Progress Review

A Methodological Appraisal of Research on Prognosis After Transient Ischemic Attacks

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We analyzed existing research on the prognosis of patients who have had a transient ischemic attack to identify studies that adhere to basic methodological principles and to identify underinvestigated questions. Studies were eligible for analysis if they were published in peer-reviewed journals after 1950, written in English, and included at least 50 patients with transient ischemia. Studies that included patients with stroke were included only if they reported outcome rates separately for the subgroup of patients with transient ischemia. All eligible studies were extracted by one investigator who recorded adherence to six key methodological principles. Among 60 eligible studies, 54 were observational cohort studies and six were randomized trials. Adherence to the six methodological principles was as follows: eight studies included an adequate description of diagnostic criteria and of procedures used to assure adherence to the criteria, 54 used appropriate end points, two assembled inception cohorts, 10 included an adequate description of end point surveillance, 22 adequately reported and analyzed censored patients, and 10 included a multivariate analysis for predictive variables. No study adhered to all six principles, but two adhered to the three most important ones (appropriate end points, inception cohort, and adequate reporting and analysis of censored patients). Aspects of prognosis after transient ischemia that have not been completely investigated include the severity of subsequent strokes and methods for estimating the outcome risk for individual patients. We conclude that only a few published investigations on prognosis after transient ischemia are methodologically complete. This finding helps explain why it is difficult to interpret many studies. Further research is needed and should target underinvestigated topics. (Stroke 1991;22:1108–1116)

Since early studies suggested that patients who have a transient ischemic attack (TIA) are subsequently at high risk for stroke and death,1,2 physicians have recognized the need for reliable information on prognosis. Investigators need the information for risk stratification in trials, and clinicians need it for counseling and managing patients. Unfortunately, more recent studies have not always improved on the earlier ones. Many aspects of TIA prognosis that were not investigated in early studies remain unexplored by newer ones.

To document underinvestigated aspects of TIA prognosis and to identify those studies providing the most reliable and accurate information, we conducted a structured appraisal of the scientific quality of existing research. We examined each of 60 published reports for adherence to well-accepted methodological principles that enhance the applicability, accuracy, and reproducibility of prognosis research.

Methods

To be included in our analysis, a study had to 1) be published after 1950 in English, 2) include more than 50 TIA patients, 3) cite the exact number of TIA patients enrolled, 4) indicate the interval over which outcome was measured, and 5) report the occurrence of any clinical end point (e.g., TIA, stroke, myocardial infarction, functional status, death). Studies were eligible without consideration of research design or purpose so that randomized and nonrandomized trials of therapy were considered in addition to studies specifically about prognosis.

Investigations that included patients with stroke as well as patients with TIA were eligible only if separate prognostic information was reported for the TIA subgroup.

To give this review broad applicability, we included studies on patients with ischemic symptoms lasting <24 hours and occurring in any vascular distribution. When investigators did not specify the duration of
symptoms but used any of the common terms for TIA (i.e., transient monocular blindness, amaurosis fugax, transient cerebral ischemia, vertebrobasilar insufficiency, etc.), we assumed the duration was short enough.

Citations of eligible studies were located from four sources: 1) a MEDLINE (National Library of Medicine MEDLARS Management System) search completed in August 1990, 2) a bibliography on carotid endarterectomy, 3) the tables of contents for issues of three journals (Stroke, Neurology, and Annals of Neurology) published during the first 6 months of 1990, and 4) reference lists of eligible articles identified from the preceding sources.

These search techniques yielded 60 studies; 222-4-24 were observational studies on patients receiving specific therapies, 321,23-55 were observational studies on patients who were not selected because of therapy, and six56-61 were randomized trials.

Using an extraction form, one of us reviewed the 60 studies for adherence to the methodological principles described below. Studies that included patients with stroke or TIA were evaluated according to their application of the principles to the TIA subgroup. All information was transcribed onto a paper spreadsheet, from which calculations were made.

From methodological guidelines recommended for studying prognosis, we chose six key principles. The six principles are as follows.

Adequate Description of Diagnostic Criteria and Monitoring Procedures

For the results of research on TIA to be evaluated, applied, and confirmed, investigators must indicate who was included in the study by specifying diagnostic criteria and procedures.

Diagnostic criteria for TIA refer to the accepted signs or symptoms and their duration. The diagnosis of TIA is always first considered because a patient reports symptoms. Because signs may persist after symptoms have resolved, however, the decision to confirm the diagnosis by one or the other is important. For example, if an investigator diagnoses TIA by the absence of neurological signs 1 day after the onset of symptoms, then his cohort will exclude some patients who have persistent signs but no symptoms.

A different investigator who diagnoses TIA by symptom resolution would include in his cohort patients who were excluded by the previously described investigator. Diagnostic criteria based on the absence of signs are not necessarily better than criteria based on the resolution of symptoms, and signs may be difficult to use because patients often delay seeking medical attention. Regardless of the diagnostic criteria an investigator chooses, however, it is important that he is consistent and avoids using signs in some patients and symptoms in others.

Diagnostic procedures are what investigators do to ensure fulfillment of the diagnostic criteria. Procedures might be administering a questionnaire, inter-viewing and examining the patient, or extracting the medical record.

In evaluating studies, we required that investigators 1) state whether diagnosis was based on the resolution of signs, symptoms, or both; 2) specify the allowable signs or symptoms; 3) specify the allowable duration; and 4) describe the procedures for ascertaining that the criteria were met. An adequate description of procedures included enough information for readers to know if the diagnostic criteria were uniformly applied to all patients.

Appropriate End Points

Hierarchical relations and choice of binary outcome categories. Appropriate end points for research on cerebrovascular disease include a choice among outcome events and combinations of events. Important outcomes include recurrent TIA, stroke, myocardial infarction, and death. Although a particular patient may develop none, one, or more than one of these outcomes, some outcomes are hierarchical and preclude others from happening. For example, a patient who dies cannot suffer a subsequent stroke, TIA, or myocardial infarction; a patient who has a stroke cannot have a TIA involving the previously infarcted tissue.

Because of these hierarchical relations, the reported occurrence of stroke alone or TIA alone may be misleading. For example, suppose deaths remove many patients in a cohort who might otherwise be at risk for stroke. The low rate of stroke in the cohort would provide false reassurance of a benign prognosis. The same problem arises for reporting recurrent TIs, except that the risk of TIA can be reduced by both stroke and death.

Accordingly, whenever stroke is reported as an outcome event in observational studies and randomized trials, the occurrence of stroke plus death should also be reported. Similarly, if TIA is reported, the occurrence of TIA plus stroke plus death should be reported as well.

If death is chosen as the outcome event, the problem of hierarchical end points is avoided since no intervening event prohibits death. In this situation, however, investigators must decide whether to report all-cause mortality, cause-specific mortality (e.g., stroke death), or both. Because judgmental decisions are often involved, assigning a cause of death can be biased. For this reason, whenever cause-specific mortality is reported, all-cause mortality should also be reported.

Managing limitations of binary outcome categories. Binary outcome categories, such as stroke or death versus alive without stroke, are often used for life table and other popular types of analysis. Binary outcomes, however, have an important disadvantage; the “failure” category in a binary scheme usually contains a mixture of events that have unequal importance. For example, because stroke is less important than death, if both are counted as failures, the count will not indicate the ratio of stroke out-
Importance of classifying stroke severity. Whenever stroke is an end point event, the conclusions can be misleading if the resulting functional deficits are not classified according to severity. In particular, because some stroke survivors may have no functional disability, morbidity may be overestimated unless severity is classified.

Criteria for evaluating end points. Table 1 summarizes our criteria for evaluating end point strategies. Although we prefer the nonbinary strategies listed in this table, we recognize that other schemes may be appropriate. We gave full credit for any reasonable alternative.

These criteria do not require the reporting of binary as well as nonbinary outcome categories or stroke severity. Such requirements might have eliminated “incomplete” studies that nevertheless contain important information. We did monitor the use of nonbinary outcomes and the reporting of stroke severity to help us identify underinvestigated aspects of prognosis.

Inception Cohort

To study prognosis, investigators must designate a moment during the course of each patient’s illness from which to measure survival or event-free survival. This moment is often referred to as zero time. Candidate zero times for a cohort of TIA patients include the time of diagnosis, referral to an investigator, or initiation of therapy. An inception cohort99 is a group of patients for whom the same event demarcates zero time and for whom zero time occurs in the same secular (calendar) era and in the same practice setting. The features and advantages of an inception cohort are further described below.

The purpose of having zero time occur in the same practice setting is to prevent referral bias. This bias can arise when cohorts assembled at teaching hospitals include atypical or unusually sick patients who have been referred from other hospitals. For example, if zero time in a hospital-based inception cohort is the date of TIA diagnosis, a patient who was diagnosed elsewhere and then referred to the study hospital(s) would be excluded. The practice setting might be a single hospital, a group of hospitals, or an entire geographic region.

The purpose of having zero time be the same event for each patient is to assure comparability among patients and to demarcate the pertinent group for applying the results. The zero time event, furthermore, should occur at about the same time after the onset of each patient’s TIA symptoms. Mixing patients whose zero time event occurs early after a TIA with patients whose event occurs late may lead to uninterpretable results if prognosis changes over time.

There are two important advantages to zero time that occurs soon after a TIA. First, in addition to being the time from which survival is measured, zero time is also when a patient is usually interviewed and classified according to baseline features. A patient’s recall for details about a recent TIA will be better than about a remote one. Second, by using an early zero time an investigator may observe early outcomes. To use an early zero time, investigators must simply require that the zero time event (e.g., diagnosis or referral to the investigator) occur within a specified interval after the TIA; a patient whose event occurs beyond the interval is excluded from study.

The purpose of requiring zero time to occur during the same calendar era for the inception cohort is to minimize the effects of secular changes in diagnostic or therapeutic practice.

For this report, we identified an inception cohort if a clearly defined zero time occurred at a similar point during the course of each patient’s illness. We also required that zero time occur in a similar secular era and practice setting for each patient. A similar secular time was defined as within the same 10-year interval. We did not require that zero time occur early after the
TIA, but we monitored the use of early zero times as part of our search for underinvestigated topics.

**Adequate Description of End Point Surveillance**

To determine if a surveillance strategy was adequate to detect all end points, readers must know exactly how surveillance was conducted. Pertinent features include 1) the identity of people responsible for surveillance, 2) the sources of their information, and 3) how these sources were combined. Suitable identification is necessary for readers to judge if the responsible people were both competent and objective. The identification of end point sources and a description of how the sources were combined is necessary because different end point sources are not always equally reliable. Candidate sources include telephone calls and written correspondence to patients, medical records, government data bases, personal physicians, and direct patient examination.

Readers of a study may have difficulty judging the relative reliability of its sources, but a judgment is nevertheless necessary for interpreting the results.

For prognosis studies, as for therapeutic trials, it is necessary to guard against bias in surveillance for outcomes. Surveillance bias occurs when a researcher believes a clinical feature (e.g., diabetes) carries a high risk for a specific outcome (e.g., stroke) and differentially interprets or detects outcomes in compared groups with and without the feature. In trials, surveillance bias is prevented by blinding the investigators to treatment. In prognosis studies, blinding is not always practical because the patients are often directly under the care of the investigators; a caregiver usually needs to know a patient's status for diabetes, heart disease, and other variables that are commonly thought to affect outcome. When blinding is not practical, other ways to prevent surveillance bias include objective diagnostic criteria for baseline features and end points, standard surveillance protocols, and external adjudicators for validating end point data.

For this review, the description of a surveillance strategy was rated adequate if it included 1) the identity of study personnel, 2) sources of end point information, and 3) how the sources were combined.

Studies received full credit on this methodological principle for adequately describing the surveillance strategy regardless of the quality of that strategy. We realize that different strategies may be more or less successful in achieving complete and unbiased ascertainment of end points. Evaluating strategies is often difficult, however, and the quality criteria we adopt might be controversial. To identify underinvestigated aspects of TIA prognosis, we tabulated efforts to reduce surveillance bias.

**Adequate Reporting and Analysis for Censored Patients**

If each member of a cohort is observed for the same length of time, with no dropouts, the proportion of patients who develop the end point is a good measure of risk. For example, if 10 of 100 original TIA patients are dead after 5 years of observation and the other 90 are known to be alive, the death rate is 10% (10/100).

A problem occurs when durations of observation are nonuniform. Nonuniform durations can occur if patients are "censored" for one of three reasons: 1) loss to follow-up, 2) removal by a competing event (e.g., an unrelated death or a change in therapy), or 3) end of the study before the patient has been observed for the desired amount of time. Whatever the reason, censoring makes the denominator of the incidence rate contain patients whose fate is unknown or who are otherwise not at risk to enter the numerator.

When censoring occurs, one analytic policy is to remove all censored patients from the cohort. The end point rates are then calculated only for patients observed for the entire duration of the follow-up period. This policy is not recommended because it fails to use partial follow-up data and may produce inaccurate or biased results. Another option is to convert the incidence rate denominators from "counted persons" into "summed person-durations." The preferred policy today is to use life table analysis. This method not only allows information for censored patients to be used up to the time of censoring, but also (unlike person-durations) can show how the risk of an end point changes over time.

Of the three sources of censoring, loss to follow-up is the most likely to bias results because there is often a high incidence of end point events (e.g., death) among lost patients. Because life table analysis will not eliminate the bias arising from censoring, readers who want to appraise both the appropriateness and the reliability of end point analysis must know both the number of patients censored and the reasons for their censoring.

We rated a study adequate if the investigator quantified and explained all censored patients. When censoring occurred, we also required life table analysis or person-duration analysis for making use of partial follow-up data.

**Multivariate Analysis of Predictive Variables**

The term multivariate analysis is used for an examination of the simultaneous relation between a target outcome variable and two or more independent variables. In prognosis research, a prime purpose of multivariate analysis is to check whether independent variables that seem to be important predictors remain important in the presence of other independent variables.

Other important purposes of multivariate analysis are to identify significant combinations of predictors and to construct prediction "instruments" for clinical and research use. These instruments usually identify distinct groups of patients with increasing risk of an outcome event. Useful examples of such instruments
have appeared in cardiology, oncology, and infectious diseases as well as in neurology.

Multivariate analytic procedures can be as mathematically complex as logistic regression or as simple as tabulations showing outcome rates for patients with none, one, and both of two predictive features.

In evaluating individual studies, we gave credit for the use of any multivariate analysis, regardless of its mathematical structure or formulation, as long as the simultaneous relation between a target outcome variable and two or more independent variables was examined. These criteria for an adequate multivariate analysis are deliberately less stringent than earlier recommendations because we did not want to exclude marginal studies that might contain useful, although not definitive, information. To identify underinvestigated topics, we searched each eligible study for efforts to develop a system for estimating outcome risk for individual patients.

Results

Adherence to Individual Principles

Adequate description of diagnostic criteria and monitoring procedures. Thirty-two studies indicated that TIA was diagnosed by signs (0 studies), symptoms (18 studies), or both (14 studies). Twenty-six studies specified the actual signs or symptoms (some by referencing published diagnostic criteria), 36 specified the allowable duration, and 15 adequately described how patients were monitored for fulfillment of the diagnostic criteria. Only eight studies met all five requirements for adequate description of diagnostic criteria and monitoring procedures.

In evaluating descriptions of monitoring procedures, we often found that investigators did not indicate how or if they attempted consistently to apply their diagnostic criteria. For example, some investigators indicated that residual signs excluded a diagnosis of TIA but did not indicate whether every patient was examined or, if an examination was required, when it occurred. Because signs often outlast symptoms, it is probably desirable to examine patients at similar times after the onset of symptoms to assure uniformity in diagnostic classification.

No investigators required that their patients be examined ≤24 hours after the onset of symptoms. As a result, some studies probably included patients with deficits lasting for >24 hours. We describe this probability to indicate one consequence of current diagnostic practices in TIA research, not because we believe that all investigators should require an early physical examination. The requirement for an early examination would impose a substantial burden on investigators of an illness for which patients often delay seeking medical care.

In summary, most investigators did not state their criteria for diagnosing a TIA, and even fewer indicated how the criteria were monitored. When diagnostic criteria for TIA included the absence of neurological signs, it was not always apparent that all patients were examined according to a uniform protocol. Because of problems in the definition and diagnosis of TIA, it was often uncertain what type of patients were under study.

Appropriate end points. The frequency of appropriate end points is indicated in Table 2. All-cause mortality was reported in most studies. Only nine studies reported on stroke or death, and only four reported on stroke, death, or recurrent TIA. No study used nonbinary end points. Thus, although 54 of the 60 studies employed at least one appropriate end point, very few included an appropriate analysis of stroke occurrence.

Among the 57 studies reporting the occurrence of stroke, 15, 17, 19, 29, 32, 33, 34, 37, 38, 40, 42, 43, 44, 45, 46, 47, 49, 54, 56, 59, 60 also classified the severity. Because each study used a different scale for severity, the results are difficult to compare. Interestingly, in eight of these 15 studies, >50% of all strokes received the investigator's most favorable classification. This suggests that most strokes that follow a TIA result in only minor disability.

Inception cohort. Zero time was clearly defined in 43 of the 60 studies. Eighteen, 8, 14, 26, 29, 32, 39, 41, 43, 46, 47, 49, 54, 56, 59, 60 of these also located zero time at the same point after the onset of each patient's TIA. The most common zero time was the date of the first TIA (11 studies); other choices were time of the initial diagnosis, start of therapy, randomization, and notification to investigators. When zero time was not the date of the TIA, investigators for these 18 studies assured that zero time occurred at a uniform time, only two also required that zero time occur during the same 10-year interval and in the same practice setting. Only these two studies, therefore, qualify as having inception cohorts. Zero time for these two studies occurred a median of 3 days after a first TIA.

If we eliminate the requirement that zero time occur during the same decade, seven studies, 5, 26, 33, 39, 47, 49 would seem to qualify as having inception cohorts. Four, 33, 39, 49 of these would still be disqualified because of specific problems in the assignment of zero time. In each of the four, zero time was the date of the first TIA, even though some patients had not come under observation until weeks or years after this date. This method
can be expected to underestimate mortality because patients must live long enough after a TIA to come under eventual observation.

In these four studies, however, there is a further problem because some TIA patients came under observation when they subsequently presented with a stroke, a recruitment practice that can be expected to overestimate mortality and stroke rates. It is difficult to know, therefore, whether the outcome rates in these studies underestimate or overestimate the actual rates. The methodological complexity of these studies has been discussed by other investigators, and the authors themselves have reanalyzed their data to correct for the possibility of outcome rate overestimation. Outcome rate underestimation in studies like these (in which some patients come under observation after the desired zero time) can be avoided by using a technique known as left-censorship. After elimination of these four studies, three meet the relaxed criteria for having an inception cohort.

**Adequate description of end point surveillance.** Among the 60 studies, 11 identified the personnel responsible for end point surveillance, 35 identified sources for end point data, and 18 described how the sources were combined. Only 10 studies described all three features of surveillance and, therefore, met the criteria for an adequate description of the surveillance mechanism.

Nine of the 10 studies also included mechanisms for preventing surveillance bias. In seven of the nine, the mechanism was a "hard" end point (i.e., death). In two of the nine studies the mechanism included blinding techniques.

**Adequate reporting and analysis for censored patients.** Thirty-seven of the 60 studies listed the number of censored patients according to the reason for censorship, but only 21 reported a very low censorship rate and should be exempted from our requirement for life table analysis. With this study added, the criteria were satisfied by 22 reports.

**Multivariate analysis of predictive variables.** Predictive variables were examined by multivariate analysis in 10 studies. All 10 principally used multivariate analysis to test the predictive effect of individual variables, and a few used it to test combinations of variables. None of the 10 studies specifically attempted to develop or validate a multivariable clinical prediction instrument. Two other investigations also used multivariate analysis but applied it to cohorts that included stroke patients.

**Overview of Adherence to Methodological Principles**

Adherence to the six methodological principles is summarized in Table 3. None of the 60 studies adhered to all six principles.

To identify possibly superior studies, we relaxed our selection criteria by eliminating three of the principles. If we assume that diagnosis is always accurate, that surveillance is always adequate, and that not every study requires a multivariate analysis, three principles remain: an inception cohort, adequate reporting and analysis for censored patients, and appropriate end points. Only two reports adhered to all three of the remaining, essential criteria.

**Discussion**

The results of this investigation show that very few reports on TIA prognosis adhered to a minimum number of key methodological principles and that several aspects of TIA prognosis have not been completely investigated. The methodological principles described are important in facilitating the interpretation and reproducibility of research. Our findings for nonadherence to the principles help explain why it has been difficult to interpret many TIA studies and to make comparisons among them.

Aspects of TIA prognosis that have not been completely investigated include the spectrum of severity of future strokes and the occurrence of nonbinary outcomes. Most importantly, no method has been developed for estimating the outcome risk for individual patients.
The two superior reports\textsuperscript{26,47} offer an important core of data on prognosis after TIA. Both reports come from the Oxfordshire Community Stroke Project. The findings show that about 6.3% of an original cohort die during each of the 5 years after a first TIA. In contrast, the proportion of an original cohort having a stroke or dying is about 12% during the first year after a TIA and falls to about 6% during years 2 and 3 (Figure 4 in Reference 47).

Beyond all-cause mortality and stroke or death, the Oxfordshire Community Stroke Project has also published occurrence rates for cause-specific mortality and for the occurrence of myocardial infarction or stroke or death. To the best of our knowledge, the Oxfordshire Community Stroke Project has not yet published a multivariate analysis of predictive variables for TIA patients.

We believe our methodological criteria accurately identified the best-designed studies on TIA prognosis. One study from the Mayo Clinic,\textsuperscript{4} however, seemed particularly strong but did not pass our criteria. This study used medical records to identify 289 stroke-free patients examined \( \geq 30 \) days after a first TIA. This study probably had excellent data on short-term survival but failed to meet our methodological criteria because patients were sampled over 24 years and because the number of censored patients was not indicated. We suspect that censoring was minimal and that the study was probably superior.

Publications that did not adhere to our methodological principles should not automatically be judged to have failed in their individual purposes. Twenty-eight of the eligible publications were not designed principally for the study of prognosis (some were clinical trials, others were observational studies of therapeutic outcome); none of these should be expected to include a multivariate analysis for predictive variables. Many eligible publications entered our study because they reported subgroup analyses for patients with TIA; it is probably unreasonable to expect explanations of censoring and multivariate analysis for subgroups. We included trials, other studies of therapy, and studies with subgroups of TIA patients because we suspected that some would contain useful prognostic information for selected TIA patients.

Among the studies we examined, some included only patients with a first TIA and others included patients regardless of whether the TIA was a first episode or recurrence. Some investigators studied TIA as the first manifestation of cerebrovascular disease, and other investigators included patients with a prior stroke. Because patients with a prior TIA or stroke may have a different prognosis from patients without either, we believe that patients with a prior TIA or stroke should probably be analyzed separately.

The results demonstrate a need for more research on TIA prognosis. In particular, the findings of the Oxfordshire Community Stroke Project should be checked in other clinical settings, and new methods are needed for estimating the prognosis for individual patients. We hope that the methodological principles described in this paper will be useful to researchers who design the new studies and to physicians who must interpret them.

References


KEY WORDS • cerebral ischemia, transient • prognosis
A methodological appraisal of research on prognosis after transient ischemic attacks.
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Stroke. 1991;22:1108-1116
doi: 10.1161/01.STR.22.9.1108

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/22/9/1108

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