A Prospective Reevaluation of Transient Ischemic Attacks As a Risk Factor for Death and Fatal or Nonfatal Cardiovascular Events

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Background and Purpose Transient ischemic attack (TIA) is generally considered a risk factor for death and cardiovascular events. This assumption is based on comparisons of the survival of the TIA population with that of the general population. Such comparisons may provide biased estimates of the risk associated with TIA because the general population is usually more healthy than TIA patients.

Methods Using a prospective case-control study design, we report the comparison of a TIA population (n=280) and a control group (n=399) with a comparable cardiovascular risk factor burden. Proportional hazards analysis was used to compare survival time and time to fatal or nonfatal stroke and/or myocardial infarction for the two study groups. Comparisons were made without adjustment for risk factors and after adjustment for age, race, sex, and major cardiovascular risk factors.

Results Before adjustment for age-race-sex or risk factors, TIA proved to be a risk factor for early mortality, stroke, and myocardial infarction (P<.05). Adjustment for age-race-sex disparities between the case and control groups explained much of the differences in mortality, as the hazard ratio was reduced from 2.2 to 1.4. However, adjustment for age-race-sex or age-race-sex and risk factors did not markedly reduce the role of TIA as a risk factor for stroke or myocardial infarction.

Conclusions Although TIA proved to be a risk factor for stroke or myocardial infarction, it apparently plays a smaller role in the risk of death.

Key Words • cerebral ischemia, transient • mortality • risk factors • survival

Transient ischemic attack (TIA) has long been considered a risk factor for stroke, myocardial infarction (MI), and death. This assumption has been made based on the comparison by many investigators, including ourselves, of the survival of TIA patients to an age-, race-, and sex-matched general population. In addition to the presence of the TIA symptom, TIA patients generally have a higher prevalence of concomitant diseases and major cardiovascular risk factors than the general population. Because of their excess risk burden, the comparison of TIA patients with the general population is inappropriate because it is not clear whether to attribute excess risk to the TIA per se or to the excess prevalence of other risk factors. Recently we retrospectively compared the survival of a cohort of 336 TIA patients with a group of patients with a similar risk factor burden and found no excess mortality associated with TIA. This comparison suggested that TIAS may not be strongly predictive for all-cause mortality, although they may identify patients already at increased risk from coexisting conditions.

In this report we describe a comparison of a new cohort of 280 TIA subjects and 399 control subjects, both accrued and followed prospectively using a similar protocol. In addition to mortality, we also report the evaluation of TIA as a risk factor for fatal or nonfatal cardiovascular events.

Subjects and Methods

An unmatched case/control analysis was used to contrast the outcome of TIA patients (cases) with that of a TIA-free control group having approximately the same degree of cardiovascular risk factors. To obtain a control group with a similarly high prevalence of cardiovascular risk factors, patients admitted for cardiac catheterization (CATH) were selected as the control group.

The study goal of screening for TIA patients was to identify all TIA patients seen at Bowman Gray. Because virtually all TIA patients, regardless of primary clinical department, are seen in the clinical ultrasound laboratory, this site was chosen as the focus of the screening effort. Patients referred to the laboratory include both hospital inpatients, outpatients referred from the Wake Forest University Physicians Clinics, and outpatients referred by other physicians in the community or region. The most frequent clinical reason for referral is cerebral ischemia, either TIA or completed stroke. Other sources of referrals include asymptomatic bruit, multiple risk factors, preoperative screening, and serial evaluation of known carotid disease. TIA patients were prospectively identified by screening more than 6000 patients evaluated in the noninvasive cerebrovascular ultrasound laboratory at North Carolina Baptist Hospital between August 1987 and July 1991. Initial screening was performed using a TIA questionnaire validated by the Asymptomatic Carotid Atherosclerosis Study. TIA patients were excluded for the following reasons: (1) stroke ipsilateral to the TIA, (2) MI or stroke in the past 6 weeks, (3) active cancer, (4) alcohol intake greater than 170 g/d, (5)
chronic kidney disease, (6) chronic liver disease, (7) class IV heart disease, (8) low hemoglobin (men, less than 12.5; women, less than 10.8), and (9) TIA more than 1 month before evaluation. Two hundred eighty TIA patients were identified through this process. Once a potential subject was identified, the participant was examined and interviewed to establish risk factor status (details described elsewhere). Records of the examination and interview, along with medical records, were reviewed by neurologists (C.T. and J.F.T.) and nurse specialists (J.F.-P. and E.M.) at weekly meetings to verify the TIA status.

The goal of control selection was to identify a cohort of patients similar to the TIA cohort but without the TIA symptom. Control subjects were selected among patients admitted for cardiac catheterization to North Carolina Baptist Hospital. Nonneurological exclusions were identical to the TIA cohort, with the additional exclusion for TIA based on the same questionnaire that is used to access subjects into the TIA arm of the study. A stratified random sampling strategy was defined by sex and 10-year age band, and samples were drawn within strata to maintain approximate proportional balance with that observed in the TIA cohort. Three hundred ninety-nine control subjects were selected. These patients were mainly admitted for examination of chest pain (70%) or valvular heart disease (30%). At the time of catheterization the following distribution of coronary disease conditions was found: no coronary disease (normal coronary arteries), 17%; nonobstructive coronary artery disease (less than 50% stenosis of all arteries), 13%; and obstructive coronary artery disease (greater than 50% stenosis of any artery), 70%. The control subjects were evaluated the evening before catheterization by the same instrument used for TIA patients. Patients in the CATH cohort received standard medical treatment for their condition as determined by their primary attending physician.

Both the TIA (case) and CATH (control) cohorts were followed for subsequent events using a single blinded system. Participants, or their relatives, were contacted at 6-month intervals soliciting information on strokes or MIs occurring during the follow-up period, hospitalizations, or death. The median follow-up time was more than 2 years (range, 6 months to 4 years). If a stroke or MI event, hospitalization, or death was reported, a release to obtain hospital chart records was solicited. The hospital records were reviewed at the weekly staff meetings by physicians and nurse specialists to verify stroke or MI events.

Standard statistical techniques were used to establish differences between the case and control groups in the time until (1) death from any cause, (2) stroke (fatal or nonfatal), (3) MI (fatal or nonfatal), (4) stroke or MI (fatal or nonfatal), and (5) any event (stroke, MI, or death from any cause). Proportional hazards analysis (Cox regression) was used to examine differences between groups (1) univariately, (2) after adjustment for age, race, and sex; and (3) after adjustment for age, race, sex, and major cardiovascular risk factors. Adjustments were made to the mean value of demographic or risk factor, which was arbitrarily chosen to represent the "average" of the patient population. Risk factors considered in the adjustment include hypertension, diabetes, smoking habit, race, sex, previous MI, and previous stroke (in case subjects, the stroke was contralateral to the TIA). Differences between the risk of the five types of events in the case and control groups were summarized by the hazard ratio, which is the ratio of the instantaneous probability of an event (conditional on being event free) between the case and control populations.

Results

A description of the two study groups is provided in Table 1. The TIA (case) group was marginally older, with a higher prevalence of previous stroke and hypertension. Conversely, the CATH (control) group had a greater proportion of men and a higher prevalence of previous MI. The two groups had a similar proportion of blacks and similar prevalence of diabetes and smoking.

Results for the five study end points are provided in Table 2. The estimated death rate in the TIA group was 6.2% at 1 year and 12.2% at 3 years, whereas the death rate in the CATH group was only 2.9% at 1 year and 5.8% at 3 years. The lower death rate in the CATH group proved significant (P=.0109), with an estimated hazard ratio of 2.2 (TIA relative to CATH). However, adjustment for age-race-sex reduced the estimated hazard ratio to 1.4, and the difference between the groups was no longer significant (P=.32). Additional adjustment (after adjustment for age-race-sex) for risk factors did not notably affect the hazard ratio or significance of group differences.

The estimated incidence of fatal or nonfatal stroke in the TIA group was 5.4% in the first year and increased to 7.8% by 3 years. The stroke rate in the control group was 1.5% in the first year and only 2.7% by the end of 3 years. The estimated univariate hazard ratio for stroke risk was 3.0, and the difference between groups proved significant (P=.0061). Adjustment for age-race-sex (or age-race-sex and risk factors) tended to increase the differences between the TIA and CATH groups.

The estimated incidence of fatal or nonfatal MI for the TIA group was 5.0% in the first year and 10.9% at 3 years. In comparison, the MI rate for the CATH group at 1 and 3 years was 1.8% and 4.1%, respectively. The estimated univariate hazard ratio was 2.8, and the difference between groups was highly significant (P=.0035). Adjustment for age-race-sex (or age-race-sex and risk factors) reduced the estimated hazard ratio to 2.3, and the difference between groups remained significant (P=.0298).

The estimated incidence of fatal or nonfatal stroke or MI (the first occurrence of either) was 9.5% in the first year for the TIA group and only 3.5% for the CATH group. By the end of 3 years the estimated stroke or MI rate was 17.9% for the TIA group and 6.8% for the

<table>
<thead>
<tr>
<th>Table 1. Description of Study Groups</th>
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<tr>
<td><strong>TIA Cases</strong></td>
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</tr>
<tr>
<td><strong>Age, y</strong></td>
</tr>
<tr>
<td>Mean</td>
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<tr>
<td>25th Percentile</td>
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<tr>
<td>50th Percentile (median)</td>
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<tr>
<td>75th Percentile</td>
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<tr>
<td><strong>Male sex</strong></td>
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<tr>
<td>50%</td>
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<tr>
<td><strong>Black race</strong></td>
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<tr>
<td>6%</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction</strong></td>
</tr>
<tr>
<td>17%</td>
</tr>
<tr>
<td><strong>Previous stroke</strong></td>
</tr>
<tr>
<td>12%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td>65%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
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<tr>
<td>15%</td>
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<tr>
<td><strong>Smoking habit</strong></td>
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<tr>
<td><strong>Previous smoker</strong></td>
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<td><strong>Current smoker</strong></td>
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TIA indicates transient ischemic attack.
CATH group. The estimated univariate hazard ratio was 2.8 ($P = .0001$), and it was not markedly affected by adjustment for age-race-sex (or age-race-sex and risk factors).

Finally, the event rate for incidence of any event (nonfatal stroke or MI, or death from any cause) was 12.9% in the first year and 24.6% in 3 years for the TIA group. The rate was lower for the control group (4.8% and 9.7%) at 1 and 3 years, respectively. The estimated univariate hazard ratio was 2.8 ($P = .0001$); it was only marginally affected by control for age-race-sex (or age-race-sex and risk factors).

**Discussion**

These data suggest that TIA is a significant risk factor for fatal or nonfatal stroke and MI when compared with a control group of patients selected from those obtaining a cardiac catheterization. There were residual differences in the risk factor profile of the TIA (case) and CATH (control) groups; however, covariate adjustment for these differences did not significantly reduce the relative risk of stroke and only marginally decreased the relative risk of MI. The hazard for a stroke was three or more times greater in those patients with TIAS compared with the control group. TIA patients also had a hazard more than two times greater for an MI. Finally, TIA patients were at increased risk for the combined end points of fatal stroke or MI, and nonfatal stroke or MI or death from any cause, with an estimated hazard more than 2.5 times greater than the control group.

In contrast, after adjustment for age-race-sex differences between the TIA and CATH groups, there was no significant difference between the two groups in the risk of death. The nonsignificant difference in death rate confirms the findings from our earlier retrospective study. The estimated hazard ratio for death was approximately 1.4. That there was an excess of both stroke and MI (fatal or nonfatal) in the TIA group would, of course, suggest there should be increased risk of death. However, a marginally higher rate of nonfatal stroke and MI events in the TIA group, an excess of deaths from other causes in the CATH group, contributed to the lack of difference in the risk of death between the groups. Although the slight increase in the risk of death for the TIA group was not significant in this study, given the increased number of stroke and MI events for the TIA patients we expect that it would be likely to reach significance with either a larger sample size or longer follow-up.

This study also provides data on the expected event rate in a series of TIA patients (see univariate rows of Table 2). Interestingly, 5.4% of the TIA patients had a stroke in the first year of follow-up, with only an additional 2.3% during the next 2 years. The excess risk of MI during the year following TIA was only marginally above the risk in the second and third years, with 5.0%
in the first year, 8.5% in the first 2 years (an additional 3.5%), and 10.9% by the end of the third year (an additional 2.4%). Likewise, there was also a slight increase in the chance of death among TIA patients during the first year, in that 6.2% died in the first year and 12.2% died by 3 years. Perhaps most interesting is the rate of the combined event of "nonfatal stroke or MI or death from any cause"; nearly one quarter (24.6%) of the TIA patients experienced at least one of these events by the end of 3 years.

We attempted to select a control group that was similar to the TIA case group, with the exception of the absence of the TIA symptom. Because of the extremely high prevalence of concomitant diseases in the TIA group, it is difficult to identify a source of patients with a similarly high risk. We believe that the CATH group represents a reasonable control group because (1) they are hospitalized at the same center and are likely to represent similar referral populations and (2) they have a similarly high concomitant disease burden. However, no control group is "perfect," and clearly the optimal approach to establishing the risk of TIA is a prospective study in which TIA is identified in a general population and followed forward. Unfortunately, TIA is too rare for this design to be fiscally possible, and hence we relied on the case-control design.

Despite a generally similar distribution of demographics and risk factors in the case and control populations, some differences did persist. Although there was an excess of deaths in the TIA group, this difference proved attributable to the slightly older age of the TIA cohort. However, the excess of stroke and MI (fatal or nonfatal) was not attributable to differences in demographics or risk factors between the two groups. While the increased risk for stroke in the TIA group was larger than that for MI, we were surprised that the TIA group proved to have any increased risk of MI at all when compared with patients admitted for cardiac catheterization. It is possible that this relative increased risk is a product of intensive cardiac management of the CATH group rather than a natural increased risk attributable to the TIA symptom.

The statistical adjustment for age-race-sex (or age-race-sex and risk factors) appears to reduce the estimated event rates for both the TIA (case) and CATH (control) groups. This reduction is a statistical artifact, as the rates are estimated from proportional hazards at an arbitrary level of the covariates. In this report, that arbitrary level was chosen as the mean value for the covariates (eg, age of 62.3 years, 24.3% with previous MI, etc). Because a disproportionate number of the events were among those with the more extreme risk factor profiles, adjustment to the mean (lower) levels makes the estimated number of events appear lower. However, this adjustment does not affect estimations of the hazard ratio or probability value, which are comparable across the three statistical models (univariate, age-race-sex adjusted, and age-race-sex and risk factor adjusted).

In conclusion, this study suggests that TIA is an important risk factor for stroke or MI, even after adjustment for other cardiovascular risk factors. However, there is insufficient evidence that TIA serves as a risk factor for future mortal events. The event rates for stroke, MI, and death in the TIA group are also presented and represent a considerable burden in this population that may be reduced by more aggressive cardiovascular care of TIA patients.

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