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Original Contributions

Determinants of Early Recurrence of Cerebral Infarction

The Stroke Data Bank

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We studied 1,273 patients with ischemic cerebral infarction who were entered into the Stroke Data Bank, a prospective, observational study involving four university hospitals and the Biometry and Field Studies Branch of the National Institute of Neurological Disorders and Stroke. Forty patients had noniatrogenic recurrent stroke within 30 days after the index cerebral infarction. Using life tables, the 30-day cumulative \pm SE risk of early recurrence for all infarctions was $3.3 \pm 0.4\%$. The risk of early recurrence was greatest for atherothrombotic infarction ($7.9 \pm 2.2\%$, eight of 113 patients) and least for lacunar infarction ($2.2 \pm 1.2\%$, eight of 337 patients). Both cardioembolic infarction ($4.3 \pm 0.9\%$, 10 of 246 patients) and infarction of undetermined cause ($3.0 \pm 0.5\%$, 14 of 508 patients) had intermediate risks. History of hypertension and diabetes mellitus, as well as diastolic hypertension and elevated blood sugar concentration at admission, were associated with early recurrence. Logistic regression analysis estimated the risk of early recurrence to be 8.56% in those with coexisting hypertension and a glucose concentration of 300 mg/dl versus 0.77% in the absence of these two abnormalities. Early recurrence was associated with longer median duration of initial hospital stay (27 vs. 14 days) and a higher 30-day case-fatality rate (20% vs. 7.4%). Increased weakness scores were associated with early recurrent stroke. Identification of the determinants of early recurrent stroke may lead to better secondary prevention and may help select high-risk patients for further study. (*Stroke* 1989;20:983-989)

Recurrent stroke continues to be a major cause of morbidity and mortality among stroke survivors. Early recurrence of ischemic infarction within the first 2 weeks is best

documented for cardiogenic embolism and may be as high as 1%/day, based largely on retrospective data.¹ Establishing the frequency and timing of early recurrent stroke, particularly for individual diagnostic stroke subtypes, is helpful in understanding the natural history of stroke whereas identifying the risk factors may have treatment implications. The National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank (SDB) provides prospectively collected data on many acutely hospitalized patients with infarction capable of addressing these important questions.

Subjects and Methods

The SDB was a prospective observational study that collected acute-care and follow-up clinical and laboratory data on patients hospitalized with acute stroke. The current study was designed to facilitate research on the characteristics, clinical course, and outcome of these patients and involved the Biometry and Field Studies Branch of the NINDS as the statistical coordinating center and four academic hospital centers (the University Hospital of Boston University Medical Center, Michael Reese Hospital

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and Medical Center, the University of Maryland Hospital, and the Neurological Institute of Columbia University). A full description of the SDB can be found elsewhere.²

Each patient was personally examined by one of the SDB investigators within 1 week (median 46 hours) after stroke onset, and most patients underwent initial and subsequent computed tomography (CT scanning) (median 20 hours after onset). For each patient, information was collected concerning the medical, neurologic, and social history, the general and neurologic examinations, results of the laboratory studies, the final diagnosis, and special data collection procedures were done for complications, stroke evolution, stroke recurrence, and death.

Used in each clinical center, a classification for the diagnosis of stroke by causal mechanism² took into account the neurologic and medical history, neurologic symptoms and signs, head CT scan and, when available, findings from angiography, electrocardiography (ECG), echocardiography, Holter monitoring, and carotid Doppler ultrasonography. By the time of hospital discharge, strokes were diagnosed as parenchymatous hemorrhage, subarachnoid hemorrhage, infarction due to large-artery atherosclerosis (ATH), lacune (LAC), embolism from a commonly accepted cardiac source (EMB), infarction with tandem arterial pathology including embolism from a carotid source (TAP), infarction of undetermined cause or with normal angiogram (IUC), or stroke from another unusual cause (OTHER). Perfusion failure distal to the site of severe stenosis or occlusion of a major vessel was attributed to ATH. LAC was diagnosed in patients with a lacunar syndrome and a normal CT scan or a small, deep infarct on CT scan. EMB was diagnosed when a cardiac source was recognized. TAP was diagnosed in patients in whom an extracranial lesion was insufficient in itself to account for a stroke on hemodynamic grounds but possibly served as an embolic source. Patients diagnosed as having IUC had no bruits or transient ischemic attacks (TIAs) ipsilateral to the hemisphere affected by the stroke and had no obvious cardiac source of embolism; if the CT scan or angiogram were abnormal, the interpretation of these findings did not provide definitive evidence of the mechanism of infarction. OTHER encompassed arteritis, dissection, fibromuscular hyperplasia, sickle cell anemia, strokes in the setting of migraine, patients with mycotic aneurysm, and other diagnosed but rare or unusual causes of stroke.

Early recurrent stroke was defined as a cerebrovascular event within 30 days after the SDB index stroke that clearly resulted in a new deficit and occurred in a different anatomic or vascular territory or was of a different subtype than the index stroke. Detection of early recurrent stroke involved neurologic follow-up of each patient during and after hospitalization by the SDB nurse or investigator.² No routine examinations were done

between discharge and 3 months after discharge; however, readmission of recently discharged patients for recurrent stroke provided additional cases.

To account for noniatrogenic recurrence, early recurrent strokes were diagnosed by causal mechanism to identify those that were procedure-related. Iatrogenic early recurrent strokes were censored. Life table analysis was used to determine the distribution of early recurrence for all strokes and for individual stroke subtypes, the cumulative risk of early recurrence, its standard error, and its 95% confidence intervals.

Among patients with early recurrent strokes, neurologic deficit and CT findings of the index and recurrent strokes were compared. Groups of patients with and without an early recurrent stroke were compared for length of initial hospital stay and 30-day case-fatality rates.

To ascertain risk factors that may influence early recurrence, the groups were compared for age, race, sex, and handedness; stroke subtype; initial neurologic syndrome, cerebral site, systolic and diastolic blood pressure, and blood sugar concentration; medical history of hypertension, myocardial infarction, valvular heart disease, atrial fibrillation, other arrhythmias, angina, congestive heart failure, diabetes, previous stroke, or TIAs; stroke severity measured by total weakness scores²; and CT scan findings using univariate χ^2 tests of association. Treatment with antiplatelet agents or intravenous anticoagulation was not analyzed because the SDB was not designed to measure treatment efficacy.

Multivariate logistic regression analysis³ was used to identify risk factors jointly predictive of early recurrence. Stroke subtype was not used as a potential risk factor in the multivariate analysis since subtype may have been determined at hospital discharge or after the recurrent stroke. Given the risk factors, the conditional probability of early recurrence is $1 / [1 + e^{-(B_0 + B_1X_1 + B_2X_2 + \dots + B_iX_i)}]$ where B_0, B_1, \dots, B_i are parameters to be estimated by maximum likelihood from the data and X_1, X_2, \dots, X_i are known risk factors for an individual patient. The set of potential risk factors identified as significant by univariate analysis was reduced by backward elimination until only those significant at $p < 0.05$ remained.

To assess the predictive ability of our logistic model, the estimated probabilities of early recurrence were calculated as a function of specified levels of the risk factors, and the categorization, based on the logistic model, was compared with the actual recurrence status of each patient.

Results

Data on 1,805 patients with stroke were available for analysis (Table 1), which was limited to the 1,273 (71%) patients whose stroke was attributed to infarction. The final diagnosis for stroke subtype was ATH for 9%, LAC for 27%, EMB for 19%, and

TABLE 1. Stroke Subtype and Risk of Early Recurrence for 1,805 Cases in Stroke Data Bank

Subtype	N	Percent of		Recurrent stroke	
		Total	Infarctions	n	Risk (%)
Hemorrhage	480				
Parenchymatous	237	13.1			
Subarachnoid	243	13.5			
Infarction	1,273			40	3.3±0.4
Atherosclerosis	113	6.3	8.9	8	7.9±2.2
Lacune	337	18.7	26.5	8	2.2±1.2
Cardioembolic	246	13.6	19.3	10	4.3±0.9
Tandem arterial pathology	69	3.8	5.4	0	0
Undetermined cause	508	28.1	39.9	14	3.0±0.5
Other	52	2.9			
Total	1,805	100.0	100.0		

Risk as 30-day cumulative proportion±SE.

TAP for 5%; 40% were classified as IUC as no proven mechanism was identified despite the use of a variety of laboratory tests during hospitalization.

The SDB index stroke was the first occurrence of stroke in 74% of all patients with infarcts, and their median age at SDB index stroke was 68 years. A more detailed account of the demographic and clinical characteristics of the patients can be found elsewhere.²

Forty of the 1,273 patients with infarcts had a noniatrogenic early recurrent stroke; 24 other recurrent strokes were censored from the analysis because they were complications of vascular surgery or angiography. Twenty-nine of the 40 early recurrent strokes occurred during the initial hospitalization; the other 11 occurred 3–20 days after discharge, but still within 30 days after the SDB index stroke.

Thirty-one of the 40 early recurrent strokes were of the same and nine were of a different stroke subtype. Of these nine, in five the index stroke was classified EMB; of the five, in two information regarding the recurrent stroke was insufficient, leading by default to a recurrent stroke subtype of IUC, two were of the OTHER subtype (one a hemorrhagic infarction, the other an intracerebral hemorrhage), and one was of the ATH subtype. The other four index strokes were classified as LAC. One patient presented with an index sensorimotor stroke and was readmitted with dysarthria, increased weakness, and vertigo and was found to have a normal angiogram; therefore the recurrent stroke was classified as IUC. In a second patient, subsequent laboratory evidence not available at the time of the index stroke revealed internal carotid artery ATH, which was thought to be responsible for the recurrent stroke diagnosed as TAP. A third patient with an index pure motor stroke and a capsular infarct had a recurrent stroke thought to be related to vasculitis and was classified as OTHER. CT demonstrated a small intracerebral hemorrhage as the cause of a recurrent stroke in one patient who presented with an index LAC.

Reliable serial examinations to document changes in neurologic examination depended on the system tested since some findings were not tested both before and after the recurrent stroke or were untestable or uncertain, such as sensory function in an aphasic patient. Worsening was documented for motor function in 25 of 31, for extraocular movements in 12 of 32, for visual fields in five of 23, for sensory function in six of 19, for language in three of 14, and for other cognitive functions in three of 14 patients with recurrent stroke. Of 31 CT scans performed at or after (0–9 days) recurrence, 15 demonstrated the recurrent stroke. Detection of recurrence was related to worsening of motor function but not to worsening of other functions. This may be an artifact of testing since deterioration of motor function is easily recognized and quantified by both the patient and the examiner and since assessments of other neurologic functions are unreliable when there are changes in cognition, language, or consciousness.

Important differences were evident between groups of patients with and without early recurrent stroke (Table 2). The median duration of initial hospitalization was 15 days for all 1,273 patients with infarcts but was prolonged to 27 days in the group of patients with early recurrent strokes.

TABLE 2. Comparison of Groups of Patients With and Without Noniatrogenic Early Recurrent Stroke

Characteristic	Early recurrence	
	With (n=40)	Without (n=1,209)
Initial hospital stay (median)	27 days	14 days
Relative change in weakness score (median)	60%	-8%
30-day case-fatality rate	20%	7.4%

Relative change in weakness score, (initial score–final score) ÷ initial score; final score, that after recurrent stroke in those with early recurrence or that before discharge in those without early recurrence.

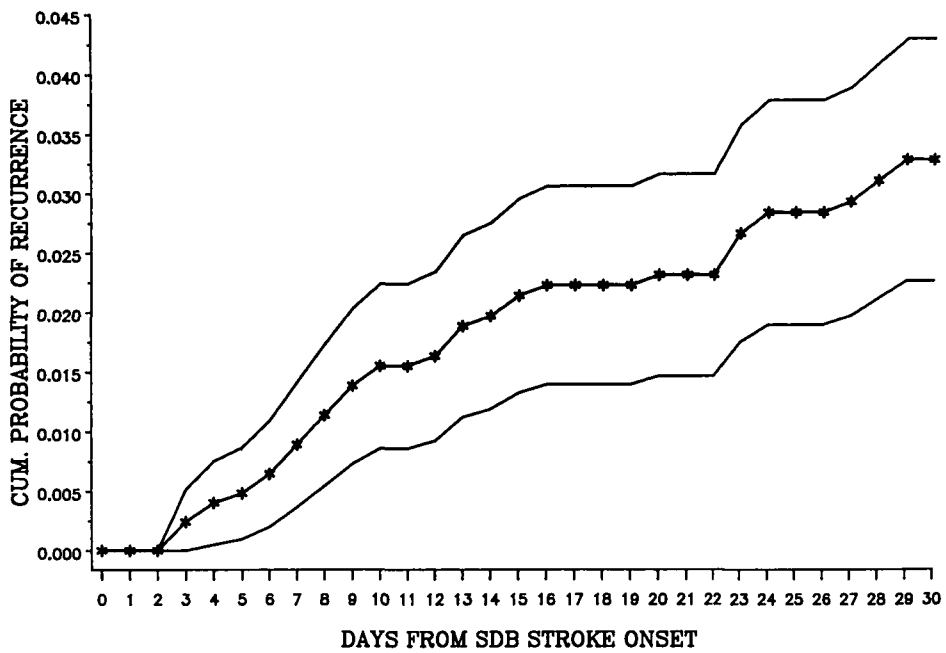


FIGURE 1. Kaplan-Meier estimates of probability of early recurrent stroke (*) with 95% confidence intervals. SDB, Stroke Data Bank.

The 30-day case-fatality rate was higher in the group with than in the group without early recurrent stroke (20%, eight of 40 vs. 7.4%, 89 of 1,209). All eight deaths in the early-recurrence group were directly (seven) or indirectly (one) related to the recurrent stroke. The postrecurrence weakness score was greater than the initial weakness score, whereas weakness scores decreased in the group without early recurrent stroke. The scores used to calculate change in weakness for the group without early recurrence were based on initial and predischarge neurologic examinations, chosen to be similar in timing to that of the group with early recurrence.

For all patients with infarctions, the cumulative risks of early recurrent stroke were $2.0 \pm 0.2\%$ 14 days and $3.3 \pm 0.4\%$ 30 days after the index stroke (Figure 1). Analysis by stroke subtype determined at discharge demonstrated lower risk for LAC, while ATH had the highest risk; the risk was intermediate for IUC and EMB. No noniatrogenic recurrent strokes occurred among the patients with TAP (Figure 2, Table 1).

Besides index stroke subtype, other characteristics of the patients were examined to define any association with early recurrent stroke (Table 3). History of hypertension, diastolic blood pressure of ≥ 100 mm Hg on admission, history of diabetes, and

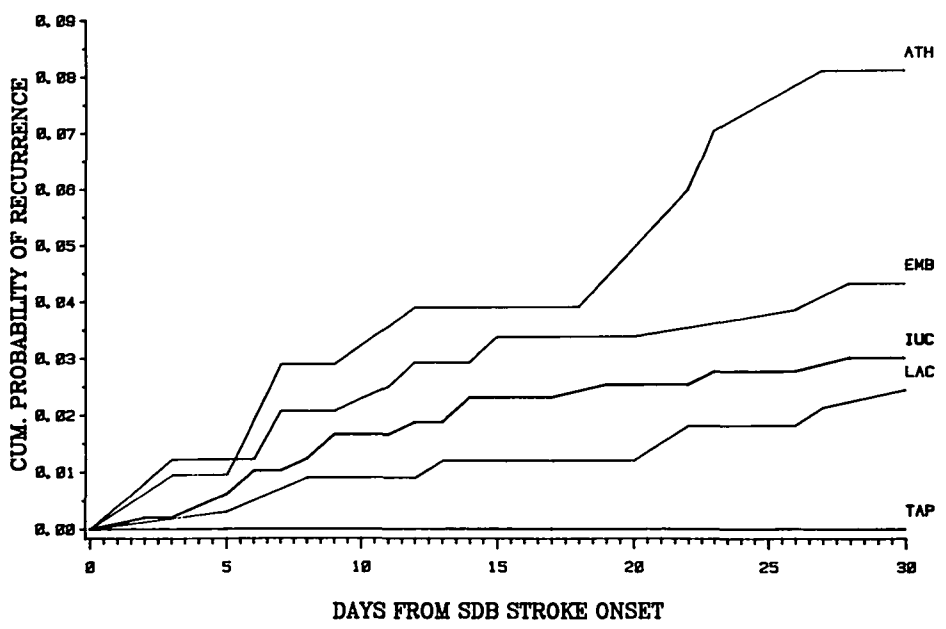


FIGURE 2. Kaplan-Meier estimates of probability of early recurrent stroke by index stroke subtype. ATH, atherosclerosis; EMB, cardioembolism; IUC, infarction of undetermined cause; LAC, lacune; TAP, tandem arterial pathology; SDB, Stroke Data Bank.

TABLE 3. Patient Characteristics Related to Early Recurrent Stroke

Characteristic	Percent of all infarcts	Early recurrence	
		Risk	<i>p</i>
Hypertension			
Yes	69%	4.02%	0.01
No	31%	1.29%	
Diastolic blood pressure			
≥100 mm Hg	25%	5.23%	0.02
<100 mm Hg	75%	2.50%	
Diabetes			
Yes	26%	4.88%	0.05
No	74%	2.65%	
Blood sugar concentration			
≥140 mg/dl	36%	6.36%	0.001
<140 mg/dl	64%	2.07%	
Systolic blood pressure			
≥160 mm Hg	51%	3.86%	NS
<160 mm Hg	49%	2.64%	
Vascular territory			
Anterior	75%	2.88%	NS
Posterior	23%	4.15%	
Other	2%	4.35%	
Race			
Black	58%	3.45%	NS
White	34%	2.82%	
Other	8%	3.06%	
Age			
≤65 years	42%	3.22%	NS
>65 years	58%	3.19%	
Weakness score			
Mild	44%	2.90%	NS
Moderate	29%	3.29%	
Severe	27%	3.61%	
Computed tomogram			
Abnormal	62%	3.42%	NS
Normal	38%	2.79%	
Electrocardiogram			
Abnormal	62%	3.76%	NS
Normal	38%	2.46%	
Hematocrit			
>45%	22%	4.44%	NS
≤45%	78%	2.99%	
History of			
Stroke			
Yes	26%	4.21%	NS
No	74%	2.79%	
Transient ischemic attack			
Yes	18%	3.98%	NS
No	82%	3.09%	
Atrial fibrillation			
Yes	10%	4.80%	NS
No	90%	3.03%	
Other arrhythmias			
Yes	9%	4.46%	NS
No	91%	3.10%	
Valvular disease			
Yes	5%	0.00%	NS
No	95%	3.35%	
Angina			
Yes	18%	3.27%	NS
No	82%	3.19%	
Myocardial infarction			
Yes	19%	2.56%	NS
No	81%	3.25%	
Congestive heart failure			
Yes	15%	2.15%	NS
No	85%	3.40%	

p by χ^2 with 1 or 2 degrees of freedom. NS, not significant.

TABLE 4. Risk of Early Recurrent Stroke Estimated by Multivariate Logistic Regression Analysis

Variables		
Hypertension	Blood sugar concentration (mg/dl)	Risk
No	100	0.77%
	200	1.38%
	300	2.47%
Yes	100	2.78%
	200	4.93%
	300	8.56%

$$\text{Risk} = 1 + [1 + e^{-(5.4533 + 1.3064 \times \text{hypertension} + 0.0059 \times \text{blood sugar})}]$$

blood sugar concentration of ≥140 mg/dl on admission were significantly more prevalent among the patients with early recurrent stroke. The risk of early recurrence was slightly higher for blacks; for patients with previous stroke, TIAs, atrial fibrillation, other arrhythmias, or angina; and for patients with initial systolic blood pressure of ≥160 mm Hg, severe weakness scores, abnormal ECG, or hematocrit of >45%. However, these differences in risk were not significant. Sex, handedness, medications at onset (data not shown), age, valvular heart disease, congestive heart failure, and findings on CT scan, Holter monitoring, and echocardiography (data not shown) were not associated with early recurrence.

Multivariate logistic regression analysis identified the importance of a history of hypertension and the blood sugar concentration at admission as the predominant predictors of early recurrence (Table 4). The estimated risk of early recurrence rose from 0.77% in the absence of both hypertension and hyperglycemia to 8.56% in those with coexisting hypertension and an initial blood glucose concentration of 300 mg/dl (Figure 3, Table 4). These risks are derived from the model and applied to the same data; the utility of our model can be evaluated best in an independent population.

Discussion

Identifying early recurrence of ischemic stroke is important to plan treatment trials and to understand the natural history of individual infarction mechanisms. Analysis requires prospective data collection and follow-up to ascertain serial changes in the neurologic examination and to distinguish between stroke progression, stroke worsening, and stroke recurrence. The SDB provides a large cohort in which to investigate early symptomatic stroke recurrence by infarct subtype.

In the SDB, the cumulative overall 30-day recurrence risk for all infarctions was 3.3±0.4%. Since the SDB was designed as an observational study, no attempt was made to control for treatment, which was determined by neurologic practice. Data on the temporal association of medications with neurologic worsening or stroke recurrence was not rou-

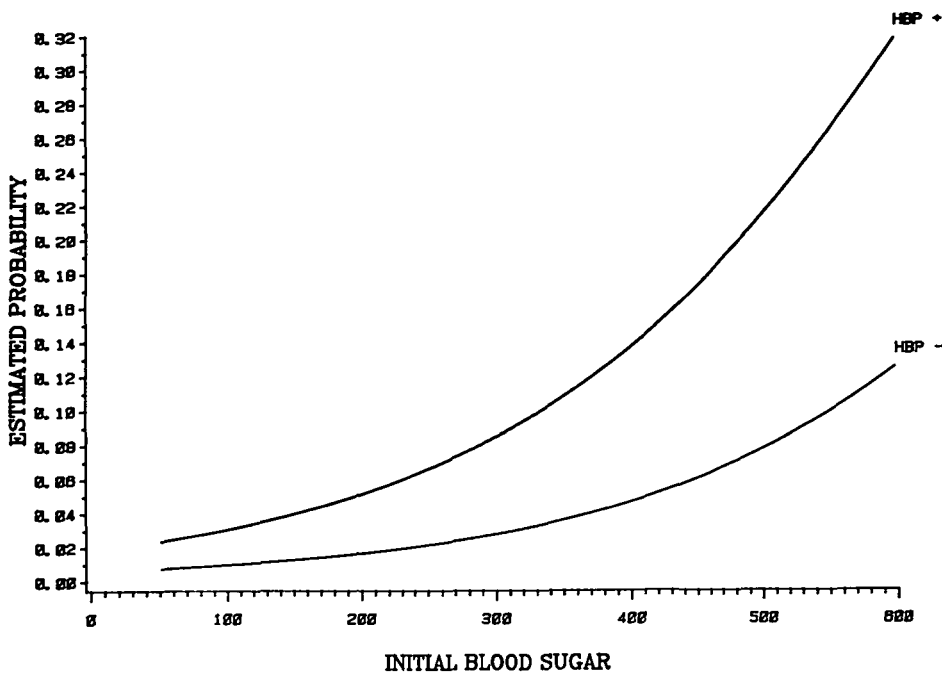


FIGURE 3. Relation between initial blood sugar concentration and estimated probability of stroke recurrence by history of hypertension (HBP).

tinely collected. The efficacy of various treatments can be assessed best through randomized controlled trials. Furthermore, the 24 early recurrent strokes associated with procedures were excluded from our analysis. Although angiography and vascular surgery provide essential diagnostic information and therapeutic benefit, they are also a source of unavoidable stroke morbidity. The risk of recurrent stroke from these procedures is not the focus of this investigation.

Early stroke recurrence is not trivial when measured by its effect on patient morbidity. Weakness scores in the group of patients with early recurrence were substantially greater than those in the group without early recurrence, and the duration of the initial hospitalization was longer in the former. Early stroke recurrence was associated with increased 30-day mortality, and the early deaths were usually a direct consequence of the recurrent stroke.

The proportion of ATH in the SDB is less than that reported in other studies.⁴⁻⁶ However, in the SDB the definition of ATH was restricted to patients in whom the mechanism of stroke was thought to be hemodynamic insufficiency, and there was a greater reliance on confirmatory laboratory evidence than in other studies. Rather than combine ATH, TAP, and LAC into a large category of atherothrombosis, every effort was made in the SDB to classify patients by infarct mechanism. Even though ATH accounted for only 9% of all infarctions, this stroke subtype had the highest early recurrence risk ($7.9 \pm 2.2\%$ by 30 days). Early identification of ATH strokes may encourage medical or surgical intervention aimed at avoiding stroke recurrence. No early recurrent strokes occurred in patients with TAP,

but our small sample size lacks the power to make any definitive statements.

EMB accounted for 19% of SDB infarctions and had a 30-day recurrence risk of $4.3 \pm 0.9\%$. Besides the clinical characteristics that suggested such infarction, most patients with EMB had a cardiac source substantiated by abnormalities on ECG, echocardiography, or Holter monitoring. The risk of recurrence for EMB has been the subject of numerous studies, with aggregate data from 15 studies suggesting that 12% recur within 2 weeks.^{1,7} The overall range (2-22%) and the individual 95% confidence limits are wide, reflecting the variability of study designs. Published risks are greater than those in our study, but previous studies had fewer cases and often were retrospective. The effect of treatment with intravenous anticoagulation, which was used in 42% of cerebral infarctions in the SDB, or other agents may partially account for the lower early recurrence risks in our study.

LAC accounted for 27% of the SDB infarctions, and the early recurrence risk was low ($2.2 \pm 1.2\%$ by 30 days). The lacunar syndrome was often substantiated by a compatible CT scan that supported a small-vessel-disease etiology. Further observations are needed to demonstrate if the relative infrequency of early stroke recurrence in patients with LAC persists with longer follow-up.

Despite adequate attempts to establish the infarct mechanism, 40% defied classification and were considered IUC. The 30-day recurrence risk ($3.0 \pm 0.5\%$) is intermediate between that of LAC and EMB. Similarities in the early recurrence risks of IUC and EMB may add to the preliminary evidence that some infarctions may be embolic without an identified source.⁸

In assessing the risk of early recurrence, stroke subtype is an important factor, particularly if the initial event is ATH. Subtype is often not clear until all test results are available; therefore, it would be difficult to use subtype alone to predict early recurrence. Other factors available upon initial presentation and associated with early recurrence are an initial blood sugar concentration of ≥ 140 mg/dl, a history of diabetes or hypertension, and an initial diastolic blood pressure of ≥ 100 mm Hg. In our logistic model, when other risk factors are held constant, history of hypertension and elevated initial blood sugar concentration are associated with early recurrent stroke. The coexistence of these two risk factors raises the probability of early recurrence substantially. Information not collected as part of the SDB on other potential risk factors such as protein C, protein S, fibrinogen, low density lipoprotein, and high density lipoprotein levels need to be assessed in future studies of early stroke recurrence.

Except for embolic infarction, comparative studies are difficult to find since prospective series of many acutely hospitalized patients with infarction are lacking. The 3-month recurrence risk for atherothrombosis in the Framingham Study was 2.3%,⁹ while in the AICLA trial the 1-month risk of stroke recurrence regardless of therapy was approximately 1%.¹⁰ In the Multicenter EC/IC Bypass Trial there was a 1.3% risk of stroke occurrence within 39 days of randomization in the medically treated group.¹¹ In an open trial with intravenous heparin treatment for cerebral infarction, 2.2% of the patients had a recurrent event during hospitalization.¹² In the Austin (Australia) Hospital Stroke Unit, a similar risk of in-hospital stroke recurrence (4.8%) was found in a group of 522 ischemic stroke patients.¹³ This latter study also suggested that a history of hypertension was a risk factor for recurrent stroke.¹³ Others have found that a history of TIAs, myocardial infarction, other coronary disease, hypertension, and diabetes increases the relative risk for recurrent stroke.¹⁴ Most studies have emphasized the effect of risk factors on late, not early, stroke recurrence.

Early stroke recurrence causes significant morbidity and mortality. History of hypertension and

elevated initial blood sugar concentration, along with stroke subtype, help predict the risk of early stroke recurrence. Understanding the natural history of various infarction mechanisms and defining the relation among stroke subtype, other risk factors, and early recurrence are preliminary steps toward improved secondary prevention.

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KEY WORDS • cerebral infarction • cerebrovascular disorders • risk factors