Hospitalization for Infection and Risk of Acute Ischemic Stroke
The Cardiovascular Health Study

Mitchell S.V. Elkind, MD; Cara L. Carty, PhD; Ellen S. O'Meara, PhD; Thomas Lumley, PhD; David Lefkowitz, MD; Richard A. Kronmal, PhD; W.T. Longstreth, Jr, MD

Background and Purpose—Little is known about the acute precipitants of ischemic stroke, although evidence suggests infections contribute to risk. We hypothesized that acute hospitalization for infection is associated with the short-term risk of stroke.

Methods—The case-crossover design was used to compare hospitalization for infection during case periods (90, 30, or 14 days before an incident ischemic stroke) and control periods (equivalent time periods exactly 1 or 2 years before stroke) in the Cardiovascular Health Study, a population-based cohort of 5888 elderly participants from 4 US sites. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by conditional logistic regression. Confirmatory analyses assessed hazard ratios of stroke from Cox regression models, with hospitalization for infection as a time-varying exposure.

Results—During a median follow-up of 12.2 years, 669 incident ischemic strokes were observed in participants without a baseline history of stroke. Hospitalization for infection was more likely during case than control time periods; for 90 days before stroke, OR\(^{3.4 (95\% CI, 1.8 to 6.5).\) The point estimates of risks were higher when we examined shorter intervals: for 30 days, OR\(^{7.3 (95\% CI, 1.9 to 40.9),\) and for 14 days, OR\(^{8.0 (95\% CI, 1.7 to 77.3).\) In survival analyses, risk of stroke was associated with hospitalization for infection in the preceding 90 days, adjusted hazard ratio\(^{2.4 (95\% CI, 1.6 to 3.4).\)

Conclusions—Hospitalization for infection is associated with a short-term increased risk of stroke, with higher risks observed for shorter intervals preceding stroke. (Stroke. 2011;42:1851-1856.)

Key Words: epidemiology ■ cerebral infarction ■ infectious diseases

Knowledge of acute stroke precipitants is primitive. Identification of particular time periods during which stroke risk is elevated could prove a valuable strategy to reduce stroke incidence through the introduction of appropriate prevention strategies during a period of vulnerability. Studies of acute precipitants lend themselves to different methodologies than do studies of chronic risk factors. In an analysis of the acute precipitants of stroke, for example, intraindividual differences may be more important than between-person differences. The factor of interest is not the characteristic making 1 person more likely than another to have a stroke, but rather what makes 1 individual more likely to have stroke at a particular point in time.

The case-crossover design is particularly suited to assessing potential precipitants.1 Case-crossover analyses are based on data about relatively short intervals of time leading to events, contrasted with data from comparable periods of time in the same individual. Events that occur more frequently just before stroke than at other time intervals are more likely to be precipitants. Each participant thus serves as his own control, and the analysis implicitly accounts for most interindividual differences. The case-crossover design has been used only sparingly to identify triggers of stroke2 compared with myocardial infarction.3–5

We hypothesized that the risk of ischemic stroke would be higher during the 90 days after hospitalization for infection compared with the same period of time 1 and 2 years before stroke. The Cardiovascular Health Study (CHS) is a multicenter, prospective study of vascular risk factors in an elderly population-based cohort. CHS afforded the opportunity to address our hypothesis with a case-crossover design and to seek confirmation with survival analyses.

Methods
Details of the CHS have been described elsewhere.6–8 In brief, a random sample of men and women age ≥65 years (n=5888) was

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From the Departments of Neurology and Epidemiology (M.S.V.E.), Columbia University, New York, NY; Department of Epidemiology (C.L.C.), University of Washington; Group Health Research Institute (E.S.O.); and Department of Biostatistics (T.L., R.A.K.), University of Washington, Seattle, WA; Department of Neurology (D.L.), Wake Forest University, Winston-Salem, NC; and Departments of Neurology and Epidemiology (W.T.L.), University of Washington, Seattle, WA.
The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.608588/DC1.
Correspondence to Mitchell S.V. Elkind, MD, 710 W 168th St, Box 182, New York, NY 10032. E-mail mse13@columbia.edu
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Case crossover design

The prevalence of exposure during these time intervals was compared with the prevalence of exposure during the same calendar period 1 and 2 years before the event (see the Figure). Confounding by age is possible, because as participants age, their risk of stroke and hospitalization for infection increase. To reduce potential confounding, only time periods ±2 years before the stroke were included. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). For analyses with <5 periods per cell, we used exact conditional logistic regression. The null hypothesis was that the prevalence of exposure would remain constant across all time intervals.

To confirm our case-crossover findings, we also fit a Cox proportional-hazards model among participants without a baseline history of stroke, by using the same ICD-9 codes for hospitalization with infection, and incident ischemic stroke as the outcome. These analyses allowed adjustment for factors (such as age) that change over time and may confound the case-crossover findings. Hospitalization for infection was treated as a time-varying exposure in the Cox model; participants were nonexposed until hospitalization; remained exposed for 14-, 30-, or 90-day intervals; and then became nonexposed until their next eligible hospitalization. Hospitalizations for infection occurring after stroke were not included in the analyses. Analyses were performed with STATA, version 10.1 (Stata Corp, College Station, TX).

Results

Description of the Cohort and Hospitalizations for Infections

During a median 12.2 years of follow-up, 5639 CHS participants without a baseline history of stroke experienced 669 incident, nonprocedure-related ischemic strokes. Baseline characteristics are provided in Table 1. Of these 669 participants, 29 had at least 1 hospitalization for infection during the preceding 90 days. Types and frequencies of infections are shown in the online-only Table (http://stroke.ahajournals.org).

Case-Crossover Analyses

Among 669 stroke cases, 8 individuals were hospitalized for infection during the 4 to 14 days before the stroke, whereas only 2 stroke cases had hospitalizations in the same 10-day time windows. For infections occurring before stroke, each hospitalization within a case or control period was considered an exposure.
Table 1. Characteristics of Participants

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Case-Crossover Analysis</th>
<th>Survival Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)*</td>
<td>669 (11.4)</td>
<td>5639 (95.8)</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>74.0±5.7</td>
<td>72.8±5.6</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>408 (61.0)</td>
<td>3287 (58.3)</td>
</tr>
<tr>
<td>Self-reported race, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>101 (15.1)</td>
<td>860 (15.3)</td>
</tr>
<tr>
<td>White</td>
<td>566 (86.6)</td>
<td>4743 (84.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.3)</td>
<td>36 (0.6)</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>74 (11.1)</td>
<td>671 (11.9)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>132 (19.7)</td>
<td>887 (15.9)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>398 (59.5)</td>
<td>2780 (57.3)</td>
</tr>
<tr>
<td>BMI, mean±SD, kg/m²</td>
<td>26.7±4.7</td>
<td>26.9±4.8</td>
</tr>
<tr>
<td>Total cholesterol, mean±SD, mg/dL</td>
<td>213.4±45.2</td>
<td>208.6±38.7</td>
</tr>
<tr>
<td>LDL cholesterol, mean±SD, mg/dL</td>
<td>130.5±36.6</td>
<td>127.2±33.9</td>
</tr>
<tr>
<td>HDL cholesterol, mean±SD, mg/dL</td>
<td>53.0±15.3</td>
<td>53.3±14.4</td>
</tr>
<tr>
<td>Triglycerides, mean±SD, mg/dL</td>
<td>152.7±104.3</td>
<td>143.5±85.3</td>
</tr>
<tr>
<td>Maximum common IMT, median (IQR), mm</td>
<td>1.03 (0.92–1.16)</td>
<td>1.07 (0.96–1.21)</td>
</tr>
<tr>
<td>Maximum internal IMT, median (IQR), mm</td>
<td>1.30 (0.99–1.77)</td>
<td>1.42 (1.07–1.90)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; IMT, carotid artery intima-media thickness; IQR, interquartile range.

*As a percentage of the initially recruited cohort, N=5888. The case-crossover analysis includes only participants who had incident stroke.

calendar periods 1 and 2 years prior (Table 2). Hospitalization for infection within 14 days was associated with an increased risk of stroke (OR = 8.0; 95% CI, 1.6 to 77.3; P = 0.007). The elevated risk persisted for each predefined time window, with a decreasing point estimate for magnitude of risk as the time interval lengthened (Table 2). The risk of stroke after hospitalization for infection during the 14-day time window was associated with a higher point estimate for risk of stroke than was hospitalization during the 30- and 90-day time windows.

Table 2. Association of Recent Hospitalization for Infection With Risk of Ischemic Stroke, Based on Case-Crossover Analyses

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Case Time Intervals, No.</th>
<th>Control Time Intervals, No.</th>
<th>OR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for infection within 14 d before stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>660</td>
<td>1194</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>2</td>
<td>8.0, 1.6–77.3*</td>
</tr>
<tr>
<td>Missing/not eligible</td>
<td>1</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for infection within 30 d before stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>655</td>
<td>1193</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>3</td>
<td>7.3, 1.9–40.9*</td>
</tr>
<tr>
<td>Missing/not eligible</td>
<td>3</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for infection within 90 d before stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>631</td>
<td>1179</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29</td>
<td>17</td>
<td>3.4, 1.8–6.5</td>
</tr>
<tr>
<td>Missing/not eligible</td>
<td>9</td>
<td>142</td>
<td></td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

*Result is from exact conditional logistic regression.

talization for infection within the previous 90 days remained elevated (OR=3.4; 95% CI, 1.8 to 6.5).

Survival Analyses

The incidence of first ischemic stroke was 11.0 per 1000 person-years in the 5639 CHS participants without a baseline history of stroke (Table 1). Of 2387 participants hospitalized for infection, 29 (1.2%) had a stroke within 90 days of the hospitalization. Most infections were classified as miscellaneous (ICD-9 codes 1 to 134), respiratory (acute respiratory infections, influenza, and pneumonia), and involving the urinary tract.

After adjusting for age, sex, and race, hospitalization for infection was associated with an increased risk of ischemic stroke in the following 30 days (hazard ratio=2.5; 95% CI, 1.4 to 4.6). The results remained essentially unchanged after additionally adjusting for diabetes and smoking (hazard ratio=2.5; 95% CI, 1.4 to 4.5). Further adjusting for cIMT did not appreciably attenuate the findings (Table 3). Hospitalization for infection during the 14-day time window was associated with a higher point estimate for risk of stroke than was hospitalization during the 30- and 90-day time windows.

The association between hospitalization for infection and risk of stroke was modified by internal cIMT in the 90-day (P=0.04), 30-day (P=0.05), and 14-day (P=0.01) windows, such that the risk of stroke associated with hospitalization decreased with increasing IMT. We found similar interactions with common cIMT. We found no significant interactions with diabetes.

Discussion

We found complementary evidence from case-crossover and survival analyses of an association between hospitalization for infection and stroke risk. A graded, temporal association was evident, such that the risk of stroke was highest within 14 days after hospitalization for infection, with a decreasing but still elevated risk during the subsequent 90 days. The effect was attenuated in survival analyses in which hospitalization for infection was treated as a time-varying exposure, but it remained significant. Many infections in the cohort were either respiratory or involved the urinary tract. These findings support hypotheses that stroke is not merely a stochastic event but is associated with particular triggers, that acute infection is a trigger, and that the risk of stroke may vary by time since infection.11–13

Moreover, we found no evidence of an effect modification by diabetes, although diabetes was a significant covariate in all models. We also found consistent evidence that the association between hospitalization for infection and risk of stroke is modified by cIMT, a subclinical measure of atherosclerosis, although our finding that hospitalization for infection is less strongly associated with incident stroke in the presence of increased carotid IMT may be counterintuitive. Our initial hypothesis was that the risk would be greater among those with preexisting vascular disease. Those with less atherosclerosis, however, may be at higher risk than those with more advanced disease, in whom an acute trigger carries less weight than their intrinsic disease. This finding is consistent with analyses of chronic inflammation as a risk
factor for stroke or atherosclerosis, whereby the effect of inflammation is greater among those with fewer atherosclerotic risk factors. A case-control analysis of recent respiratory infection as a trigger for stroke similarly provided evidence that the effect of infections was attenuated among those at higher underlying risk.

Previous case-control studies have reported that recent infection (for example, within 1 week), primarily upper respiratory infection, is associated with stroke. Such studies are limited, however, by potential confounding owing to underlying risk factors, such as smoking, that could lead to both infection and stroke. In a prospective analysis of >50,000 stroke patients with the case-series method, both recent upper respiratory and urinary tract infections were associated with an increased risk of stroke. The risk of stroke in the 3 days after infection was 3 times as high as during infection-free periods and gradually diminished during the following 3 months. Our results are consistent with those findings and extend them to incident strokes among a biracial group of elderly US residents.

Specific viral infections, such as influenza, have been associated with an increased short-term stroke risk. Case-control studies provide evidence that influenza vaccination is associated with a 50% reduction in risk of stroke. Pilot clinical trials in patients with coronary disease also suggest that vaccination reduces cardiovascular risk. Recent guidelines recommend annual flu vaccination for cardiovascular patients to prevent not only flu but also cardiovascular disease. Further indirect evidence that acute infection precipitates stroke is available from studies of leukocyte count and stroke risk. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial, for instance, patients were monitored for neutropenia, and increases in leukocyte count were associated with a short-term increased stroke risk. Among 211 patients who had an ischemic stroke during follow-up, leukocyte levels in the prior week, but not earlier, were significantly increased above baseline (mean difference, $+5 \times 10^8 \text{cells/L}$).

Several direct biologic mechanisms could account for the increased risk of stroke associated with infections. Severe infections are associated with hypercoagulability and platelet activation that contribute to tissue ischemia and necrosis of many organs during sepsis. Even subacute infections increase platelet reactivity and platelet-leukocyte interactions, leading to an increased risk of platelet aggregation, potentially precipitating stroke. Platelet activation assessed by P-selectin expression, and platelet-leukocyte aggregates, were both increased in stroke patients compared with controls. These effects are even greater among stroke patients with a history of infection within 1 week before stroke. Organisms implicated in causing atherosclerosis and ischemic events have also been associated with platelet aggregation, including Chlamydia pneumoniae, Helicobacter pylori, and periodontal infections.

Infections may also impair endothelial function. Leukocyte count has been related to reduced endothelial reactivity in cross-sectional studies. Acute upper respiratory infections may also transiently impair endothelium-dependent relaxation in children. Among 135 children with acute infection, brachial artery flow-mediated dilation was reduced compared with children 2 weeks out from infection and control children. Brachial artery reactivity of the acutely infected children returned to normal by 1 year later.

More general reasons may also explain why patients hospitalized for infection have stroke. Patients with acute infections may become dehydrated, either because of fever and increased insensible fluid losses, or because of decreased appetite and thirst. Pulmonary infections may increase the chance for cardiac dysfunction and atrial arrhythmias that could lead to embolism. More severely infected patients may become immobilized when hospitalized, increasing the risk for deep venous thrombosis and paradoxical embolism. Data allowing us to classify the specific etiologic subtypes of ischemic stroke were limited. Also, factors that influence admission, rather than infection itself, may be related to the risk of stroke. Patients who are frail or have comorbidities

### Table 3. Association of Recent Hospitalization for Infection With Risk of Ischemic Stroke, Based on Survival Analyses

<table>
<thead>
<tr>
<th>Time Interval After Hospitalization</th>
<th>Unadjusted</th>
<th>Adjusted for demographics (age, sex, black race)</th>
<th>Adjusted for above and diabetes and smoking</th>
<th>Adjusted for above and ln (common carotid intima–media thickness)</th>
<th>Adjusted for demographics, diabetes, smoking, and ln (internal carotid intima–media thickness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 d</td>
<td>4.4 (2.2–9.3)</td>
<td>4.0 (2.0–8.2)</td>
<td>3.9 (1.9–8.0)</td>
<td>3.9 (1.9–7.9)</td>
<td>3.9 (1.9–7.9)</td>
</tr>
<tr>
<td>30 d</td>
<td>2.9 (1.6–5.3)</td>
<td>2.5 (1.4–6.7)</td>
<td>2.4 (1.5–4.9)</td>
<td>2.4 (1.3–4.9)</td>
<td>2.4 (1.3–4.9)</td>
</tr>
<tr>
<td>90 d</td>
<td>2.9 (2.0–4.2)</td>
<td>2.5 (1.7–6.3)</td>
<td>2.4 (1.7–5.3)</td>
<td>2.4 (1.6–3.5)</td>
<td>2.4 (1.6–3.4)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; ln, natural logarithm.
may be more likely to be hospitalized for infection than are healthier patients. Our study has limitations. The number of participants in the time-interval groups was small, and thus, our findings should be interpreted with caution. We relied on hospital discharge codes to identify infections. Thus, our findings cannot be generalized to nonhospitalized infections. We also did not have data on whether patients discontinued use of stroke-protective medications, such as antiplatelet agents, when hospitalized. In addition, our case-crossover analyses may be confounded by participant aging, because both the risk of stroke and hospitalization increase with age.35 We limited this bias by analyzing only the 2 years before stroke, rather than more remote time intervals, and by using a confirmatory study design less susceptible to this bias. We also cannot exclude the possibility that hospitalization itself or factors associated with hospitalization, rather than infection per se, are responsible for the association with stroke. Our study cannot establish causality. Strengths of our study include its well-characterized cohort with a long follow-up and the large number of incident ischemic stroke events. Events were adjudicated by a group of specialists in cerebrovascular disease, and hospital discharge summaries were available in all cases.

The identification of a short-term state of elevated stroke risk after infection could have therapeutic implications. For example, the period during and soon after hospitalization for infection could constitute a “treatable moment,” during which patients could be evaluated for cardiovascular risk and standard preventive strategies could be instituted, including antiplatelet agents and statins. Although we were unable to confirm an effect modification by diabetes but did identify a potential effect modification by atherosclerotic burden, additional studies are needed to determine which patients with acute infection may be at greatest risk. Among those at high risk, there may be a role for increased doses of antiplatelet agents or statins during times of fever or infection, although this approach would require testing in a clinical trial. Alternatively, therapies directed at preventing infectious stressors could be targeted to stroke patients. Currently, guidelines for influenza vaccine36 include patients >50 and debilitated stroke patients at increased risk of respiratory complications. Our results, as well as other recent evidence,23–25 suggest that prevention of influenza in high-risk patients may prevent not only influenza but also stroke.

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Disclosures
None.

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http://stroke.ahajournals.org/content/suppl/2011/05/05/STROKEAHA.110.608588.DC1

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### Supplemental Table: Types and frequencies of infections in the 90 days preceding stroke

<table>
<thead>
<tr>
<th>General infection class</th>
<th>ICD-9 code(s)</th>
<th>Frequency* (% of infections) during case period</th>
<th>Frequency* (% of infections) during control period**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>460-466, 480-487</td>
<td>15 (42%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Assorted</td>
<td>001-134</td>
<td>10 (28%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>599.0, 595, 590</td>
<td>7 (19%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>680-686</td>
<td>2 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>790.7</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>730.0-730.2</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Individuals may have been hospitalized more than once or had multiple ICD9 codes at each hospitalization.

**Data are shown for case-crossover analyses only. Ninety day control periods are 1 and 2 years before the corresponding case period.