Very Early Risk of Stroke After a First Transient Ischemic Attack

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Background and Purpose—The commonly quoted early risks of stroke after a first transient ischemic attack (TIA)—1% to 2% at 7 days and 2% to 4% at 1 month—are likely to be underestimates because of the delay before inclusion into previous studies and the exclusion of patients who had a stroke during this time. Therefore, it is uncertain how urgently TIA patients should be assessed. We used data from the Oxford Community Stroke Project (OCSP) to estimate the very early stroke risk after a TIA and investigated the potential effects of the delays before specialist assessment.

Methods—All OCSP patients who had a first-ever definite TIA during the study period (n = 209) were included. Three analyses were used to estimate the early stroke risk after a first TIA starting from 3 different dates: assessment by a neurologist, referral to the TIA service, and onset of first TIA.

Results—The stroke risk from assessment by a neurologist was 1.9% [95% confidence interval (CI), 0.1 to 3.8] at 7 days and 4.4% (95% CI, 1.6 to 7.2) at 30 days. The 7- and 30-day stroke risks from referral were 2.4% (95% CI, 0.3 to 4.5) and 4.9% (95% CI, 1.9 to 7.8), respectively, and from onset of first-ever TIA were 8.6% (95% CI, 4.8 to 12.4) and 12.0% (95% CI, 7.6 to 16.4), respectively.

Conclusions—The early risk of stroke from date of first-ever TIA is likely to be higher than commonly quoted. Public education about the symptoms of TIA is needed so that medical attention is sought more urgently and stroke prevention strategies are implemented sooner. (Stroke. 2003;34:e138-e142.)

Key Words: cerebral ischemia, transient n stroke n stroke prevention

A pproximately 15% of ischemic strokes are preceded by a transient ischemic attack (TIA).\(^1\) Guidelines highlight the need for rapid-access TIA clinics,\(^2\) but it is uncertain how urgently patients must be seen, and there is great variation in practice.\(^5\) The danger of delaying investigation and treatment after a TIA depends on the early risk of stroke. Risks of 1% to 2% at 7 days and 2% to 4% at 1 month are usually quoted.\(^1,4\) However, these are likely to be underestimates because of the delay before patients were included into previous hospital-based studies and clinical trials. Any patients who had a major stroke during this period were excluded.

A recent study of patients presenting to an emergency department, almost all of whom were enrolled within 24 hours of the TIA, reported a stroke risk of 5.3% at 2 days.\(^6\) However, this population was self-selected, and there are no equivalent data from population-based studies. In contrast to stroke incidence and prognosis studies, population-based studies of TIA are scarce.\(^7\) One early population-based TIA incidence study provided some information on the risk of stroke from the date of TIA, but the analysis was based on retrospective case-note review, and some patients did not come under observation until several years after their TIA.\(^8\) The only population-based prospective TIA incidence study that followed up patients and that satisfies the criteria for a high-quality TIA prog-

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nosis study is the Oxfordshire Community Stroke Project (OCSP).\(^7,9\) However, the previously reported prognosis of TIA in the OCSP was based on a pragmatic analysis of the risk of stroke after presentation to medical attention and referral to hospital—ie, a few days or weeks after the TIA.\(^9\) We therefore reanalyzed the OCSP data to estimate the risk of stroke in the first few days after a TIA and investigated the potential effects of the delays before specialist assessment.

Methods

The methods of the OCSP have been described in detail elsewhere.\(^10\) Briefly, by collaboration with 50 family practitioners (FPs) in 10 practices, an urban and rural population of ~105 000 people in Oxfordshire (UK) was studied. FPs were encouraged to report all patients who they thought might have suffered a TIA or stroke during the study period (1981 to 1986).

The aim of the OCSP was to determine the incidence, risk factors, and outcome of first-ever-in-a-lifetime TIA and stroke in a population, unbiased by hospital admission or outpatient referral practice. Stroke and TIA (including ocular TIA) were diagnosed according to standard clinical criteria; the definitions of incident cases have been described previously.\(^11\)
Incident cases of TIA included only cases with no previous diagnosis of TIA or stroke. We included all patients (n=209) registered as incident cases of TIA or stroke and who had a first-ever definite TIA during the study period (Figure 1). In contrast to the previous analysis,9 this study included 30 patients who had a first-ever TIA during the study period but who were registered only after they had a stroke. Data on past history of a TIA in these patients were recorded by means of a detailed history taken by a neurologist at registration and through FP and hospital records. To minimize recall bias, only those patients considered to have had a definite TIA by a neurologist were included.

We performed 3 analyses of stroke-free survival after a first-ever TIA, starting from date of onset of first TIA, date of referral to the TIA service (usually by the FP), and date seen by the study neurologist. Two separate analyses were also performed from date of onset of first TIA: 1 that excluded those patients who never presented to medical attention before having a stroke, and 1 that separated those patients with cerebral TIsAs from those with purely ocular events. Survival free of stroke was determined at 7 and 30 days by Kaplan-Meier analysis with SPSS for Windows version 10.0.

Results
We included 209 patients (mean age, 69.4 years; SD, 12.3 years; 54% male, 17% ocular TIsAs) in the analyses (Figure 1). The median interval from first-ever TIA to notification was 7 days (interquartile range, 2 to 48 days; Figure 1). For the 179 patients who were notified as incident cases of TIA, the median interval from presenting TIA to notification was 3 days (interquartile range, 2 to 8 days; Figures 1 and 2) and from first-ever TIA to notification was 6 days (interquartile range, 2 to 37 days; Figure 2). Further characteristics of the study population have been reported previously.11 Twenty-five patients had a stroke in the first 30 days after their first-ever TIA. The risk of stroke was 8.6% (95% confidence interval [CI], 4.8 to 12.4) at 7 days and 12.0% (95% CI, 7.6 to 16.4) at 30 days (Figure 3). If the 17 patients who did not report their symptoms to medical attention until after they had a stroke were excluded, the 7- and 30-day risks of stroke were 4.2% (95% CI, 1.4 to 6.9) and 6.3% (95% CI, 2.8 to 9.7), respectively, from date of onset of symptoms. For the 176 patients who had cerebral TIsAs, the estimated risks of stroke from first-ever TIA were 5.1% (95% CI, 1.8 to 8.4) at 2 days, 10.3% (95% CI, 5.8 to 14.7) at 7 days, and 14.3% (95% CI, 9.1 to 19.4) at 30 days. In contrast, no patients with purely ocular events (n=33) had a stroke within 30 days.

Ten patients had a stroke within 30 days of referral and within 30 days of specialist assessment. The risk of stroke from date of referral was 2.4% (95% CI, 0.3 to 4.5) at 7 days and 4.9% (95% CI, 1.9 to 7.8) at 30 days. From specialist assessment, the risk of stroke was 1.9% (95% CI, 0.1 to 3.8) at 7 days and 4.4% (95% CI, 1.6 to 7.2) at 30 days (Figure 3).

Discussion
There have been no high-quality population-based studies published since the OCP with sufficient sample size and follow-up to provide equivalent information on recurrent stroke risk. Using these data, we tried to obtain estimates of the early risks of stroke after a TIA in the community and found a 7-day risk of 8.6%. This may be an overestimate because the analysis included 17 patients who presented to medical attention after a stroke but excluded an unknown number of patients who had a TIA but did not seek
medical attention and did not subsequently have a stroke. However, when these 17 patients were excluded, the 7-day risk of stroke was still double that commonly quoted (4% versus 2%). Moreover, at least some of these patients would have been seen after their TIA by their FP if they had not had a stroke first because >60% of patients with TIA take >3 days to report their symptoms to medical attention, and 7 of these patients (41%) had a stroke within 3 days of their first TIA. Therefore, exclusion of these patients is likely to underestimate the real early risk.

Furthermore, any overestimation of risk is offset by 2 factors. First, the analysis started at the date of first-ever TIA even if the patient had further TIAs before presentation to medical attention. Although first symptoms were distant from study assessment in some patients (>3 months in 14% of patients with incident TIAs; Figure 2), exclusion of such patients or an analysis from subsequent TIAs would have led to further overestimation of stroke risk. Any error in recall of distant symptoms was minimized by use of FP records and by including only those patients with a definite history of TIA. Second, some patients with TIA who had a subsequent stroke may not have been identified because we excluded those in whom it was impossible to obtain a definite history of TIAs because they were aphasic, confused, or unconscious or in whom the diagnosis of previous TIA was considered only probable or possible.

The only previous study of the very early risk of stroke after a TIA was based on patients presenting to an emergency department. The population was likely to have overrepresented patients with severe events or with a prior diagnosis of cerebrovascular or ischemic heart disease. Indeed, the proportion with events lasting >10 minutes was greater than in the OCSP (84% versus 64%, \( P<0.001 \)). Nevertheless, the 5.3% 2-day stroke risk in that study is comparable to the 5.1% 2-day risk from the time of the first-ever cerebral TIA in the OCSP.

Our results have important clinical implications. First, if patients are seen very soon after TIA, the early risk of stroke is likely to be much higher than is usually quoted. Immediate specialist assessment and treatment are therefore essential, particularly for those in whom cardiac embolism or carotid stenosis is suspected. TIA patients with atrial fibrillation may require anticoagulation, and the risk of stroke in patients with severe carotid stenosis is \( \approx 5\% \) per week during the period before endarterectomy.

Second, although it is widely recommended that all TIA patients be seen in rapid-access clinics, unless patients present to medical attention earlier, an urgent TIA service is unlikely to be effective in the prevention of stroke. Although this study was performed 15 years ago, recent research suggests that many patients still delay seeking medical attention; consequently, currently available treatments such as lipid lowering or antihypertensive therapies are unlikely to affect the 7-day stroke risk unless people seek medical attention immediately.

In conclusion, although the commonly quoted risk of stroke in the 7 days after a TIA is only 1% to 2%, our data suggest that it may be as high as 8%. These population-based results confirm the findings of a previous hospital-based study and illustrate the potential for stroke prevention if all patients with TIA seek medical attention urgently and are seen without delay. More research is required into current patient knowledge, attitudes, and behavior after a TIA or minor stroke so that effective public education can be implemented.

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References

TIAs are common events: a prevalence of 2.3% for a physician-rendered diagnosis of TIA was recently reported among US adults in a large community-based survey, equivalent to an estimated 4.9 million Americans carrying this diagnosis. An equal or greater number may have experienced an undiagnosed TIA.

Patients with TIAs are at significant short-term risk of stroke, ranging from 4% to 8% in the first month, with an immediate risk of 5% in the first 2 days. Of those experiencing a stroke after a TIA, 21% will do so within the first month. Early evaluation of these patients seems prudent, but the urgency depends on an accurate determination of early risk since hospital admission of all TIA patients is likely to be financially prohibitive.

The present report adds to previous data showing an early risk of stroke after TIA. The authors reanalyze data collected between 1981 and 1986 in the Oxfordshire Community Stroke Project (OCSP), which prospectively followed a population of patients presenting to their primary care provider with a TIA and/or completed stroke. The OCSP was a rigorously conducted study based on a clinical evaluation of each subject by a study neurologist with access to complete medical records throughout the course of the study. It is one of the few prospective studies of outcome following TIAs in nonhospitalized patients.

The original OCSP study reported a moderate 4.4% risk of stroke in the first month following a recent TIA. In the present study, the authors recalculate this risk and suggest that it is much higher than the initial estimate: 8.6% and 12.0% at 7 and at 30 days, respectively. These conflicting results can be explained by a major change in the definition of the index TIA: the original OCSP study reported stroke rate following the most recent TIA and excluded those patients who presented with a stroke which had been preceded by a TIA. The present report calculates the risk of stroke after a first-in-lifetime TIA occurring at any time during the 5 years of the study, and includes patients presenting with stroke preceded by a TIA. Including such patients in the analysis doubles the 7-day risk of stroke after TIA from 4.2% to 8.6%. This dramatic difference in estimated risk demonstrates the extreme sensitivity of predictive models of TIA outcome on study design and inclusion criteria. The authors of the original OCSP study made a strong case for excluding these same patients so as not to unfavorably bias outcome predictions.

It would be most appropriate to include patients presenting with strokes following a TIA in a study defining the natural history of TIAs in the general community: in that case, all outcomes following the TIA would be relevant irrespective of the mode of presentation to medical attention. From a health care system perspective, however, where the risk to a defined population (eg, those presenting with TIA, not with a stroke) is sought, inclusion of such patients seems less justifiable.

Does the present study report the natural history of TIAs in the general community? Although it is labeled a “community-based” study to distinguish it from hospital-based ones, it actually evaluates a selected population reporting a stroke or TIA to their primary care provider. Such a design does not capture patients who fail to recognize the symptoms of TIA or who do not report them to medical attention. The number of such patients is likely to be sizable: in a recent survey of American adults, only 8.6% could identify a symptom associated with a TIA, and more than half of those experiencing symptoms of TIA never reported them to medical attention. Citizens of the United Kingdom did no better: in a previous publication by the OCSP investigators, 54% of patients who experienced a TIA preceding their stroke did not report it to medical attention until after their stroke.

Other methodological details of the study are worth noting: the index TIA may have preceded referral to the study by up to 5 years. While the median time from the first-ever TIA to study referral was a very reasonable 7 days, 14% of all patients were entered into the study 3 or more months after their TIA, and some after more than 18 months. Recall bias is likely to play a role in some of these patients: in a recent survey, only 39% of individuals recalling a physician diagnosis of TIA actually had such a diagnosis in their medical records, but only 55% of those with such a diagnosis in their records recalled the event. As pointed out by the authors, the meticulous methods used to confirm TIAs by the OCSP investigators is likely to minimize such source of inaccuracies. Finally, these data were collected up to 21 years ago; medical care has changed significantly since that time and the applicability of these findings to the current population is uncertain.

Despite the methodological controversies which are inevitably raised in the study of such ephemeral events, the 2-day risk of stroke following a TIA reported in this study is nearly identical to the risk reported by Johnston et al in patients presenting to an emergency department (5.1% versus 5.3%). Both are estimates of stroke risk in a selected population of TIA patients presenting to outpatient medical attention. For such patients the current study adds to the mounting evidence of an early risk of stroke which warrants rapid evaluation and treatment. The risk in the general population experiencing a TIA may be lower due to the potentially large number of patients who do not report their symptoms; determination of this risk awaits the results of further studies.

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References


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