Early Recurrent Ischemic Stroke
A Case–Control Study
Larry B. Goldstein, MD, and April Perry, RN

Background and Purpose: Data concerning potentially treatable risk factors for early recurrent stroke are limited. Therefore, we carried out a retrospective case–control study to identify factors predisposing to early reinfarction.

Summary of Review: We identified all patients admitted to Duke University Hospital or the Durham Veterans Administration Medical Center during 1 year having two documented ischemic strokes within 90 days (n=12 of 273). Twelve randomly selected patients matched for age, sex, and race but having only a single stroke served as controls. There were no significant differences between the groups with respect to a variety of factors including the presence of hypertension, diabetes, a history of transient ischemic attack, a history of stroke, cerebral site of the index stroke, and subtype of the index stroke. A potential cardioembolic source was more frequently identified in the patients with early recurrent stroke (seven of the 12 case–control pairs were discordant for a potential cardioembolic source; McNemar's χ² test, p≤0.02).

Conclusions: Of the variables examined, the presence of a potential cardioembolic source was the single statistically significant factor associated with reinfarction within the first 90 days after ischemic stroke. The limitations and possible therapeutic implications of these results are discussed. (Stroke 1992;23:1010–1013)

Key Words • cerebral infarction • cerebrovascular disorders • risk factors

Therapeutic interventions following acute ischemic stroke are generally directed at secondary prevention, reduction of complications, and improving functional outcome through rehabilitation. Secondary prevention is particularly important because 14–17% of patients may have a second stroke during the next 1–2 years. Recurrence during the first 30 days after the index stroke is approximately 1–4%. A variety of factors have been suggested to increase the risk of early recurrence. The risk of reinfarction during the first year in patients with atrial fibrillation ranges from 13% to 32%. Recurrence during the first 2 weeks in these individuals is between 2% and 20%, with an average risk of approximately 1%/day for the first 10 days. Data concerning other risk factors for early recurrent stroke are limited. Therefore, we carried out a retrospective case–control study to identify potentially treatable factors predisposing to early reinfarction.

Subjects and Methods
We identified the cases through a prospective stroke registry that included all patients diagnosed with acute cerebrovascular disease who were admitted to Duke University Hospital or the Durham Veterans Administration Medical Center. Diagnosis was based on clinical history, neurological examination, and imaging studies (either head computed tomography [CT] or magnetic resonance imaging [MRI]) and reflected the final opinion of the patient’s primary physician. For the purposes of this study, cases were defined as patients having two documented ischemic strokes within 90 days, with the index stroke occurring between May 1989 and June 1990. An equal number of control patients who had only a single ischemic stroke during the same period were then selected from the registry and matched with the cases, first by age (within 10 years), then by sex and race.

The study patients’ hospital records were then reviewed. Stroke risk factors including a history of hypertension, cigarette smoking, diabetes mellitus, cardiac disease, prior transient ischemic attacks (TIAs), and family history of stroke were recorded. The results of diagnostic studies including electrocardiography, Holter monitoring, echocardiography, brain CT or MRI, carotid Doppler ultrasonography, and cerebral angiography were reviewed. The serum glucose concentration, systolic blood pressure (SBP), and diastolic blood pressure (DBP) at the time of hospital admission were recorded. Mean arterial blood pressure (MAP) was calculated as DBP + 0.67(SBP–DBP). Stroke subtype (large-vessel thrombotic, cardioembolic, “lacunar,” or “uncertain”) was assigned using modified Harvard Stroke Registry criteria after review of the patient’s clinical presentation, neurological examination, and available laboratory studies following the index stroke. Potential cardiogenic sources of emboli included non-valvular atrial fibrillation, acute myocardial infarction,
ventricular aneurysm, valvular heart disease, and dilated cardiomyopathy. Patients whose strokes could be due to more than one causal mechanism (e.g., appropriate carotid pathology in addition to a potential cardioembolic source) and patients who had infarction of undetermined cause were classified as "uncertain." The cerebral site of the stroke was determined based on review of the patient's neurological examination and CT or MRI scan. The use of anticoagulants following the index stroke was noted.

The $\chi^2$ test was used to compare categorical variables and Student's $t$ test to compare continuous variables between cases and the remaining patients in the registry. Cases and controls were compared for sex, race, a history of hypertension, cigarette smoking, diabetes mellitus, cardiac disease, prior TIAs, prior stroke, family history of stroke, the presence of a potential cardioembolic source, and the cerebral site of the index stroke using McNemar's $\chi^2$ test for dichotomous variables. For categorical variables that differed significantly, the odds ratio (OR) was calculated to assess the proportions of discordant pairs of cases and controls (a Woolf-Haldane-type adjustment was used to compute an estimated OR when the cell frequency was 0%).

For categorical variables that differed significantly, the odds ratio (OR) was calculated to assess the proportions of discordant pairs of cases and controls (a Woolf-Haldane-type adjustment was used to compute an estimated OR when the cell frequency was 0%). Age, SBP, DBP, MAP, and serum glucose concentration at the time of hospital admission were compared using paired $t$ tests, and stroke subtype was compared using Lehmacher's test for matched pairs with variables having more than two categories. A multivariate analysis was not carried out because univariate analyses revealed that only a single variable was significantly associated with reinfarction within 90 days after the index stroke. All tests of significance were two-tailed.

### Results

From May 1989 to June 1990, 340 patients were entered into the stroke registry. One hundred patients (29%) were classified as having embolic stroke, 84 (25%) had ischemic stroke of uncertain subtype, 46 (14%) had lacunar stroke, 43 (13%) had large-vessel thrombotic stroke, 51 (15%) had intracerebral hemorrhage, and 16 (5%) had subarachnoid hemorrhage. Of the 273 patients with ischemic stroke, 12 (4.4%) had a second documented infarction within 90 days after the index stroke. Four patients had the second stroke within the first week after the index stroke; one patient had the second stroke during week 2, two during week 7, two during week 10, one during week 11, and two during week 12. There were no significant differences between the 12 cases and the remaining 261 ischemic stroke patients in the registry with respect to age ($p=0.10$), sex ($p=0.54$), race ($p=0.71$), prior TIAs ($p=0.59$), prior stroke ($p=0.65$), hypertension ($p=0.88$), diabetes mellitus ($p=0.29$), ischemic cardiac disease ($p=0.88$), or cigarette smoking ($p=0.34$).

Table 1 gives the numbers of concordant and discordant pairs of cases and controls with respect to stroke risk factors. No difference was significant. The mean±SEM age of the cases and controls were 72±3 and 72±3 years, respectively (paired $t$ test, $p=0.62$). Tables 2, 3, and 4 compare the cases and controls with respect to characteristics of the index stroke. As expected, SBP, DBP, and MAP were higher in patients with a history of hypertension ($n=19$) than in those without such a history ($n=5$), although the difference in

---

### Table 1. Demographic Characteristics and Historical Stroke Risk Factors for Cases and Controls

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases</th>
<th>Controls</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>0</td>
<td>≤0.48</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>7</td>
<td>0</td>
<td>≤1.00</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>History of hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>3</td>
<td>≤0.62</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension and diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>3</td>
<td>≤0.62</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Cigarette smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9</td>
<td>1</td>
<td>≤1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>3</td>
<td>≤0.48</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>History of transient ischemic attack</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>3</td>
<td>≤0.68</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Prior stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>4</td>
<td>≤0.75</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Data are number of pairs of cases with early recurrent stroke and matched controls. Probabilities calculated using McNemar's $\chi^2$ test for dichotomous variables.

*Family history available for 16 patients.

DBP was not significant (mean±SEM DBP, 164±5 versus 125±10 mm Hg, $p=0.002$; mean±SEM DBP, 94±5 versus 80±8 mm Hg, $p=0.16$; and mean±SEM MAP, 141±4 versus 110±7 mm Hg, $p=0.004$ for patients with and without a history of hypertension, respectively). Similarly, mean±SEM serum glucose concentration was higher in patients with a history of diabetes ($n=8$) than in those without ($n=16$) (168±23 versus 112±10 mg/dl, respectively; $p=0.013$). There were no significant differences in SBP, DBP, MAP, or serum glucose concentration between the cases and the controls (Table 2). Although cardioembolic strokes were more frequent among the cases, there was no overall significant difference in stroke subtype between the groups (Table 3). There also was no significant difference in the vascular distribution of the index stroke (Table 4). However, regardless of stroke subtype or vascular distribution of the index stroke, a potential
The thrombotic source was identified more frequently in the cases than in the controls, there was no overall difference in stroke subtype between the groups. The disparity between the presence of a cardioembolic source and the diagnosis of cardioembolic stroke occurred because the identification of a potential cardioembolic source was a necessary but not sufficient criterion for the diagnosis of embolic stroke. In patients in whom the mechanism of stroke was unclear despite the presence of a cardioembolic source were categorized as having a stroke of uncertain subtype.

In contrast to our results, the Stroke Data Bank investigators found that the risk of recurrence within the first 30 days after an index stroke varied with stroke subtype. The risk of recurrence was greatest for patients with atherothrombotic infarction, least for those with lacunar infarction, and intermediate for those with cardioembolic infarction or infarction of undetermined cause. Similar results were found when the period of observation was extended to 2 years. However, the design of the Stroke Data Bank prohibited a multivariate analysis with index stroke subtype as a predictor of recurrence. In addition, the Stroke Data Bank study used diagnostic criteria somewhat different from those employed in the present study. For example, "tandem arterial pathology" and "stroke from another unusual cause" were included in the Stroke Data Bank study as separate categories. The application of diagnostic criteria for stroke subtype may vary between the studies. In a separate study, the Stroke Data Bank investigators found only slight initial interobserver agreement in the diagnosis of stroke subtype. This improved to substantial, but not complete, agreement when all diagnostic studies had been completed. Other researchers also found considerable disagreement among specialists in the diagnosis of stroke subtype, even after reviewing extensive clinical data. Finally, differences in study populations and study designs resulting in selection biases and the possibility of a type II error in our analysis are other possible explanations for this and other differences (discussed below) between the studies.

In agreement with our results, the Stroke Data Bank study did not find significant relations between early recurrence and a history of TIA or cardiac disease. The central finding of our retrospective case-control study is that, of the variables examined, the presence of a potential cardioembolic source was the single statistically significant factor associated with reinfarction within the first 90 days after ischemic stroke. Although cardioembolic strokes were more frequent in the cases than in the controls, there was no overall difference in stroke subtype between the groups. The disparity between the presence of a cardioembolic source and the diagnosis of cardioembolic stroke occurred because the identification of a potential cardioembolic source was a necessary but not sufficient criterion for the diagnosis of embolic stroke. Patients in whom the mechanism of stroke was unclear despite the presence of a cardioembolic source were categorized as having a stroke of uncertain subtype.

In contrast to our results, the Stroke Data Bank investigators found that the risk of recurrence within the first 30 days after an index stroke varied with stroke subtype. The risk of recurrence was greatest for patients with atherothrombotic infarction, least for those with lacunar infarction, and intermediate for those with cardioembolic infarction or infarction of undetermined cause. Similar results were found when the period of observation was extended to 2 years. However, the design of the Stroke Data Bank prohibited a multivariate analysis with index stroke subtype as a predictor of recurrence. In addition, the Stroke Data Bank study used diagnostic criteria somewhat different from those employed in the present study. For example, "tandem arterial pathology" and "stroke from another unusual cause" were included in the Stroke Data Bank study as separate categories. The application of diagnostic criteria for stroke subtype may vary between the studies. In a separate study, the Stroke Data Bank investigators found only slight initial interobserver agreement in the diagnosis of stroke subtype. This improved to substantial, but not complete, agreement when all diagnostic studies had been completed. Other researchers also found considerable disagreement among specialists in the diagnosis of stroke subtype, even after reviewing extensive clinical data. Finally, differences in study populations and study designs resulting in selection biases and the possibility of a type II error in our analysis are other possible explanations for this and other differences (discussed below) between the studies.

In agreement with our results, the Stroke Data Bank study did not find significant relations between early recurrence and a history of TIA or cardiac disease.
However, the risk of early reinfarction was higher in patients with either hypertension or diabetes. The greatest risk was in patients with coexisting hypertension and hyperglycemia. In a preliminary report of a case-control study, Bornstein and coworkers found that atrial fibrillation in addition to hypertension, diabetes, and cigarette smoking were significant independent risk factors for reinfarction. However, the length of follow-up was not stated in that study. Although we found a higher frequency of hypertension and diabetes in our cases, these differences as well as differences in SBP, DBP, MAP, and serum glucose concentration were not significant. Our small sample size precludes definitive conclusions with regard to these other potential risk factors.

The present study of early recurrent cerebral infarction does not address treatment. Routine acute anticoagulation of all patients with ischemic stroke cannot be advocated because of significant risk and uncertain benefit. We found that patients with an identified potential cardioembolic source (most frequently atrial fibrillation) were at greater risk for reinfarction within 90 days. The acute use of anticoagulants for secondary prevention in patients with presumed cardioembolic stroke has been the subject of extensive investigations. Data concerning acute anticoagulation for patients with atrial fibrillation notwithstanding the subtype of the index stroke are limited. One retrospective study found that, regardless of index stroke subtype, 8% (three of 38) of untreated patients with atrial fibrillation had a second stroke within 10 days while none (0 of 18) of the anticoagulated patients had early reinfarction.

Whether short-term anticoagulation in individuals at high risk for early reinfarction but not deemed to be candidates for long-term anticoagulation will prove to be efficacious is not certain. Confirmation of other risk factors reported as being associated with early recurrent stroke awaits further study.

Acknowledgment

The authors wish to thank Dr. George Divine for his helpful suggestions.

References

Early recurrent ischemic stroke. A case-control study.
L B Goldstein and A Perry

Stroke. 1992;23:1010-1013
doi: 10.1161/01.STR.23.7.1010

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/23/7/1010

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/