure and the risk of early recurrence has been shown.[11]

No specific location (supratentorial or infratentorial) of the index stroke was significantly associated with recurrence. Index stroke subtype as atherosclerotic (atherosclerosis or tandem arterial pathology), embolic from a cardiac source, lacunar, or IUC is shown in Table 2. The IUC subtype included 49 patients with infarcts and a normal angiogram. Stroke recurred in 29 patients with an atherosclerotic index stroke, 24 embolic, 41 lacunar, and 35 IUC. Most recurrent strokes, where known, were of the same subtype as the index stroke. Estimates of the

**TABLE 1. 2-Year Cumulative Stroke Recurrence Rates by Demographic and Medical History Characteristics**

| Characteristics | *N* | 2-year cumulative recurrence rate: All patients | 2-year cumulative recurrence rate: Patients with no prior strokes | *p* | Early recurrence[11] |
|---|---|---|---|---|---|
| *Demographic* | | | | | |
| Age (yr) | | | | | |
| ≤44 | 78 | 6.9 | 5.2 | 0.49 | NS |
| 45–54 | 145 | 16.5 | 14.8 | | |
| 55–64 | 281 | 16.0 | 12.1 | | |
| 65–74 | 390 | 15.8 | 14.6 | | |
| 75+ | 379 | 11.1 | 10.1 | | |
| Sex | | | | | |
| Male | 605 | 13.4 | 12.8 | 0.99 | ... |
| Female | 668 | 14.7 | 11.5 | | |
| Race | | | | | |
| White | 438 | 13.9 | 11.6 | 0.91 | NS |
| Black | 734 | 13.7 | 12.3 | | |
| Other | 101 | 16.2 | 11.3 | | |
| *Medical history* | | | | | |
| Hypertension | | | | | |
| No | 395 | 10.8 | 10.5 | 0.12 | $p<0.01$ |
| Yes | 860 | 15.9 | 13.3 | | |
| Diabetes | | | | | |
| No | 925 | 12.3 | 11.4 | 0.005 | $p<0.05$ |
| Yes | 332 | 19.8 | 15.2 | | |
| Myocardial infarction | | | | | |
| No | 1,007 | 13.0 | 12.0 | 0.12 | NS |
| Yes | 234 | 19.6 | 13.9 | | |
| Valvular heart disease | | | | | |
| No | 1,189 | 14.1 | 12.0 | 0.90 | NS |
| Yes | 59 | 13.7 | 16.1 | | |
| Atrial fibrillation | | | | | |
| No | 1,112 | 13.9 | 12.1 | 0.34 | NS |
| Yes | 125 | 15.7 | 9.9 | | |
| Previous stroke | | | | | |
| No | 912 | 12.5 | ... | 0.003 | NS |
| Yes | 316 | 20.7 | ... | | |
| Transient ischemic attack | | | | | |
| No | 953 | 13.3 | 11.2 | 0.58 | NS |
| Yes | 211 | 15.3 | 13.8 | | |
| *Total* | 1,273 | 14.1 | 12.1 | ... | ... |

Rates are Kaplan-Meier estimates at 2 years per 100 patients. Probability by log rank tests for all patients. NS, not significant.

cumulative probability of recurrence are presented for all patients (Figure 2) and for only those with no prior strokes (Figure 3). Early recurrences accounted for 30% (39 of 129) of recurrent strokes in this cohort. Patients with IUC had a lower risk of recurrence than patients with other stroke subtypes (Table 2). In the 1,065 patients with supratentorial lesions, an index stroke due to atherosclerosis was associated with a higher risk of stroke recurrence.

Laboratory data collected included hematocrit, glucose level, and sodium concentration as well as results from computed tomography (CT), electrocardiography (ECG), Holter monitoring, and echocardiography. An abnormal CT scan (any abnormality) was associated with an increased risk of stroke recurrence. Early recurrence, however, was not associated with an abnormal CT scan but was associated with an elevated blood glucose level.[11] Abnormalities on Holter monitoring or echocardiography did not affect the risk of stroke recurrence. Discharge medications (either aspirin or anticoagulants) were not indicators of stroke recurrence.

Based on univariate analysis, the seven factors significantly predicting stroke recurrence were his-

**TABLE 2. 2-Year Cumulative Stroke Recurrence Rates by Clinical and Neurological Features**

| Feature | *N* | 2-year cumulative recurrence rates: All patients | 2-year cumulative recurrence rates: Patients with no prior strokes | *p* | Early recurrence[11] |
|---|---|---|---|---|---|
| *Clinical* | | | | | |
| Ventricular premature beats | | | | | |
| No | 674 | 15.0 | 13.1 | 0.37 | ... |
| Yes | 82 | 18.3 | 18.1 | | |
| First ECG after index stroke | | | | | |
| Normal | 457 | 11.6 | 9.1 | 0.06 | NS |
| Abnormal | 756 | 15.3 | 13.6 | | |
| Holter monitor | | | | | |
| No new findings | 262 | 11.2 | 9.8 | 0.35 | ... |
| New findings | 170 | 12.8 | 13.4 | | |
| Echocardiography | | | | | |
| Normal | 362 | 12.5 | 10.8 | 0.90 | ... |
| Abnormal | 352 | 10.8 | 11.9 | | |
| Heparin/warfarin | | | | | |
| No | 1,088 | 13.9 | 11.8 | 0.53 | ... |
| Yes | 165 | 15.1 | 14.2 | | |
| Aspirin/dipyridamole | | | | | |
| No | 1,113 | 13.4 | 11.1 | 0.69 | ... |
| Yes | 160 | 16.8 | 17.3 | | |
| Blood pressure (mm Hg) | | | | | |
| Systolic | | | | | |
| <160 | 639 | 11.9 | 11.8 | 0.04 | NS |
| ≥160 | 634 | 16.4 | 12.4 | | |
| Diastolic | | | | | |
| <100 | 778 | 13.1 | 12.4 | 0.15 | $p<0.02$ |
| ≥100 | 495 | 15.5 | 11.7 | | |
| Blood glucose (mg/dl) | | | | | |
| <140 | 917 | 13.5 | 12.1 | 0.60 | $p<0.001$ |
| ≥140 | 356 | 15.8 | 12.2 | | |
| First CT scan after index stroke | | | | | |
| Normal | 472 | 10.9 | 11.0 | 0.03 | NS |
| Abnormal | 782 | 16.6 | 13.6 | | |
| *Neurological* | | | | | |
| Stroke subtype | | | | | |
| Infarct of unknown cause | 508 | 10.5 | 8.3 | 0.01 | ... |
| Atherosclerotic | 182 | 21.9 | 21.8 | | |
| Embolic | 246 | 14.7 | 12.4 | | |
| Lacunar | 337 | 14.6 | 12.3 | | |
| Extraocular movements | | | | | |
| Normal | 891 | 14.6 | 13.1 | 0.57 | ... |
| Abnormal | 367 | 12.1 | 9.2 | | |
| Sensory deficits | | | | | |
| No | 530 | 16.8 | 15.1 | 0.06 | ... |
| Yes | 630 | 12.2 | 10.0 | | |
| Visual fields | | | | | |
| Normal | 842 | 13.7 | 11.8 | 0.61 | ... |
| Abnormal | 314 | 17.1 | 16.8 | | |
| Language deficits | | | | | |
| No | 714 | 13.4 | 11.7 | 0.07 | ... |
| Yes | 319 | 18.4 | 17.1 | | |
| Cerebral site | | | | | |
| Supratentorial | 1,065 | 15.2 | 13.0 | 0.16 | ... |
| Infratentorial | 207 | 8.0 | 7.4 | | |
| *Total* | 1,273 | 14.1 | 12.1 | ... | ... |

Rates are Kaplan-Meier estimates at 2 years per 100 patients. Probability by log rank tests for all patients. ECG, electrocardiography; CT, computed tomography; NS, not significant.

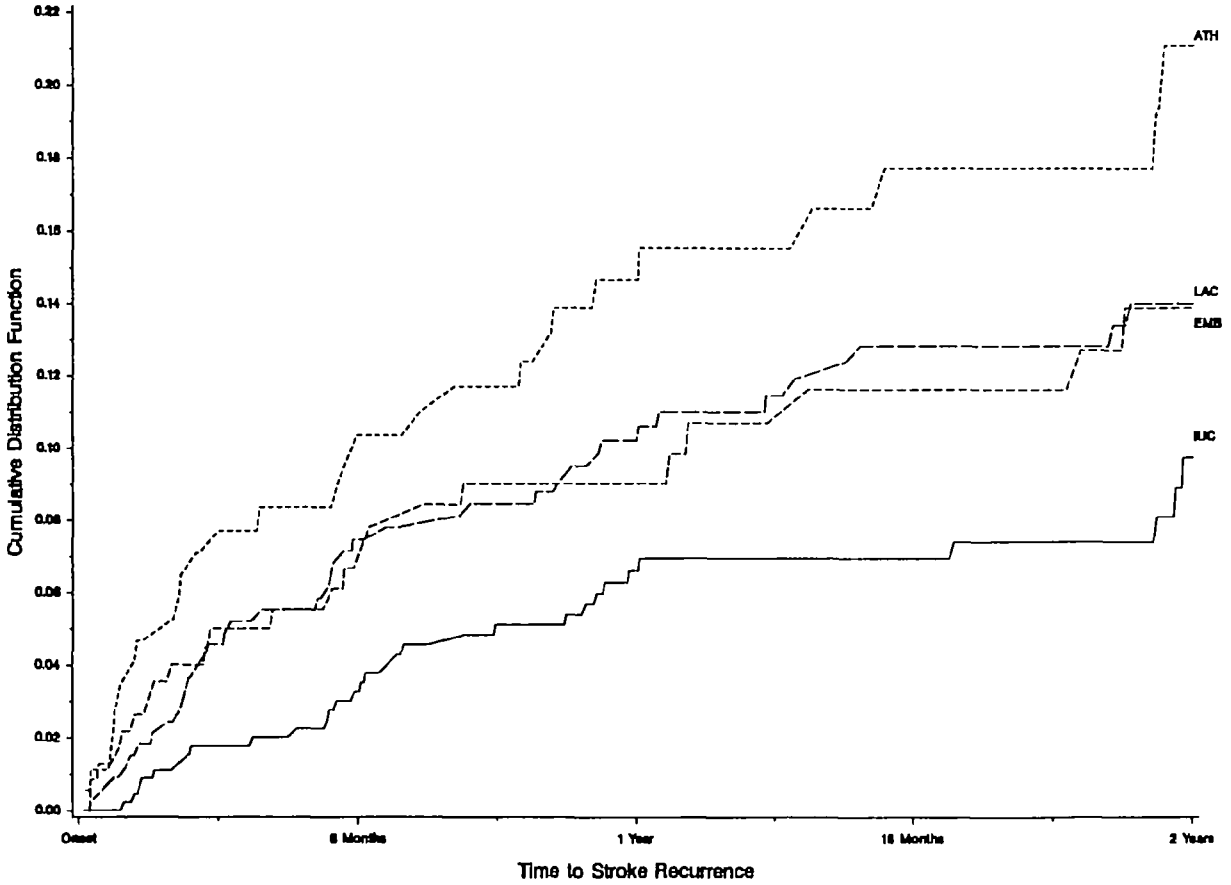


FIGURE 2. *Stroke recurrence within 2 years by index stroke subtype in all patients. ATH, atherosclerotic; LAC, lacunar; EMB, embolic; IUC, infarct of unknown cause.*

tory of stroke, stroke subtype, history of diabetes, initial blood pressure, abnormal initial CT scan, history of hypertension, and initial blood glucose level. Ten patients were excluded from multivariate analysis due to missing data. Of the six factors known at initial evaluation (stroke subtype excluded), four (history of diabetes, initial diastolic hypertension, history of stroke, and IUC) were retained in a multivariate model (Table 3). Since an abnormal initial CT scan (significantly associated with recurrence in the univariate analysis) was not retained in the multivariate model, no further attempt was made to adjust for lesion volume as a measure of stroke severity. The estimated relative risk of stroke recurrence for a (high-risk) diabetic, hypertensive patient with a prior stroke and any non-IUC infarct subtype (e.g., an atherosclerotic infarct) is 2.9 times that for a (low-risk) nondiabetic, normotensive patient with no prior stroke who has IUC. The observed proportion of strokes recurring within 2 years was 9.5% for the low-risk patients and 24.5% for the high-risk patients.

## Discussion

Predictors of recurrent stroke after ischemic infarction are not well established. Based on data collected in Europe from a white, approximately 65% female cohort, Marquardsen[14] estimated the annual recurrence rate to be 8–11% (compared with a stroke incidence of 0.1–0.2%/yr in the general population). However, Marquardsen concluded that while certain factors such as "manifest heart disease are known to increase the risk of recurrences, it is at present impossible to distinguish between patients who are likely to have recurrences and those who are not." The purpose of our study was to identify a subgroup of ischemic stroke patients at high risk for stroke recurrence.

Various researchers have considered the risk factors for stroke recurrence. Significantly elevated risk ratios were found by Alter et al[15] for TIA (41.4), myocardial infarction (8.0), other coronary disease (8.4), hypertension (4.5), and diabetes (5.6). Sacco et al[1] examined predictors of stroke recurrence in 394 index strokes (57% due to cerebral infarction) in the Framingham Study. After cerebral infarction, the 5-year cumulative recurrence rate was 42% for men and 24% for women. Unlike Marquardsen[14] or Meissner et al,[16] Sacco et al[1] found a significantly higher stroke recurrence rate in men than in women. These authors also found that hypertension and cardiac comorbidity were associated with a higher risk of stroke recurrence. Sage and van Uitert[2] suggested that atrial fibrillation is associated with a high risk of stroke recurrence (20%/yr). Hart et

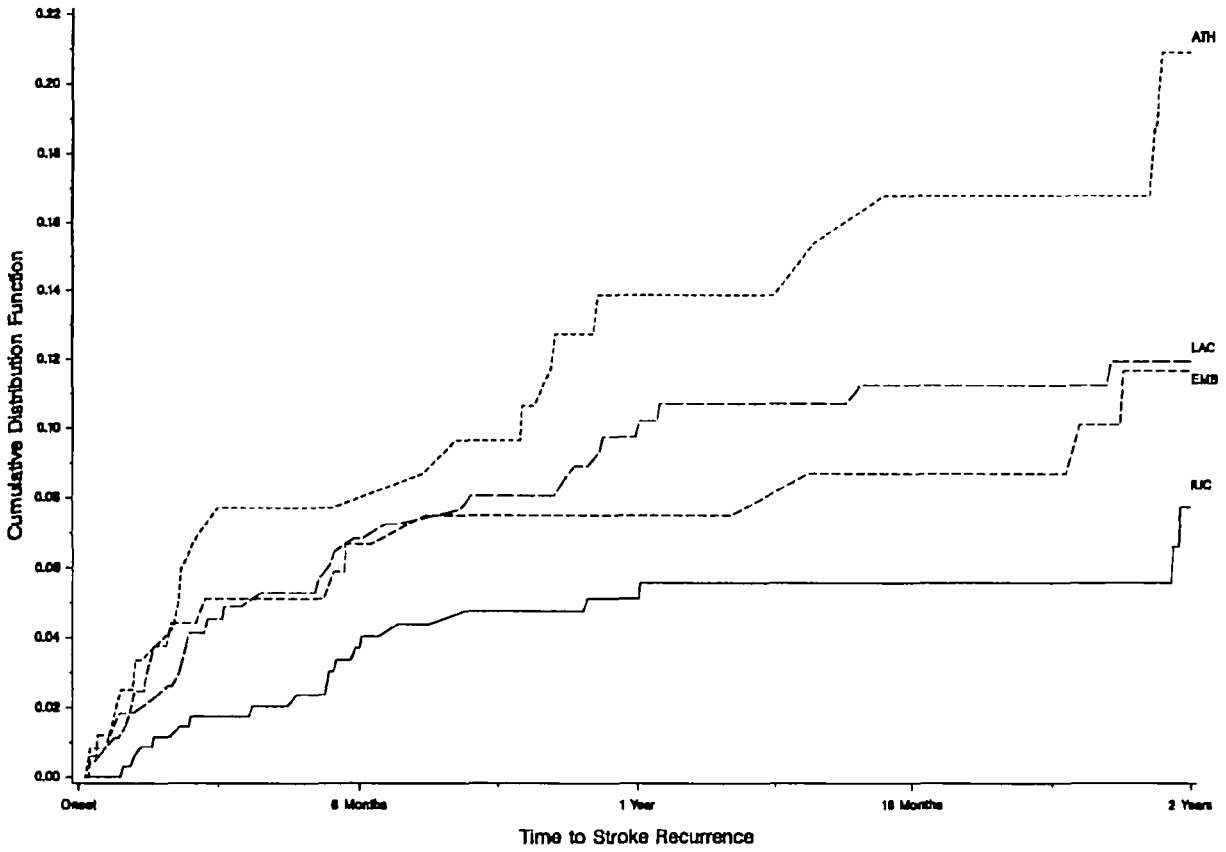


FIGURE 3. *Stroke recurrence within 2 years by index stroke subtype (patients with strokes prior to index stroke excluded). ATH, atherosclerotic; LAC, lacunar; EMB, embolic; IUC, infarct of unknown cause.*

al[17] also emphasized the high rate of stroke recurrence in patients with atrial fibrillation. Marquardsen[14] found that age at index stroke occurrence was not a predictor of stroke recurrence, but recurrence was associated with a history of stroke, a history of congestive heart failure, absent or minimal motor findings, atrial fibrillation, ECG abnormalities, and elevated diastolic and systolic blood pressures. Many of these researchers studied population-based cohorts. The Stroke Data Bank has compiled data not on a population-based cohort, but rather on a selected cohort of patients referred to four university medical centers. This cohort is not necessarily representative of the general U.S. population. Generalization of these results to that or other populations must be carefully considered.

We examined many possible predictors of stroke recurrence, including demographic variables, medical history, neurological history, aspects of the neurologic examination, stroke diagnosis, and laboratory results. We were unable to confirm the suggestions of Sacco et al[1] that male sex and of Marquardsen[14] that increasing age are predictors of stroke recurrence. Only a few factors (hypertension, diabetes mellitus, prior stroke, abnormal ECG, and abnormal CT scan) proved to be significant predictors of stroke recurrence. Like Marquardsen[14] and Sacco et al,[1] we found that hypertension was a significant predictor of recurrence. Not surprisingly, when an etiology for the infarct was not established (IUC), the risk of stroke recurrence is lower than when a mechanism for the infarct was known.

Early recurrence accounted for 30% (39 of 129) of recurrent strokes in this cohort. In a previous report,[11] 3.3% of patients with ischemic infarction had a recurrent stroke within 30 days. Infarct subtypes had different early stroke recurrence rates. Lacunar

TABLE 3. Multivariate Analysis of Risk Factors Associated With Stroke Recurrence

| Risk factor | Estimated relative risk | 95% confidence interval |
|---|---|---|
| History of diabetes | 1.663 | 1.142–2.423 |
| Diastolic hypertension (≥100 mm Hg) | 1.012 | 1.003–1.021 |
| Prior stroke | 1.739 | 1.187–2.549 |
| Infarct of unknown cause | 0.601 | 0.404–0.893 |

infarcts had the lowest (2.2±1.2%) while atherosclerotic infarcts had the highest (7.9±2.2%) rate at 30 days; IUC and cardioembolic infarcts had intermediate rates. While we describe the recurrence patterns observed in the Stroke Data Bank and speculate that strokes of different etiologies have different recurrence patterns, the structure of the Stroke Data Bank prohibits a multivariate analysis with index stroke subtype as a predictor of recurrence. The index stroke subtype was not determined until hospital discharge, frequently after a recurrent stroke. Clearly, knowledge of a recurrence can influence the determination of the index stroke subtype.

Similar to 2-year recurrence, Sacco et al[11] reported that the determinants of 30-day stroke recurrence were history of hypertension, admission diastolic blood pressure of >100 mm Hg, history of diabetes, and admission blood glucose level of >140 mg/dl. The risk of early recurrence was slightly, but not significantly, higher in patients with either a history of stroke or an abnormal admission ECG. The independent predictors of early recurrence were history of hypertension (odds ratio=3.7) and initial blood glucose level (odds ratio=1.8 for 100-mg/dl increment).

Our study differs from that of Sacco et al[11] in focusing on the long-term risk of stroke recurrence. By restricting their interest to early recurrences, Sacco et al[11] reported a fixed 30-day follow-up in all patients. We looked at the maximum (up to 2 years) available follow-up for each patient. Since the Stroke Data Bank was an observational study with no proffered intervention to induce patients to adhere to a follow-up schedule, long-term follow-up was difficult to maintain (median follow-up was only 13 months). Additionally, there was the opportunity for recall bias in that remote (in time) recurrences were less likely to be recalled at a follow-up visit than recent recurrences and ascertainment bias in that patients with recurrent stroke may have returned for follow-up at a different rate than those without recurrence.

Although statistically significant, the relative risk ratios for the predictors of stroke recurrence at 2 years are quite modest. These results suggest that identifying a subgroup of stroke patients at high risk for recurrence is difficult. These findings may have implications for therapeutic trials designed to prevent stroke recurrence and suggest that although certain patients (those with a prior stroke, hypertension, diabetes, or an abnormal ECG) are at a somewhat higher risk for recurrence, nearly all patients who have had at least one stroke are at a substantial risk of having a recurrent stroke.

The lowest risk of recurrence occurs in normotensive, nondiabetic patients without a history of stroke whose index stroke is IUC. The effects of aggressive management of hypertension, diabetes mellitus, and cardiac abnormalities on the risk of stroke recurrence are only beginning to be studied.[18] Prospective studies are needed to determine whether effective management of these risk factors can decrease the risk of stroke recurrence.

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KEY WORDS • cerebral infarction • risk factors