Long-Term Risk of Recurrent Stroke After a First-Ever Stroke

The Oxfordshire Community Stroke Project

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Background and Purpose There have been few community-based studies of long-term prognosis after acute stroke. This study aims to provide precise estimates of the absolute and relative risks of stroke recurrence in an unselected cohort of patients with a first-ever stroke.

Methods Six hundred seventy-five patients were registered in a community-based stroke register (the Oxfordshire Community Stroke Project) and prospectively followed for up to 6.5 years. Their relative risk of recurrent stroke was calculated using age- and sex-specific incidence rates for first stroke in Oxfordshire.

Results One hundred eighty recurrent episodes of stroke were identified, of which 135 were first recurrences. Given survival, the actuarial risk of suffering a recurrence was 30% (95% confidence interval, 20% to 39%) by 5 years, about nine times the risk of stroke in the general population. The risk was highest early after the first stroke: 13% (95% confidence interval, 10% to 16%) by 1 year, 15 times the risk in the general population. After the first year the average annual risk was about 4%. The risk of stroke recurrence did not appear to be related to age or pathological type of stroke.

Conclusions The absolute and relative risks of recurrent stroke are highest early after the first stroke but remain elevated for several years thereafter. Efforts at secondary prevention should be initiated as soon as possible and continued for several years to gain greatest benefit. (***Stroke.* 1994;25:333-337.**)

Key Words • cerebrovascular disorders • epidemiology • prognosis

After nondisabling ischemic stroke there are effective surgical[1,2] and medical[3-5] treatments that reduce the risk of recurrent stroke. Use of these treatments in individual patients will be influenced by the anticipated absolute risk of stroke recurrence. The urgency with which treatments are started will depend on the level of risk in the first few months, and the duration of treatment will be guided by the duration of any elevated risk. The present study aimed to estimate the risk of stroke recurrence in an unselected cohort followed up from the time of the first-ever stroke in a lifetime (first stroke), and compare this with the risk of stroke in the general population. We have also attempted to identify patient groups at particularly high or low risk of stroke recurrence. The overall survival of this cohort has been described previously.[6]

Subjects and Methods

The Cohort

The Oxfordshire Community Stroke Project (OCSP) identified all patients with a first stroke from a study population of about 105 000 over 4 years. The methods used to identify and assess cases have been described elsewhere.[7,8]

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Follow-up

Surviving patients were followed up at 1 month, 6 months, 1 year, and then annually from the date of their first stroke by a study nurse. Follow-up interviews were coded onto forms designed to aid the detection of new stroke and other vascular events. The medical records held by the primary care team were reviewed at the time of each interview. Patients who had left the study area were traced via their general practitioner, and in all cases contact was established by a visit, letter, or telephone interview with either the patient or a relative. Patients with a suspected stroke recurrence were reexamined by the study neurologist as soon as possible after the event and the diagnosis was discussed at regular consensus meetings of the study team. One of the study neurologists (J. Burn) visited all surviving patients for a final assessment between August 1987 and November 1988, and he also reviewed all the hospital and primary care records of all patients, including those who had died, before the end of the study. Any case considered to have had an "uncertain" recurrence at a consensus meeting was discussed again at a second meeting at which a final decision on the classification of the recurrence according to pathology, cerebral location, and severity was made. No patient was lost to follow-up.

Definitions

The definition of stroke recurrence was the same as the definition of stroke[9] but qualified by the following conditions. (1) There had to be evidence of either a new neurological deficit or an exacerbation of a previous deficit that could not be ascribed to a toxic effect of drug therapy or an intercurrent acute illness. Elderly patients who deteriorated in their capacity to undertake activities of daily living, but without any new neurological deficit, were not classified as suffering a recurrence. (2) Stroke recurrences were clinical events and asymptomatic new cerebral lesions demonstrated on computed tomography (CT) scan or at autopsy were not included. (3) For the purpose of this analysis we, like others,[10-12] defined stroke

recurrence as any new event occurring more than 21 days after the index stroke or, if earlier, clearly in another part of the brain (eg, contralateral hemisphere) after the preceding stroke. We were not in a position to assess accurately the frequent neurological changes known to occur[13] within the first few days of the stroke since many patients remained at home throughout their illness. Recurrences of subarachnoid hemorrhage were included even if they occurred within 21 days of the first stroke.

A stroke recurrence was classified as disabling if it was judged to have led to a new disability in the activities of daily living covered by the Barthel Index.[14] A disabling recurrence with symptoms that lasted longer than 7 days was classified as being "severe."

The pathological type of stroke recurrence was determined by a CT scan within 28 days of the recurrence or examination of the brain at autopsy. We used the Guy's Hospital Diagnostic Score to define pathological type of first stroke but not recurrent stroke because of the relative paucity of clinical data available for the latter group. The cause of death was coded using the definitions given by Dennis et al.[6]

Statistical Methods

Actuarial analysis was used. Log rank methods of comparison were used for univariate analysis[15] with the results expressed as odds ratio with confidence intervals (CIs). Average annual rates were calculated according to the formula $1-((1-P)^{1/n})$, where P equals the cumulative risk of recurrence at n years.[16] CIs for proportions or rates were calculated according to Gardner and Altman.[17] Comparisons between the risk of first recurrence in stroke survivors and the risk of stroke in the same general population used age- and sex-specific stroke incidence from the OCSP[7] and the Person Years Program[18] to calculate the expected frequency of stroke. CIs for the ratio of the observed to the expected frequency were calculated from the Poisson distribution.[17]

Results

Six hundred seventy-five patients with a first stroke were registered during a 4-year period. Their mean age was 72 years, and 318 (47%) were male. The pathological type of first stroke was cerebral infarction in 545 (81%), primary intracerebral hemorrhage in 66 (10%), subarachnoid hemorrhage in 33 (5%), and stroke of unknown pathological type in 31 (5%). Surviving patients were followed for a minimum of 2 and up to 6.5 years.

Few of the long-term survivors of stroke in this cohort were treated with antiplatelet or anticoagulant drugs. Twenty-eight (6%) of the 496 patients who survived at least 6 months received antiplatelet drugs, 6 (1%) were anticoagulated, and 83 (17%) were treated with an antihypertensive drug.

One hundred eighty recurrent strokes occurred during the follow-up period. One hundred thirty-five were first recurrences, 39 were second recurrences, 5 were third recurrences, and 1 was a fourth recurrence. The pathological type of recurrence was determined in only 57 (42%) of the 135 first recurrences, but of the 47 where the pathology was known after cerebral infarction, 45 (96%) were ischemic (Table 1). Of the 31 patients with a first stroke in whom the pathological type was not defined by CT, autopsy, or the Guy's Hospital Diagnostic Score, only 3 survived to have a recurrent stroke.

Thirty-two (24%) of the 135 first recurrences and 8 (21%) of the 39 second recurrences were rapidly resolving with symptoms lasting less than a week. Fifty-two (39%) first recurrences and 10 (26%) second recurrences were severe; 94 (14%) of the 675 patients suffered 1 severe recurrence, 20 (3%) patients suffered 2. Twenty-three (17%; 95% CI, 11% to 24%) patients died within 30 days of their first recurrence, not significantly different from the 30-day case fatality of first stroke (19%).[6] Nine (23%; 95% CI, 10% to 36%) died within 30 days of their second recurrence.

TABLE 1. Pathology of the First Recurrent Stroke According to the Pathological Type of the First Stroke

	First Recurrence				
	CI	PICH	SAH	Unknown	Total
First stroke					
CI	45	2	0	75	122
PICH	2	2	0	3	7
SAH	0	0	3	0	3
Unknown	3	0	0	0	3
Total	50	4	3	78	135

CI indicates cerebral infarction; PICH, primary intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.

Absolute Risks

For all patients, a Kaplan-Meier survival curve showing the percentage of patients free of recurrence (excluding deaths due to causes other than recurrent stroke) is shown in Fig 1, and the absolute risks of suffering a first recurrence within 5 years of the first stroke are shown in Table 2. The risk of having a severe recurrence was 20% (95% CI, 14% to 31%) by 5 years. The period of highest absolute risk of recurrence was in the first 6 months. The risk by 6 months was 9% (95% CI, 6% to 11%) and that in the first year was 13% (95% CI, 10% to 16%). This was significantly higher than the average annual risk over the subsequent 4 years (estimated at 4.3%). The absolute risk of recurrent stroke in patients with cerebral infarction (n=545) was 29.7% (95% CI, 19% to 40%) by 5 years, very similar to that for all strokes.

The risk of stroke recurrence should be considered in the context of the high fatality rate after stroke. Both death and stroke recurrence represent poor outcomes and patients who have died are not at risk of another stroke. When death and recurrent stroke were combined the risk of suffering a recurrence or dying by 5 years after first stroke was 63% (95% CI, 53% to 73%) (see Fig 2). The majority of deaths were cardiac.[6] There was a 41% (95% CI, 32% to 51%) risk of suffering either a cardiac death or a stroke recurrence within 5 years of the stroke.

Relative Risks

The risk of having a first recurrent stroke after a first stroke compared with the risk of first-ever stroke in people of similar age and sex in the general population is shown in Table 3. Despite a trend for the absolute risk of first recurrence to decrease with time, it remained significantly higher than the risk of a first stroke in the general population in every year after stroke, apart from the fifth. As only 87 patients who had not suffered a stroke recurrence were still being followed 5 years after the stroke, these estimates of relative risk became less precise in later years. The relative risk of recurrence in

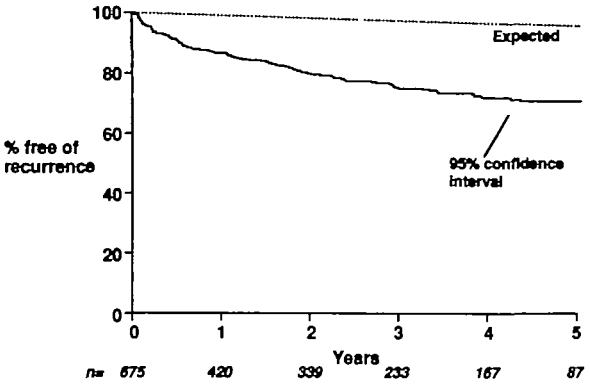

FIG 1. Graph showing the probability that, given survival, stroke patients will remain free from a stroke recurrence, compared with the expected probability of subjects in the same general population remaining free from a first stroke (derived from Oxfordshire Community Stroke Project incidence data, 1981 to 1986). Stipples indicate 95% confidence intervals. n indicates number at risk at the beginning of each year.

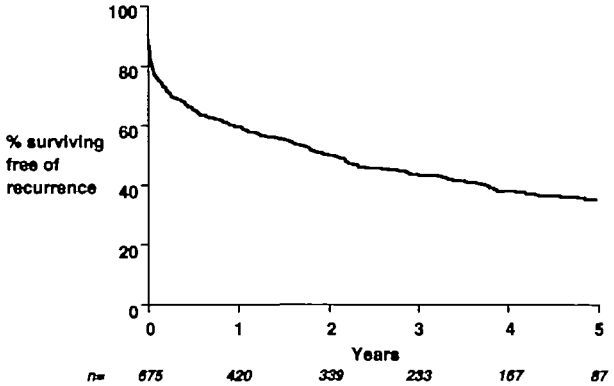

FIG 2. Graph showing the probability of stroke patients surviving free from stroke recurrence. In this survival curve both death and stroke recurrence are included as end points. Stipples indicate 95% confidence intervals. n indicates the number at risk at the beginning of each year.

patients with a stroke caused by cerebral infarction was very similar to those for all stroke, ie, 15.4 (95% CI, 12% to 20%) by the end of the first year and 9.4 (95% CI, 8% to 11%) over the entire follow-up period.

Prognostic Variables

There was no significant difference in the risk of recurrence between men and women (odds ratio, 1.2; 95% CI, 0.8 to 1.7). In this cohort, men (mean age, 70.5 years) were significantly younger than women (mean age, 76.4 years). Despite an increased incidence of first stroke in older age groups there was, after the stroke, no clear increase in the risk of recurrence with age (Fig 3; χ^2 trend [df=1] 0.38; P>.5).

There was no significant difference in the risk of stroke recurrence between the different pathological types of stroke (Fig 4; χ^2 [df=2] 1.3; P=.5), but only three patients suffered a recurrent subarachnoid hemorrhage and these all occurred early, on days 6, 11, and 33. The risk of recurrence after primary intracerebral hemorrhage appeared to be similar to the risk after cerebral infarction (log rank odds ratio, 1.12; 95% CI, 0.54 to 2.31) but after the first year only 27 patients were alive and free of recurrence.

Nine vascular risk factors were analyzed for an association with stroke recurrence in patients presenting with cerebral infarction (n=545). Log rank odds ratios (Table 4) were calculated from Kaplan-Meier curves stratified by age where there was an association (heart failure, hypertension, atrial fibrillation, and smoking). The data were more than 95% complete for all the baseline predictors, but data on blood pressure (BP) at the 1-month follow-up visit were available for only the 260 patients registered during the last 2 years of the study. The only statistically significant association on univariate analysis was with current smoking at the time of the stroke. The lack of an association with either a documented history of hypertension or a diastolic BP >100 mm Hg at 1 month poststroke was examined further by looking for an association with a BP in excess of 160/90 at notification (odds ratio, 1.2; 95% CI, 0.9 to 1.5) or a trend of increasing risk with increasing systolic (χ^2 trend [df=1] 0.04, P>.5) or diastolic (χ^2 0.02, P>.5) BP at notification, but in no case was there a significant association.

Discussion

Survivors of stroke are naturally anxious about the possibility of recurrence[19] and if recurrence does occur it can have a devastating effect on morale and be the final insult that prevents a patient from regaining independence.[20] Patients were most at risk of stroke recurrence in the first 6 months, with the risk in the first year being more than twice the average annual risk of the subsequent 4 years. Although there was a trend toward a lower annual risk with increasing time after the stroke, patients were still at significantly greater risk of stroke than the general population up to 5 years after the first stroke. Measures to prevent recurrent strokes therefore need to be started as soon as possible and continued for at least 4 years.

Although it has not been a universal finding,[21,22] previous studies have found a higher risk of recurrence in the first year poststroke[23,24] and this may be an explanation for the higher average annual risk of recurrence recorded in studies with a short follow-up (eg, 10% a year recorded by Terent[25]). Population-based studies with longer follow-up periods report an average annual risk of stroke recurrence ranging, as in this study, between 4% and 6%.[11,21,23,26,27] Interestingly, the risk of stroke after transient ischemic attack in the

TABLE 2. Actuarial Risks of a First Recurrent Stroke Within Defined Time Intervals After the First Stroke

	0-6 Months	6-12 Months	2 Years	3 Years	4 Years	5 Years
% Risk,	8.6	4.6	6.7	5.0	3.3	1.3
95% confidence interval	6.5-10.7	2.6-6.6	2.7-7.3	1.0-5.6	0.0-3.0	3.0-15.0
% Cumulative risk,	8.6	13.2	19.9	24.9	28.2	29.5
95% confidence interval	6.5-10.7	10.0-16.4	15.3-23.7	19.2-30.4	21.3-34.9	19.8-39.0
No. at risk	675	463	420	339	233	167

TABLE 3. Number of First Stroke Recurrences In Each Calendar Year After the First Stroke Compared With the Expected Number of First Strokes In the Same General Population

Year	Observed (O)	Expected (E)	O/E	95% Confidence Interval of O/E
1	70	4.5	15.4	12.1-19.0
2	31	3.6	8.5	5.6-11.8
3	17	2.6	6.7	3.9-10.7
4	9	2.0	4.5	2.1-8.6
5	2	1.0	2.0	0.3-7.4
0-6.5	135	14.0	9.6	8.0-11.3

OCSP has also been estimated to be higher in the first year after the transient ischemic attack, at about 12%, falling to much lower risks in subsequent years.[28]

The cumulative risk of stroke recurrence after cerebral infarction in the OCSP, 30% at 5 years, was significantly higher than a 19% risk recorded from Rochester, Minnesota,[21] despite a virtually identical risk of first stroke in the general population. There may be methodological reasons for the difference. The OCSP was, in principle, prospective while the Rochester study was retrospective, relying on documentation of stroke recurrence in the Rochester medical record linkage system, and mild recurrences may have been missed. It should be stated however that, despite a prospective design, many stroke recurrences in the OCSP were not identified until the next follow-up visit, which could have been up to a year after the recurrence occurred. In these cases, the identification of stroke recurrences depended on accurate recall by the patient and/or adequate documentation in the medical record. The Rochester medical record system is efficient and, as it achieves a high level of case ascertainment of incident cases,[29] it is reasonable to assume that it is about as sensitive to recurrent cases as our system. If the difference in recurrence risk between the OCSP and Rochester studies is real, it is surprising; in the decades that have elapsed between the studies measures have been introduced that might have reduced the incidence of stroke recurrence. It may reflect more intense secondary prevention of vascular disease in Rochester than was practiced in Oxfordshire, but we have no comparative data on which to test this hypothesis.

This study offers no simple clinical criteria for selective application of secondary prevention measures after

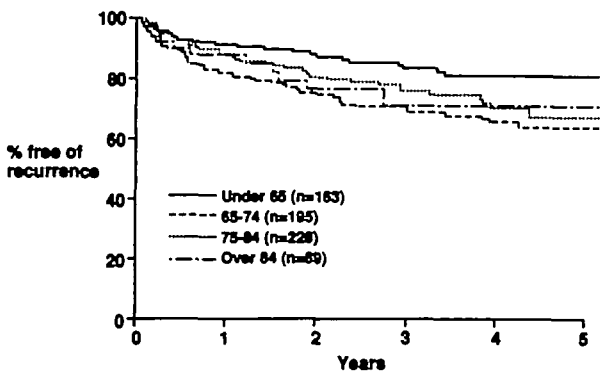

FIG 3. Graph showing the probability that, given survival, stroke patients will remain free from a stroke recurrence, stratified by age.

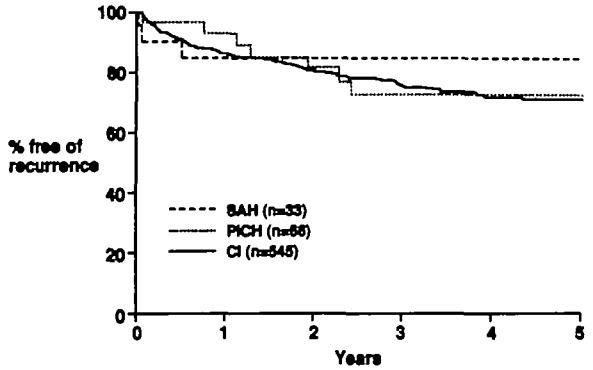

FIG 4. Graph showing the probability that, given survival, stroke patients will remain free from a stroke recurrence, stratified by the pathological type of first stroke. SAH indicates subarachnoid hemorrhage; PICH, primary intracerebral hemorrhage; and CI, cerebral infarction.

stroke. We failed to confirm an increased risk of stroke recurrence among men, as originally reported in the Framingham Study,[27] or an increased risk with age. Patients under 65 years at the time of the stroke did have a somewhat lower risk than older age groups reflecting, perhaps, less widespread vascular disease. The risk of recurrence following primary intracerebral hemorrhage was similar to that following cerebral infarction and, despite the undoubted effect of hypertension[30] and atrial fibrillation[31] on the incidence of first stroke, a previous history of hypertension, ischemic heart disease, or atrial

TABLE 4. Prognostic Variables Associated With Stroke Recurrence In 545 Patients With a First Stroke Due to Cerebral Infarction

Feature	Odds Ratio* for Stroke Recurrence, 95% Confidence Interval	
Smoking	1.66	1.10-2.51
Diabetes	1.71	0.90-3.26
Atrial fibrillation	1.24	0.73-2.11
Cardiac failure	1.14	0.78-1.67
Transient ischemic attack	1.13	0.72-1.77
Angina/myocardial infarction	1.08	0.71-1.73
Intermittent claudication	1.05	0.64-1.41
Hypertension	1.01	0.71-1.46
BP >100 mm Hg diastolic at the 1-month visit	1.13	0.57-2.0

Smoking indicates current pipe, cigar, or cigarette smoking at stroke onset (n=67); Diabetes, previous diagnosis of diabetes mellitus at stroke onset (n=59); Atrial fibrillation, atrial fibrillation documented on ECG either at initial examination or at some time previous to the stroke (n=97); Cardiac failure, diagnosed at initial examination or from a cardiothoracic ratio >50% on chest radiography (n=212); Transient ischemic attack, history of one or more transient ischemic attacks before the stroke (n=100); Angina/myocardial infarction, past history of angina or documented myocardial infarction (n=132); Intermittent claudication, past history of intermittent claudication (n=67); Hypertension, previous diagnosis of hypertension documented in primary care record (n=257); BP >100 mm Hg diastolic, blood pressure (V sound) measured using a standard mercury sphygmomanometer (n=43).

*An odds ratio of 1 indicates that the variable was equally common among patients with and without a subsequent stroke recurrence.

fibrillation was not associated with an increased risk of recurrence after an initial cerebral infarct. These observations are limited by the small number of events, the univariate method of analysis, and, in the case of blood pressure, our failure to use a strictly standardized method of measurement. However, the factors that increase the risk of a first stroke may not necessarily be so important in predicting a recurrent stroke.

Survivors of stroke are advised to seek information from their doctor on the risks of a further stroke and measures that can be used to prevent recurrence.[32] In response, physicians can reassure patients that, if this is their first stroke, the risk of a recurrence falls after the first year to about 4% per year and about 40% of recurrences will not be of functional significance. These estimates should be considered in the context of the low probability of surviving to 5 years without a stroke recurrence and, as no subgroup of ischemic stroke survivors has been identified as having a particularly low risk of recurrence, all suitable patients should promptly be offered an antiplatelet agent and carotid endarterectomy as a first step toward secondary prevention.[1-3] Further trials are needed on other methods of secondary prevention, such as BP reduction in the normotensive range[30] and the use of cholesterol-lowering drugs.

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