Short-Term and Long-Term Risk of Incident Ischemic Stroke After Transient Ischemic Attack

Evan L. Thacker, SM; Kerri L. Wiggins, MS, RD; Kenneth M. Rice, PhD; W.T. Longstreth, Jr, MD, MPH; Joshua C. Bis, PhD; Sascha Dublin, MD, PhD; Nicholas L. Smith, PhD; Susan R. Heckbert, MD, PhD; Bruce M. Psaty, MD, PhD

Background and Purpose—The relative risk of ischemic stroke associated with transient ischemic attack (TIA) is not well defined because most studies of stroke after TIA did not include comparison groups. We sought to estimate short-term and long-term relative risks of ischemic stroke associated with clinically diagnosed TIA.

Methods—We used data from a population-based case–control study. Cases were hypertensive men and women and postmenopausal women, ages 30 to 79, with incident ischemic stroke. Control subjects were sampled within strata of age, sex, hypertension status, and calendar year. The index date was the stroke date for cases and a random date for control subjects. Clinically diagnosed TIA was ascertained from medical records. We used logistic regression to calculate ORs.

Results—The study included 1914 stroke cases and 9874 control subjects. Clinically diagnosed TIA was present in 215 (11.2%) cases and 252 (2.5%) control subjects. Analyses focused on the most recent TIA before the index date. For TIA 1 month before the index date, the adjusted OR for stroke was 30.4 (95% CI, 10.4 to 89.4); for TIA 1 to 3 months before the index date, it was 18.9 (8.58 to 41.6); for TIA 4 to 6 months before the index date, it was 3.16 (1.27 to 7.82); and for TIA >5 years before the index date, it was 1.87 (1.22 to 2.85).

Conclusions—The relative risk of ischemic stroke was high for TIA diagnosed within the past 3 months and moderately high for TIA diagnosed >5 years in the past compared with no history of clinically diagnosed TIA. (Stroke. 2010;41: 239-243.)

Key Words: case–control study ■ epidemiology ■ stroke ■ transient ischemic attack

Transient ischemic attack (TIA) is a risk factor for ischemic stroke, and clinically diagnosed TIA is an opportunity for stroke prevention. Stroke rates after TIA are well characterized, especially over short intervals. Meta-analyses of cohorts of patients with clinically diagnosed TIA have shown the short-term risk of stroke after TIA to be approximately 3% at 2 days, 5% at 7 days, 8% at 30 days, and 9% at 90 days. Some of the studies included in these meta-analyses followed patients with TIA for longer periods, finding stroke risks of 7% to 21% at 1 year after TIA. However, most studies of TIA and stroke risk have focused on patients with TIA without reference to comparison groups of TIA-free individuals. Therefore, the relative risk of stroke in patients with TIA compared with TIA-free individuals is not as well defined.

Studies comparing stroke rates after TIA with expected stroke rates based on age and sex have indicated that the relative risk of stroke after TIA is highest during the early period after TIA and then declines over time but remains elevated for several years. Some study with concurrent follow-up of patients with TIA and TIA-free participants found that TIA was associated with more than twice the risk of ischemic stroke over many years of follow-up but did not assess short-term and long-term relative risks separately. To refine our knowledge of the temporal relationship between TIA and ischemic stroke risk, we sought to estimate short-term and long-term relative risks of incident ischemic stroke associated with clinically diagnosed TIA in a general population in routine care.

Methods

Setting and Design
The setting for this study was Group Health (GH), an integrated healthcare system in western Washington State. The data for these analyses were obtained as part of an ongoing population-based case–control study of myocardial infarction and stroke conducted among GH members from 1989 onward. The study was approved...
by the GH Human Subjects Review Committee. Waiver of consent was granted for patients with language or cognitive difficulties and for patients who had died. All other participants provided verbal consent by telephone or written consent.

Study Participants
Men and women with pharmacologically treated hypertension and postmenopausal women, ages 30 to 79, with ≥4 GH visits were eligible to be included in the study and comprised the study population. Eligible cases and control subjects who refused to give permission to use their medical records were excluded from the study. A total of 93.5% of all eligible stroke cases and 89.7% of all eligible control subjects were included in the study.

Cases were eligible participants with a confirmed incident fatal or nonfatal ischemic stroke that occurred between July 1, 1989, and December 31, 2005. Diagnostic criteria for stroke were adapted from the Cardiovascular Health Study.11 Stroke was defined as the rapid onset of a neurological deficit or subarachnoid hemorrhage with deficits persisting for at least 24 hours (unless death ensued within 24 hours of symptoms or there was evidence of an ischemic or hemorrhagic lesion on CT or MRI consistent with the symptoms) and no underlying brain trauma, tumor, or infection to cause the symptoms. Ischemic stroke was defined as a focal deficit without evidence of blood on CT or MRI (except bleeding secondary to ischemia) or surgery or autopsy evidence of infarction. Incident ischemic or hemorrhagic stroke cases were identified by International Classification of Diseases, 9th Revision codes (430 through 438) and International Classification of Diseases, 10th Revision codes (I63 and I64 through I66) from GH hospitalization discharge records, which included hospital stays at GH facilities and at non-GH facilities and from Washington State death records matched to GH records, which included hospital stays at GH facilities and at non-GH facilities.

Information on estrogen replacement therapy was obtained from the GH computerized pharmacy database. Exposure and Covariates
Exposure and covariate data were collected by abstractors from the GH ambulatory medical records using a standard protocol with structured forms. Data collection from the medical records was restricted to information recorded before the index date. Additional information on smoking status was obtained from telephone interviews conducted with consenting control subjects and surviving cases. Information on estrogen replacement therapy was obtained from the GH computerized pharmacy database.

The exposure of interest was history of TIA. Uniform diagnostic criteria were not used. Instead, TIA diagnosis was based on physician diagnosis as recorded in the medical record. Abstractors recorded whether the medical record, covering a median of 18.7 years of clinical care, contained a clinical diagnosis of TIA at any time before the index date, and calendar year and the following ischemic stroke risk factors: last systolic blood pressure before the index date, history of coronary artery disease (defined as myocardial infarction, angina, coronary angioplasty, or coronary artery bypass grafting), chronic congestive heart failure, atrial fibrillation (classified as current or past), peripheral vascular disease (defined as claudication or a peripheral vascular disease procedure such as angioplasty or bypass grafting of peripheral vessels), carotid endarterectomy, prostatic heart valves, medically treated diabetes, current smoking, and current estrogen use (women only; defined as having received at least one estrogen prescription before the index date with enough estrogen pills to last until the index date, assuming 80% compliance with prescribing instructions).12 Covariate data collected for the time period before the index date were not necessarily restricted to the time period before the most recent TIA.

Statistical Analyses
We used multiple logistic regression to model the association between clinically diagnosed TIA and incident ischemic stroke. ORs from these models can be interpreted as rate ratios because control subjects were sampled according to person-time at risk for ischemic stroke (risk set sampling).13 First, we calculated the OR of ischemic stroke for ever having had a clinically diagnosed TIA. Then we created indicator variables for the following mutually exclusive categories of months from most recent clinically diagnosed TIA to the index date: <1, 1 to 3, 4 to 6, 7 to 12, 13 to 24, 25 to 36, 37 to 48, 49 to 60, and >60 months. For this categorization, if the year of the most recent clinically diagnosed TIA was available but the month was missing (3 cases and 10 control subjects), we considered the TIA to have occurred in the sixth month of the year. We used these indicator variables to calculate the ORs of ischemic stroke for TIA having been clinically diagnosed most recently in each of the time periods with no history of clinically diagnosed TIA as the reference group. Models were adjusted for the matching factors and additional ischemic stroke risk factors listed previously.

We explored whether the pattern of short-term and long-term relative risks differed across strata defined by age group (ages 30 to 69; ages 70 to 79), sex, and treated hypertension status (among women only; all of the men in the study had treated hypertension). The numbers of cases and control subjects with past TIA were too small in some of the time intervals described to assess interactions across all the time intervals, so for these exploratory analyses, we collapsed the time intervals from most recent TIA to index date into one short-term category (≤3 months) and one long-term category (≥4 months) and created interaction terms for these categories with age group, sex, and hypertension.

Results
The study included 1914 incident ischemic stroke cases (mean age, 69.7 years; 1282 [67.0%] women) and 9874 control subjects (mean age, 65.9 years; 5304 [53.7%] women). Ischemic stroke cases compared with control subjects were more likely to have cardiovascular conditions such as coronary heart disease, chronic congestive heart failure, and atrial fibrillation and to have a greater burden of vascular risk factors such as diabetes and current smoking (Table 1).

There were 215 (11.2%) ischemic stroke cases and 252 (2.5%) control subjects with clinically diagnosed TIA before the index date (Table 2). Among ischemic stroke cases with a history of clinically diagnosed TIA, the temporal distribution of the most recent TIA diagnosis was heavily concentrated in the few months before the index date, whereas
among control subjects, this distribution was relatively uniform and the prevalence was much lower (Figure 1).

The OR of ischemic stroke for having clinically diagnosed TIA at any time in the past was 4.21 (95% CI, 3.45 to 5.14) adjusted for the matching factors age, sex, hypertension status, and calendar year, and was 3.85 (95% CI, 3.08 to 4.82) adjusted for additional ischemic stroke risk factors. Analyses accounting for the timing of the TIA diagnosed most recently before the index date revealed a high short-term relative risk and moderately high long-term relative risk for ischemic stroke (Figure 2). The fully adjusted ORs were 30.4 (95% CI, 10.4 to 89.4) for most recent TIA diagnosed 1 month before index date, 18.9 (95% CI, 8.58 to 41.6) for 1 to 3 months, and 3.16 (95% CI, 1.27 to 7.82) for 4 to 6 months before the index date. For most recent TIA diagnosed >5 years before the index date, the fully adjusted OR was 1.87 (95% CI, 1.22 to 2.85).

Table 1. Characteristics of Ischemic Stroke Cases and Control Subjects, 1989 to 2005

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ischemic Stroke Cases (n=1914)</th>
<th>Control Subjects (n=9874)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>69.7 (8.5)</td>
<td>65.9 (9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, %</td>
<td>67.0</td>
<td>53.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated hypertension, %</td>
<td>75.8</td>
<td>73.6</td>
<td>0.051</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, mean (SD)</td>
<td>145.4 (22.7)</td>
<td>138.6 (19.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>31.3</td>
<td>19.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic congestive heart failure, %</td>
<td>12.7</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current, %</td>
<td>14.1</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past, %</td>
<td>5.2</td>
<td>2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>9.3</td>
<td>4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid endarterectomy, %</td>
<td>1.8</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prosthetic heart valves, %</td>
<td>1.3</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29.2</td>
<td>11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>15.3</td>
<td>11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current estrogen use (women), %</td>
<td>17.8</td>
<td>20.0</td>
<td>0.068</td>
</tr>
</tbody>
</table>

* t tests for differences of means; χ² tests for differences of proportions.

Table 2. History of Clinically Diagnosed TIA in Ischemic Stroke Cases (n=1914) and Control Subjects (n=9874)

<table>
<thead>
<tr>
<th>History of Clinically Diagnosed TIA</th>
<th>Ischemic Stroke Cases</th>
<th>Control Subjects</th>
<th>OR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never, n (%)</td>
<td>1699 (88.8)</td>
<td>9622 (97.5)</td>
<td>1</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever, n (%)</td>
<td>215 (11.2)</td>
<td>252 (2.5)</td>
<td>3.85 (3.08 to 4.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Most recent TIA prior to index date†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month, n (%)</td>
<td>27 (1.41)</td>
<td>4 (0.04)</td>
<td>30.4 (10.4 to 89.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1–3 months, n (%)</td>
<td>39 (2.04)</td>
<td>10 (0.10)</td>
<td>18.9 (8.58 to 41.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4–6 months, n (%)</td>
<td>12 (0.63)</td>
<td>19 (0.19)</td>
<td>3.16 (1.27 to 7.82)</td>
<td>0.013</td>
</tr>
<tr>
<td>7–12 months, n (%)</td>
<td>13 (0.68)</td>
<td>21 (0.21)</td>
<td>1.88 (0.97 to 3.64)</td>
<td>0.062</td>
</tr>
<tr>
<td>13–24 months, n (%)</td>
<td>29 (1.52)</td>
<td>32 (0.32)</td>
<td>4.70 (2.67 to 8.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25–36 months, n (%)</td>
<td>17 (0.89)</td>
<td>19 (0.19)</td>
<td>3.00 (1.34 to 6.68)</td>
<td>0.007</td>
</tr>
<tr>
<td>37–48 months, n (%)</td>
<td>12 (0.63)</td>
<td>25 (0.25)</td>
<td>2.42 (1.14 to 5.10)</td>
<td>0.021</td>
</tr>
<tr>
<td>49–60 months, n (%)</td>
<td>16 (0.84)</td>
<td>23 (0.23)</td>
<td>2.74 (1.31 to 5.70)</td>
<td>0.007</td>
</tr>
<tr>
<td>&gt;60 months, n (%)</td>
<td>42 (2.19)</td>
<td>96 (0.97)</td>
<td>1.87 (1.22 to 2.85)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*ORs are adjusted for age, sex, hypertension status, calendar year, systolic blood pressure, coronary heart disease, chronic congestive heart failure, atrial fibrillation, peripheral vascular disease, carotid endarterectomy, prosthetic heart valves, medically treated diabetes, current smoking, and current estrogen use.

†Data on the timing of the most recent TIA in relation to the index date was available for 207 (96.3%) of ischemic stroke cases with TIA and 249 (98.8%) of control subjects with TIA. Eight ischemic stroke cases with TIA and 3 control subjects with TIA had no data on the timing of the most recent TIA and were dropped from analyses of time intervals from TIA to index date.
Ischemic stroke risk was also elevated, although clinically diagnosed TIA and ischemic stroke remained several times greater than ischemic stroke cases. Odds ratios are adjusted for age, sex, hypertension status, calendar year, systolic blood pressure, coronary heart disease, chronic congestive heart failure, atrial fibrillation, peripheral vascular disease, carotid endarterectomy, prosthetic heart valves, medically treated diabetes, current smoking, and current estrogen use.

In exploratory analyses, when we collapsed the time intervals from most recent TIA to the index date into one short-term category (≤3 months) and one long-term category (≥4 months), the ORs were 22.2 (95% CI, 11.8 to 41.9) for most recent TIA ≤3 months before the index date and 2.58 (95% CI, 2.00 to 3.32) for most recent TIA ≥4 months before the index date. This pattern of high short-term relative risk and moderately high long-term relative risk was similar across all strata we examined. We observed no significant differences in models of the short-term and long-term ORs for younger (ages 30 to 69 years) versus older (ages 70 to 79 years) age groups (P=0.24), for women versus men (P=0.06), or for nonhypertensive women versus hypertensive women (P=0.12).

**Discussion**

In this population of men and women with treated hypertension, and postmenopausal women, TIA diagnosed most recently within the past 3 months was associated with short-term ischemic stroke risk 20 to 30 times greater than ischemic stroke risk for patients without a history of clinically diagnosed TIA. Ischemic stroke risk was also elevated, although to a lesser degree, for TIA diagnosed 4 months to 5 years in the past. For patients with TIA diagnosed ≥5 years in the past, long-term ischemic stroke risk was nearly twice as high as for patients without a history of clinically diagnosed TIA.

The short-term and long-term relative risks we observed in our study were similar to the relative risks observed in prior studies. In the Oxfordshire Community Stroke Project, the observed stroke incidence among patients with TIA was compared with the expected stroke incidence based on age and sex. The age- and sex-adjusted relative risk of stroke after TIA was estimated as 80.0 during the first month, 13.4 during the first year, and ranged from 4.7 to 6.4 during 5 subsequent years, similar to the temporal pattern observed in our study. In Rochester, Minn, the observed stroke incidence among patients with TIA compared with the expected stroke incidence based on age and sex yielded relative risk estimates of 16.5 during the first year after TIA and 9.5 during the full follow-up period averaging 7 years after TIA. In the Rotterdam Study, the relative risk of stroke after TIA was estimated using a comparison cohort of TIA-free individuals and adjustment for many potential confounders. The relative risk of ischemic stroke over an average of 10 years of follow-up, adjusted for age, sex, and a propensity score based on TIA and stroke risk factors, was estimated as 2.5, similar to the long-term relative risk seen in our study.

A strength of our study was that ischemic stroke cases and control subjects were drawn from a defined population with clinically diagnosed TIA documented prospectively in medical records before the occurrence of stroke. Other strengths of our study were a high proportion of participation among eligible participants in a general population in routine care, data collection according to the same structured protocol for cases and control subjects, and adjustment for many stroke and TIA risk factors.

A limitation of our study was the lack of more detailed information about TIA history among the ischemic stroke cases and control subjects. We did not have data on specific TIA characteristics that would have allowed uniform application of TIA diagnostic criteria; instead, we relied on the treating physician’s diagnosis of TIA as documented in the medical records. We also did not have results of neuroimaging performed at the time of clinical evaluation for TIA, although neuroimaging has been recognized as an important component of accurate TIA diagnosis. We did not have the date of the first ever clinically diagnosed TIA or the total number of TIA cases in the past (we only had the month and year of the most recent TIA). Therefore, we could not address the question of stroke risk associated with first TIA. However, another study of TIA history in patients with stroke found that the distribution of time from most recent TIA to stroke was similar to the distribution of time from first TIA to stroke with both the first TIA and the most recent TIA tending to have occurred in the recent period before stroke rather than in the distant past. Another limitation of our study was the possibility of a diagnostic bias, in which a past diagnosis of TIA may make patients more likely to seek care for stroke symptoms and physicians more likely to diagnose stroke given certain symptoms. Other limitations of our study were that nonhypertensive men were not included, and covariate data collected for the time period before the index date were not necessarily restricted to the time period before the most recent TIA. Finally, the numbers of TIA cases occurring during some of the discrete time intervals before stroke were small; therefore, the adjustment for confounding was not as good for the smaller categories as for the larger categories.

TIA and ischemic stroke share the same set of risk factors; therefore, an association between TIA and ischemic stroke could arise simply because of these shared factors. However, when we adjusted our models for risk factors including age, sex, hypertension, cardiovascular disease history, diabetes, current smoking, and estrogen use, the association between clinically diagnosed TIA and ischemic stroke remained...
strong, suggesting that clinically diagnosed TIA was not solely a marker for stroke risk factors documented in the medical record, but was also a marker for underlying ischemic stroke risk that was not discernible based on the other factors documented in the medical records. Factors that could partially explain the association between TIA and ischemic stroke include subclinical vascular disease manifestations such as carotid artery plaques or stenoses.

We did not evaluate the impact of clinically diagnosed TIA on subsequent risk factor evaluation and management among our study participants. Stroke prevention efforts initiated or enhanced after TIA may have increased during the years of our study (1989 to 2005) because TIA was becoming more widely recognized as an emergency opportunity for stroke prevention.16 To the extent that ischemic stroke was actually prevented after TIA in the population we studied, our results would have underestimated the association between TIA and ischemic stroke.

The results of our study emphasize that both short-term and long-term ischemic stroke risks are relevant to patients with clinically diagnosed TIA. Based on a growing body of evidence from observational and experimental studies, recent guidelines emphasize the urgency of evaluating patients with TIA and implementing treatment and risk factor control for stroke prevention.17,18 Based on our results, the opportunity for more effective stroke prevention would appear to be greatest in the short term, within the first 3 months after TIA diagnosis, but prevention opportunities would likely persist through the long term, even ≥5 years after clinically diagnosed TIA.

Acknowledgments
We thank the participants and staff of the Heart and Vascular Health Studies.

Sources of Funding
This research was supported in part by grants HL043201, HL068639, HL073410, HL074745, HL085251, and HL087652 from the National Heart, Lung, and Blood Institute (NHLBI). E.L.T. was supported by NHLBI training grant T32 HL007902. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NHLBI or the National Institutes of Health.

Disclosures
None.

References
Short-Term and Long-Term Risk of Incident Ischemic Stroke After Transient Ischemic Attack

Evan L. Thacker, Kerri L. Wiggins, Kenneth M. Rice, W.T. Longstreth, Jr, Joshua C. Bis, Sascha Dublin, Nicholas L. Smith, Susan R. Heckbert and Bruce M. Psaty

Stroke. 2010;41:239-243; originally published online December 3, 2009;
doi: 10.1161/STROKEAHA.109.569707

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/41/2/239

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/