Underestimation of the Early Risk of Recurrent Stroke
Evidence of the Need for a Standard Definition
Andrew J. Coull, MRCP; Peter M. Rothwell, FRCP

Background—There is considerable variation in the definitions used for recurrent stroke. Most epidemiological studies exclude events within the first 28 days (eg, Monitoring Trends and Determinants in Cardiovascular Disease [MONICA]) or events within 21 days in the same territory as the presenting event (eg, most stroke incidence studies). However, recurrence is most common during this early period and these restrictive definitions could underestimate the benefits of early prevention.

Methods—We determined the 90-day risk of recurrence after incident ischemic stroke in 2 population-based cohorts (Oxford Vascular Study [OXVASC] and Oxfordshire Community Stroke Project [OCSP]) with the 3 most common definitions: any stroke ≥24 hours after the incident event excluding early deterioration not caused by a stroke (definition A); as above, but excluding any stroke within 21 days in the same territory as the incident event (definition B); and any stroke ≥28 days after the incident event (definition C).

Results—657 patients had 93 recurrent strokes between 24 hours and 90 days after the incident event. The 90-day recurrence risks (95% CI) using definition A were 14.5% (11.5 to 17.5) in the OCSP and 18.3% (10.8 to 25.8) in the OXVASC. The equivalent risks using definitions B and C were 8.3% (5.9 to 10.8) and 4.8% (2.8 to 6.7), respectively, in the OCSP and 7.0% (1.6 to 12.4) and 5.9% (1.0 to 10.9) in the OXVASC. The definition A risk of recurrence was particularly high after partial anterior (22.9%, 17.5 to 28.2) and posterior (19.5%, 13.0 to 25.9) circulation strokes.

Conclusions—The 3 most widely used definitions of recurrent stroke yield markedly different 90-day risks. We suggest that, where possible, definition A be adopted as the standard to avoid underestimation of risk and to allow valid comparison of different studies. (Stroke. 2004;35:000-000.)

Key Words: epidemiology ■ ischemia ■ recurrence ■ stroke, ischemic

Approximately 30% of strokes in population-based studies are recurrent events, and these recurrent strokes are more likely to be disabling or fatal than first strokes. Prevention of recurrent stroke is therefore of considerable importance to both individual and public health. Reliable data are required on the absolute risk of recurrent stroke so that stroke prevention services can be organized appropriately and the likely cost-effectiveness of preventive treatments can be assessed. A standard definition of recurrent stroke is also required so that different studies can be compared or meta-analyzed appropriately, time trends in risk can be determined accurately, and absolute risk reductions with treatment can be properly compared across trials.

The risk of stroke in the 3 months after a transient ischemic attack (TIA) is as much as 15% to 20% in population-based studies, whereas the equivalent risk after a first-ever ischemic stroke is usually reported as 2% to 6%. The majority of studies reporting these low risks excluded any potential recurrences that occurred within 21 days or 28 days after the incident stroke. The 28-day definition used in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study and other influential population-based studies exclude all strokes within 28 days of the incident event, whereas other studies exclude only those events in the same vascular territory as the original event. The same distinction is made in studies that use the 21-day definition, either excluding all strokes within 21 days or only those strokes in the same vascular territory as the original stroke. However, the distinction is relatively unimportant because most early recurrences are in the same territory as the initial stroke, particularly in patients with large artery atherosclerosis in whom the risk of early recurrence is highest. In contrast, other studies have used definitions that included all events occurring ≥24 hours after stroke, requiring only 24 hours of neurological stability before any recurrence, and some appear to have also included new episodes occurring in a different vascular territory within 24 hours of the index stroke: either a new focal neurological deficit occurring at any time after the index stroke, or an event that is “clearly in another part of the brain after the preceding stroke.” Finally, some studies have given...
no definition and relied on the clinical judgment of collaborating physicians or have not specified any time restriction.

Given the importance of accurate determination of the risk of recurrent stroke, the potential for confusion because of the widespread use of very different definitions, and the possibility that some definitions underestimate the risk, we determined the effect of the most widely used definitions on the measured early risk of recurrent stroke in 2 high-quality population-based stroke incidence studies. Population-based data are important to minimize selection bias.

Methods
The methods of the Oxfordshire Community Stroke Project (OCSP) and the Oxford Vascular Study (OXVASC) are similar and have been described in detail elsewhere. Both studies aimed to determine the incidence, risk factors, and outcome of first-ever stroke in a prospective population-based study fulfilling the standard methodological criteria. In OCSP (1981 to 1986), all patients in a population of 105,000 registered with 50 family physicians (FPs) in 10 practices in both urban and rural settings. The OXVASC population covered 90,542 patients registered with 63 FPs from 9 practices, all of which had taken part in the OCSP. Each study developed multiple, comprehensive, overlapping search strategies to ensure as complete ascertainment as possible and collaborated very closely with FPs, who were encouraged to report all patients with a suspected acute cerebrovascular event during the study periods. Collaborating practices provided an accurate age–sex register with accurate and up-to-date estimates of the denominator, allowing easy identification of cross-boundary flow and turnover within the population.

In both studies, patients were assessed as soon as possible after the acute event by a study physician in a study clinic, in a hospital, or in the community. If a patient died before being seen, we attempted to obtain an eyewitness account and reviewed information with the FP and in hospital or ambulance service notes. In addition to a detailed clinical assessment and routine blood tests, patients in both studies had CT brain imaging and all incident strokes were subtyped as ischemic or hemorrhagic according to the Bamford classification.

In both studies, the date and time of onset of first stroke and the date and time of any acute neurological deterioration in the acute phase or suspected stroke during follow-up were recorded. All hospitalized patients were reviewed if any neurological deterioration was suspected. After discharge, for patients who were not admitted to hospital, follow-up was of 2 kinds. First, patients presenting to medical attention with a recurrent stroke would be reassessed by the same clinical subtypes. Second, all patients were also reviewed face-to-face by a research nurse at 1, 6, and 12 months after the incident stroke for incident strokes. Second, all patients were also reviewed face-to-face by a research nurse at 1, 6, and 12 months after the incident stroke for incident strokes. Any recurrent stroke occurring within 24 hours of onset of the incident stroke, irrespective of vascular territory, was suspected and investigations, including brain imaging, were repeated.

A potential recurrent stroke was defined as any new acute neurological event with symptoms lasting >24 hours occurring after the initial ictus of the incident stroke (ie, definite acute worsening of an established nonprogressive deficit) that was not attributable to edema, brain shift, hemorrhagic transformation, intercurrent illness, hypoxia, or drug toxicity. Sudden worsening was required for consideration as a potential recurrent event, and gradual progression of an acute deficit was excluded. Recurrences were assessed in the same way as incident strokes, seen as rapidly as possible, and had urgent brain imaging. Strokes occurring in patients who had a definite TIA (ie, they returned entirely to normal within 24 hours), but had a subsequent stroke within 24 hours of onset of the TIA, were also excluded.

Results
The OXVASC enrolled 128 first-ever strokes, of whom 123 (96%) had brain imaging or postmortem. The OCSP registered 675 first-ever strokes, of whom 542 (80%) had brain imaging or postmortem. Thirteen OXVASC patients and 104 OCSP patients presented with primary intracerebral hemorrhage (PICH) or subarachnoid hemorrhage (SAH) and were excluded. A further 29 (5%) OCSP patients were excluded because of inadequate documentation of the course of the acute phase after the incident stroke. A total of 657 patients (OXVASC, 115; OCSP, 542) with a first-ever ischemic stroke were therefore studied. The mean (SD) age and proportion of females were aged 75 years (11.6) and 54% (n = 62), respectively, in the OXVASC, and aged 73.2 years (12.8) and 50% (n = 272), respectively, in the OCSP. The vascular territories of incident strokes were carotid territory in 498 patients (75.8%: OXVASC, 91; OCSP, 407) and posterior circulation in 150 patients (22.8%: OXVASC, 24; OCSP, 126). Vascular territory was uncertain in 9 (1.4%) OCSP patients. The Bamford classification of incident strokes was as follows: 154 (23.4%: OXVASC, 28; OCSP, 126) lacunar infarcts (LACI); 230 (35.1%: OXVASC, 49; OCSP, 181) partial anterior circulation infarcts (PACI); 152 (23.1%: OXVASC, 25; OCSP, 127) posterior circulation infarcts (POCI); and 121 (18.4%: OXVASC, 13; OCSP, 108) total anterior circulation infarcts (TACI).

The risks of recurrent stroke at 3 months based on the 3 different definitions were highly consistent across the 2 studies (Table). If recurrence was confined to strokes occurring >28 days after the incident stroke (definition C), the 3-month risk was 4.8% (95% CI, 2.8 to 6.7) in the OXVASC and 5.9% (1.0 to 10.9) in the OCSP. The corresponding risks using the 21-day exclusion (definition B) were 8.3% (5.9 to 10.8) and 7.0% (1.6 to 12.4), respectively. In contrast, if only events within the first 24 hours after initial ictus were excluded (definition A), the risks increased to 14.5% (11.5 to 17.5) and 18.3% (10.8 to 25.8), respectively. Figure 1 shows
the Kaplan–Meier curves for survival free of stroke for each of the definitions of recurrence.

Figure 2 shows the 3-month risk of recurrent stroke according to the clinical subtype. There was no statistically significant heterogeneity in risks between the OXVASC and OCSP for any subtype, and the data from the 2 studies were therefore pooled. The difference in prognosis between the different subtypes was qualitatively similar with each definition, but was most clear cut for definition A. Patients presenting with a PACI and POCI were at highest risk of an early recurrence with each of the different definitions, with the 3-month risk ranging from 8.1% (0.7 to 16.2) and 6.6% (2.2 to 11.0), respectively, for definition C to 22.9% (17.5 to 28.2) and 19.5% (13.0 to 25.9), respectively, for definition A. TACIs and LACIs had the lowest risk of early recurrence. These differences in risk were nonsignificant with definition C ($P=0.07$), moderately significant with definition B ($P=0.01$), but highly significant statistically with definition A ($P<0.0001$).

**Discussion**

Analysis of data from 2 population-based studies with well-defined inclusion criteria and detailed follow-up has demonstrated that the definition used for recurrent stroke has a major effect on the measured risk of stroke risk at 3 months. The use of these different definitions partly explains the differences in risks of recurrent stroke that have been reported after a first-ever ischemic stroke (e.g., 1-year risks of 7%,7 10%,10 12%,3,12 and 15%15). We believe that the 24-hour exclusion definition of recurrence (definition A) is most clinically valid. The use of data from previous epidemiological studies that have used the more restrictive definitions in health economic and other effectiveness analyses will underestimate the potential benefits of early preventive treatment.

### Risk of Recurrent Stroke 3 Months After a First-Ever Ischemic Stroke According to the 3 Different Definitions in 2 Population-Based Studies (OXVASC and OCSP)

<table>
<thead>
<tr>
<th>Definition</th>
<th>3-Month % Risk (95% CI)</th>
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<tbody>
<tr>
<td>A Any recurrence &gt;24 hours not attributable to edema brain shift or hemorrhagic infarction</td>
<td>OXVASC n=115 / OCSP n=542</td>
</tr>
<tr>
<td>B Any recurrence &gt;21 days or if &lt;21 days, new neurological deficit in different vascular territory</td>
<td>18.3 (10.8 to 25.8) / 14.5 (11.5 to 17.5)</td>
</tr>
<tr>
<td>C Any recurrence &gt;28 days</td>
<td>7.0 (1.6 to 12.4) / 8.3 (5.9 to 10.8)</td>
</tr>
<tr>
<td>C Any recurrence &gt;28 days</td>
<td>5.9 (1.0 to 10.9) / 4.8 (2.8 to 6.7)</td>
</tr>
</tbody>
</table>

**Figure 1.** Kaplan–Meier curves for survival free of stroke after a first-ever ischemic stroke in the OXVASC and OCSP for each of the definitions of recurrence.

**Figure 2.** The 3-month risk of recurrent stroke according to Bamford clinical subtype23 in the OXVASC and OCSP combined.
A standard definition of recurrent stroke is also required so that different studies can be compared or meta-analyzed appropriately, time trends in risk can be determined accurately, and absolute risk reductions with treatment can be properly compared across trials. Our data suggest that comparisons are likely to be highly biased unless definitions of recurrence are the same. If information on the early clinical course of patients is insufficiently detailed to use definition A reliably in certain types of large-scale epidemiological studies, for example, and more restrictive definitions are therefore necessary, it is important that researchers be aware of the potential underestimation of risk.

It is, of course, important that progression of the initial stroke, hemorrhagic transformation of infarction, systemic disturbances, or edema and mass effect resulting in fluctuations in cerebral perfusion are not misclassified as recurrent strokes. For this reason, it has been argued that neurological deterioration occurring \(\geq 24\) hours after the incident event should only be included as a potential recurrent stroke if the neurological deficit was clearly different from the index stroke or was of a different clinical subtype, or if it occurred after an unequivocal period of neurological stability for \(\geq 24\) hours. These stipulations are reasonable, although it should be noted that early recurrence is most common after minor ischemic stroke in which hemorrhagic transformation, edema and mass effect, and systemic disturbances are least likely.

It is also important to note that the use of the different definitions also leads to biases in analyses of the relationships between risk of recurrence and subtype of stroke. For clinical subtype, there was no significant difference in risk of recurrence when definition C was used, but there was highly significant heterogeneity with definition A, with higher risks in patients with PACI and POCI strokes. This difference is caused by recurrent events that tend to occur early in these subtypes of stroke. Patients with PACI have the highest prevalence of carotid stenosis, which has been shown to be associated with a high early risk of stroke, and a high proportion of POCI strokes are thought to be caused by large artery atherosclerosis. Indeed, published studies show that the risk of recurrent stroke following a posterior circulation TIA or minor stroke is significantly higher than the risk in patients with carotid territory events in studies with follow-up that commenced at the time of the event, but the risk is significantly lower in studies in which patients were recruited after the acute phase.

Our study has a number of potential shortcomings. First, we relied on the accuracy of the clinical recording of recurrent events. However, we were conservative in our definition of possible recurrent stroke by only including sudden acute neurological deterioration if there was considered to be a low probability that it was caused by edema, brain swelling, drugs, or other potential complications of stroke, or if there was definite evidence of recurrent stroke on brain imaging. The low early risk of recurrent stroke in patients with TACI syndromes suggests that we were not misdiagnosing nonspecific neurological deterioration as stroke. Moreover, the similar stroke recurrence risks measured in the OCSP and OXVASC suggested that interobserver agreement was likely to be good. If anything, we may have underestimated the early risk of recurrent events, particularly minor strokes, because patients were not reviewed between hospital discharge and 1 month, unless they sought medical attention with a further event. Second, we excluded sudden acute neurological deterioration that occurred within 24 hours of the onset of the initial stroke. Such early events have not previously been regarded as recurrent strokes, partly because the initial event cannot strictly be called a stroke based on current definitions before 24 hours have elapsed. However, early deteriorations do occur in >10% of patients randomized in acute stroke trials, in the absence of signs of raised intracranial pressure or hemorrhagic transformation, and are often associated with new ischemic lesions on brain imaging. Sudden deterioration within 24 hours in patients who had not recovered from their initial event may therefore represent potentially preventable recurrent ischemic episodes. Interestingly, in the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial placebo arm, patients not on aspirin at the time of their stroke were more likely to have early clinical deterioration. Further research, including studies of the interobserver agreement in the diagnosis of recurrence, is required.

In conclusion, we have shown that the risk of recurrence after first-ever ischemic stroke varies several-fold depending on the definition used. We have also shown that 2 of the definitions most widely used in epidemiological studies substantially underestimate the risk, particularly in patients with PACI and POCI syndromes. A standard definition of recurrent stroke is required so that different studies can be compared or meta-analyzed appropriately, time trends in risk can be determined accurately, and absolute risk reductions with treatment can be properly compared across trials. Comparisons are likely to be biased unless definitions of recurrence are the same.

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References


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