Reevaluation of Transient Ischemic Attacks as a Risk Factor for Early Mortality

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The prevailing belief that transient ischemic attack is a risk factor for cardiovascular morbidity and mortality is based primarily on comparisons of survival of patients after transient ischemic attacks to that of an age-, race-, and sex-adjusted general population. Concomitant conditions that carry a high risk of premature mortality or morbidity, such as ischemic heart disease, hypertension, and diabetes, are very prevalent among patients with transient ischemic attacks. Hence, the poor prognosis of such patients may be attributable to these factors rather than their transient ischemic attack per se, which may only serve to bring patients into the medical system. We compared the survival of 336 patients after transient ischemic attack to that of a control group with a similar risk factor profile consisting of 6,710 patients evaluated for cardiac catheterization. Survival estimates, both unadjusted and adjusted for risk factors, did not differ between the two groups. Three-year survival estimates, after adjustment to the mean value of covariates, were 94% for the patients with transient ischemic attacks and 91% for the controls. These results suggest that the transient ischemic attack may not be an independent risk factor for mortality, although it may identify patients already at increased risk from coexisting conditions. (Stroke 1991;22:582–585)

As long ago as the early 1950s, Fisher and Cameron expressed a concern that transient ischemic attacks (TIAs) were associated with an increased risk of cerebrovascular events. Such comments initially stressed the increased risk of stroke in TIA patients, but at that time, or indeed today, there were no reliable estimates of the expected incidence of stroke in the general population. Although the stroke rate in the TIA population could be estimated from available data on TIA patients, without knowledge of the stroke rate in the general population, the excess risk of stroke associated with TIA could not be estimated.

Many authors, including ourselves, contrasted the survival of TIA patients to that of an age-, race-, and sex-matched general population. These reports generally showed the survival of TIA patients to be significantly worse than would be expected in the general population and the cause of death in the TIA population to be most often coronary, rather than cerebrovascular, disease.

However, based on data from the Cooperative Study of Transient Ischemic Attacks and our own TIA population, TIA patients have a significantly higher prevalence of cerebrovascular and coronary heart disease risk factors, including hypertension, ischemic heart disease, diabetes, cigarette smoking, and previous stroke, than is present in the general population. We have shown previously in our TIA cohort that patients with none of these risk factors, and even TIA patients with a single risk factor, fare as well as the age-, race-, and sex-matched general population. In contrast, those TIA patients with two or more of these risk factors have survival estimates that are clearly less than that of the general population. Because most TIA patients have two or more risk factors and because these risk factors so dramatically affect survival, the comparison of the survival of TIA patients to a general population is biased toward showing a relatively poor prognosis for TIA patients. To evaluate the hazard associated with TIA while minimizing the confounding from other risk factors, we first selected a more comparable control group and then removed remaining differences in risk factors through covariate analysis.

Subjects and Methods
We performed a case/control analysis contrasting the survival of TIA patients (cases) with that of a
control group having roughly equivalent risk factor prevalence. We chose the group of patients admitted for cardiac catheterization (CATH) as the control group because their prevalence of major risk factors was similar to that observed in our TIA population.

Since the early 1970s, the Department of Neurology and Section of Cardiology at North Carolina Baptist Hospital has maintained TIA and cardiac catheterization registries that provide historical information regarding risk factors for cardiovascular disease and comorbid conditions. In the case of the TIA registry, a standard questionnaire assessing traditional and nontraditional risk factors for cerebrovascular and coronary heart disease, including smoking behavior and history of hypertension and diabetes, was administered by trained interviewers during hospitalization, with methods detailed elsewhere. Data for the catheterization registry were collected using a standard questionnaire assessing similar traditional cardiovascular risk factors. Patient report was used to establish a history of hypertension, diabetes, ischemic heart disease, previous stroke, and cigarette smoking. Unfortunately, definitions differed on smoking, with the TIA patient smoking history being recorded as ever/never (ever=current+past smoking; never=never smoking), whereas the CATH patient smoking history was recorded as current/nonsmoking (current=current; nonsmoking=past+never). Because smoking is considered an important risk factor, the analysis was performed both with and without smoking as a covariate.

Based on a previously reported algorithm,10 we determined deaths in both cohorts using information supplied from the National Death Index. Patients who matched National Death Index death records were classified as deceased if 1) the death occurred in North Carolina, the social security number (if present on both records) matched on at least eight digits, and the first name matched exactly or both phonetically and on first initial; 2) the death occurred outside of North Carolina, but the social security number matched on all nine digits; or 3) the death occurred in one of nine southeastern states, our records listed no social security number, the day of the month born matched exactly, and the year of the birth matched within 10 years. Vital status was known through the National Death Index and the identical algorithm that date, resulting in a TIA study cohort of 338 patients (accrued between 1979 and 1984). Details of their accrual are available in these previous publications. The control group consisted of the 6,872 patients admitted to North Carolina Baptist Hospital during the same period for cardiac catheterization. Because we wished to eliminate surgical mortality (primarily due to endarterectomy for TIA patients and coronary artery bypass grafts for CATH patients) associated with the specific admission, we then excluded all patients who died during the first 30 days after admission for both groups, and survival analysis was performed conditional to the patients surviving this initial period. This exclusion process removed two TIA patients (1%) and 162 CATH patients (2%) from the study population, leaving 336 TIA patients and 6,710 CATH patients for use in the subsequent analysis.

We then used proportional hazards (Cox regression) modeling to establish significant risk factors related to survival. After these factors had been established, we considered the patient group (TIA versus CATH) in this model to test the marginal risk associated with TIA after adjustment for residual differences in risk factor profiles of the two groups. This modeling procedure allows for the control of biasing factors and is an accepted alternative to matching or stratification in case/control studies.11,12 Survival estimates for both groups were produced at the mean level of covariates using techniques detailed by Kalbfleisch and Prentice.13

### Results

Table 1 shows the prevalence of major risk factors for both groups. The TIA group was, on average, older and had a higher prevalence of hypertension, previous stroke, and cigarette smoking, but a lower prevalence of ischemic heart disease. However, if one
TABLE 2. Proportional Hazard Estimates of the Effect of Significant Demographic and Risk Factors on Survival

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.300</td>
<td>0.0003</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>1.378</td>
<td>0.0114</td>
</tr>
<tr>
<td>Age*</td>
<td>1.634</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.652</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.271</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.307</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.638</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Effect of age was estimated for a 10-year interval.

discards the number of major risk factors, the two populations have remarkably similar distributions.

The survival of the TIA and CATH groups, unadjusted for differences in risk factor profiles, did not differ significantly (p>0.05). To remove any residual differences in the specific risk factors between the two populations, we developed a proportional hazards model relating demographic and risk factors to survival. In this analysis, we found that sex, race, age, diabetes mellitus, hypertension, cigarette smoking, and previous stroke were jointly associated with survival. In this analysis, we found that sex, race, age, diabetes mellitus, hypertension, cigarette smoking, and previous stroke were jointly associated with survival.

Figure 1 shows the survival curves, adjusted to the mean level for all covariates. We found similar results (no differences between TIA and CATH) when smoking was omitted as a covariate.

**Discussion**

There was no significant difference between the survival of TIA patients and that of a control group with a similar risk factor profile. This may imply that differences in survival between TIA patients and the general population result from different risk factor prevalences in the two populations, rather than being an independent effect of TIAs. It should be expected that the TIA population would have a higher mortality, as well as stroke and myocardial infarction rates, than the general population, given the prevalence of major risk factors in TIA patients. Previous studies may have implicated TIA as a risk factor for mortality because they failed to control for these different concomitant disease prevalences. Clearly, the proportion of these concomitant diseases in the general population is far less than that observed in the TIA population. The population chosen for comparison in the present report is reasonably similar to other reported TIA series because it has a very high prevalence of concurrent diseases, which are themselves major risk factors for early mortality. We then tried to remove the effect of remaining differences in the risk factor profile of the two groups using covariate analysis.

This study has a number of limitations. First, although the workup of the TIA and CATH patients was similar, it was not performed under the same protocol. It is natural to assume that the neurologists responsible for the TIA patients were more aware of mild cerebrovascular events than were the cardiologists responsible for the CATH patients. Conversely, the cardiologists would be more sensitive to mild cardiovascular symptoms. Not only does this introduce inconsistent measurement errors between the two groups, but it also allows for some contamination of the control group (CATH) of individuals with undiagnosed TIAs. Nevertheless, we believe this contamination to be minimal, although we have no evidence to support this belief. Also, because we could not examine nonfatal cerebrovascular or myocardial infarction events, we cannot dismiss the possibility that TIAs may serve as an independent indicator of excess risk for future nonfatal coronary or cerebrovascular events. Lastly, the two populations were similar in the number of risk factors, but there were considerable differences in prevalence of specific risk factors. Statistical modeling techniques employed in this report are one of the three well-accepted methods to adjust for such differences. Many of these concerns will be more directly addressed through the prospective study, currently gathering risk factor data and following similar TIA and coronary patients.

Most importantly, although these data suggest that TIAs may not represent an independent risk factor for mortality, they still may be viewed as a marker for other significant concurrent diseases. That is, our data support the position that the TIA itself is not a risk factor for early mortality; however, they do identify a group of patients who have risk factor profiles greatly exceeding those of the general population. As such, an extensive workup of these patients to establish the exact extent of known risk factors and to discover risk factors that are present but previously undocumented appears quite warranted. In addition,
as heart disease continues to be highly prevalent in the TIA population and continues to be the leading cause of death in this population, involvement of cardiologists in this evaluation would appear sound.

Acknowledgments
The authors wish to express their appreciation for the ongoing discussions and input of Dr. James F. Toole, who was particularly helpful in the development of this manuscript. Also, we wish to acknowledge the valuable contributions of Joni Brockschmidt Evans, MS, who contributed the development of the algorithm for the categorization for the National Death Index.

References

KEY WORDS: cerebral ischemia, transient • mortality • risk factors
Reevaluation of transient ischemic attacks as a risk factor for early mortality.
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Stroke. 1991;22:582-585
doi: 10.1161/01.STR.22.5.582

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/22/5/582

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