Long-Term Risk of First Recurrent Stroke in the Perth Community Stroke Study

Graeme J. Hankey, MBBS, MD, FRCP, FRCPE, FRACP; Konrad Jamrozik, MBBS, DPhil, FAFPHM; Robyn J. Broadhurst, BA, BSc; Susanne Forbes, RN; Peter W. Burvill, MBBS, MD, FRANZCP; Craig S. Anderson, MBBS, PhD, FRACP, FAFPHM; Edward G. Stewart-Wynne, MBChB, FCP(SA), FRACP

Background and Purpose—Few community-based studies have examined the long-term risk of recurrent stroke after an acute first-ever stroke. This study aimed to determine the absolute and relative risks of a first recurrent stroke over the first 5 years after a first-ever stroke and the predictors of such recurrence in a population-based series of people with first-ever stroke in Perth, Western Australia.

Methods—Between February 1989 and August 1990, all people with a suspected acute stroke or transient ischemic attack of the brain who were resident in a geographically defined region of Perth, Western Australia, with a population of 138 708 people, were registered prospectively and assessed according to standardized diagnostic criteria. Patients were followed up prospectively at 4 months, 12 months, and 5 years after the index event.

Results—Three hundred seventy patients with a first-ever stroke were registered, of whom 351 survived >2 days. Data were available for 98% of the cohort at 5 years, by which time 199 patients (58%) had died and 52 (15%) had experienced a recurrent stroke, 12 (23%) of which were fatal within 28 days. The 5-year cumulative risk of first recurrent stroke was 22.5% (95% confidence limits [CL], 16.8%, 28.1%). The risk of recurrent stroke was greatest in the first 6 months after stroke, at 8.8% (95% CL, 5.4%, 12.1%). After adjustment for age and sex, the prognostic factors for recurrent stroke were advanced, but not extreme, age (75 to 84 years) (hazard ratio [HR], 2.6; 95% CL, 1.1, 6.2), hemorrhagic index stroke (HR, 2.1; 95% CL, 0.98, 4.4), and diabetes mellitus (HR, 2.1; 95% CL, 0.95, 4.4).

Conclusions—Approximately 1 in 6 survivors (15%) of a first-ever stroke experience a recurrent stroke over the next 5 years, of which 25% are fatal within 28 days. The pathological subtype of the recurrent stroke is the same as that of the index stroke in 88% of cases. The predictors of first recurrent stroke in this study were advanced age, hemorrhagic index stroke, and diabetes mellitus, but numbers of recurrent events were modest. Because the risk of recurrent stroke is highest (8.8%) in the first 6 months after stroke, strategies for secondary prevention should be initiated as soon as possible after the index event. **(*Stroke*. 1998;29:2491-2500.)**

Key Words: Australia ■ prognosis ■ recurrence ■ stroke outcome

Whenever a stroke occurs, the patient, the patient's family, and the physician want to know the risk of another stroke, the likely timing of another stroke, how severe it may be, and whether it can be prevented. Many studies of recurrent stroke have been fraught with methodological problems such as retrospective design, hospital settings (predisposing to referral bias and the study of nonrepresentative samples of patients), nonstandard definitions, and lack of blinding to details of the primary event, such as the pathological nature of the initial stroke. The few prospective, large, community-based studies indicate that the risk of recurrence after stroke varies from 1.7% to 4% in the first 30 days, 6% to 13% in the first year, and 5% to 8% per year for the next 2 to 5 years, culminating in an absolute risk of recurrence within 5 years of 19% to 42%.[1–14]

The factors reported to have been associated with an increased risk of recurrent stroke in community-based and hospital-based series include increasing age,[2,5,9] male sex,[6] female sex,[15] clinical stroke syndrome (partial anterior and posterior circulation syndromes 4.9% and 4.8% within the first 30 days, compared with lacunar syndrome 0.3% in the first 30 days[13]), history of transient cerebral ischemic attack,[10,14] hypertension,[6,10–12,14,16,17] initial elevated blood pressure,[11,17] low blood pressure,[18] cigarette smoking,[13] alcohol abuse,[7] diabetes mellitus,[5,10,16,17] elevated blood glucose,[7,16] history of coronary heart disease,[6,9,15] atrial fibrilla-

Received May 21, 1998; final revision received September 28, 1998; accepted September 28, 1998.

From the Stroke Unit, Department of Neurology, Royal Perth Hospital, Perth, Western Australia (G.J.H., E.G.S-W.); Departments of Public Health (K.J., R.J.B., S.F.) and Psychiatry and Behavioral Science (P.W.B.), University of Western Australia, Perth; and Faculty of Medicine and Health Science, University of Auckland, Auckland, New Zealand (C.S.A.).

Correspondence to Dr Graeme J Hankey, Stroke Unit, Department of Neurology, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia 6001, Australia. E-mail gjhankey@cyllene.uwa.edu.au

Stroke **is available at http://www.strokeaha.org**

tion,[12,14] valvular heart disease and congestive heart failure,[15,19] peripheral vascular disease, abnormal initial cranial CT scan,[17] ECG evidence of left ventricular hypertrophy, echocardiographic evidence of atherosclerotic disease of the aortic arch,[20] severity of carotid artery stenosis,[21,22] and the occurrence of dementia after stroke.[15] A reduced risk of recurrent stroke has been associated with a low diastolic blood pressure, no history of stroke, no history of diabetes, and an infarct of unknown cause.[17] However, no independent factor has consistently been associated with an increased or decreased risk of recurrence.

We conducted a prospective community-based study of a cohort of patients with stroke followed over 5 years to document their outcome in the long term and to identify the factors present at baseline that predicted a first recurrent stroke.

Subjects and Methods

Study Design

Between February 20, 1989, and August 19, 1990 inclusive, the Perth Community Stroke Study (PCSS) registered all episodes of possible acute cerebrovascular disease in a geographically defined segment of Perth, Western Australia.[23,24] The study population comprised all persons living in the central business district and inner northern suburbs of the Perth metropolitan area and was defined by the Swan River to the south and east, a major arterial road to the west, and the city limit to the north. The study area comprised 8 complete postal code districts plus part of a ninth that was actually bisected by the road on the western side. Based on the Australian Bureau of Statistics 1986 Census, the estimated population of the study area (on June 30, 1989) was 138 708 persons (69 008 males and 69 700 females). Comparison with census figures for the remainder of Perth showed that the population of the study area contained proportions of elderly persons and those born overseas (particularly from Southern European countries) that were slightly higher than average. Otherwise, the socioeconomic characteristics, patterns of admission to the hospital, and length of time in the hospital for stroke were generally representative of those for the whole city (total population, 1.2 million).

Baseline Assessment

All cases meeting the clinical criteria for inclusion (resident in the PCSS geographic area and suffering a stroke, as defined below, between February 20, 1989, and August 19, 1990) underwent a standardized neurological assessment. Information obtained at baseline included data on associated illnesses, risk factors for cardiovascular disease, and patterns of disability and social activity in the immediate premorbid period.[23,24] The physical signs recorded for each patient at the onset of stroke included an assessment of the level of consciousness, the severity of limb paresis, and the presence or absence of urinary incontinence, cardiac failure, and atrial fibrillation. Level of consciousness at the time of presentation was measured by means of the Glasgow Coma Scale;[25] a score of 3 to 9 was defined as comatose, 10 to 14 as drowsy, and the top score of 15 as normal. The severity of limb paresis was only measured in patients assessed within 2 weeks of onset of the stroke. Severe paresis was defined as Motricity Index score of 0 to 50, moderate paresis 51 to 95, and normal or minimal paresis 96 to 100.[26] Patients were classified as incontinent if they had accidents, needed help, or needed an indwelling catheter during admission to hospital. Atrial fibrillation must have been confirmed on ECG within 1 month after the onset of stroke. Premorbid and baseline levels of disability were assessed with the modified scale of the Barthel Index of activities of daily living.[27,28] Patients were defined as independent if they had a score of 20 and as having some measure of dependency if they had a score of <20.

Follow-Up

Surviving patients were followed up prospectively at 4 months, 12 months, and 5 years, with vital status at the latter point initially being ascertained by electronic linkage of the study records to mortality data supplied by the Registrar General of Births, Marriages, and Deaths for Western Australia. Admissions to the hospital for stroke during the period of follow-up were identified by an equivalent linkage to the Hospital Morbidity Data System, a computerized, name-identified register of all admissions to hospitals in Western Australia that is maintained by the State Health Department.

Survivors at the time of the 5-year follow-up study were asked to participate in a structured interview and assessment at home by the study research nurse. The interview schedule included questions aimed at detecting a new stroke or other vascular event that had occurred during the period of follow-up.

For patients who had died or were suspected of having had a recurrent stroke or other vascular event, we independently reviewed all of the available clinical information and results of investigations obtained from records held by hospitals and physicians in private practice, and we reviewed the findings at necropsy (if one was performed) for patients whose death certificates indicated that the cause of death was vascular disease. We classified these events using standardized diagnostic criteria (see below).[29] The physician (G.J.H.) assessing whether a recurrent stroke had occurred and, if so, its type was blind to the pathological and etiologic nature of the initial stroke.

Definitions

Stroke was defined according to the World Health Organization criteria as "rapidly developing symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin."[30] The term "global" refers mainly to subarachnoid hemorrhage.

Like others,[8,13] we defined a recurrent stroke as a stroke, using the above definition,[30] in which (1) there was clinical evidence of the sudden onset of a new focal neurological deficit with no apparent cause other than that of vascular origin (ie, the deficit could not be ascribed to an intercurrent acute illness, epileptic seizure, or toxic effect) occurring at any time after the index stroke; or (2) there was clinical evidence of the sudden onset of an exacerbation of a previous focal neurological deficit with no apparent cause other than that of vascular origin occurring >21 days after the index stroke.

Each recurrent stroke was classified as ischemic, hemorrhagic, or of undetermined nature on the basis of a CT or MRI scan performed within 28 days of recurrence or autopsy examination of the brain. Etiologic subtypes of ischemic stroke were defined according to standardized criteria.[24]

Statistical Analysis

Crude associations between the occurrence of recurrent stroke outcome events and each of 26 independent categorical variables recorded at baseline were assessed by preliminary cross-tabulations with the χ^2 test and SAS software.[31] The Kaplan-Meier product-limit technique was used to generate survival probabilities and survival curves. In addition, we compared the cumulative incidence of first recurrent strokes over 5 years of follow-up with the expected incidence of strokes in the general population, derived from the age- and sex-specific rates of first-ever stroke from the PCSS[23] using statistical techniques developed at the Mayo Clinic[32] and calculated using the SAS macro Survexp.[31] Confidence limits (CL) for the ratio of the observed to the expected frequency were calculated from the Poisson distribution.[33] Multiple regression with the use of Cox proportional hazards analysis modeling and EGRET software[34] was used to develop statistical models predicting occurrence of a new stroke within 5 years of a first stroke. The 26 independent variables were screened by univariate associations; after adjustment for age and sex, each variable was considered individually. When a variable was significant at the 0.1 level, it was chosen to contribute to the multivariate model. When a most parsimonious model was obtained

TABLE 1. Pathological Subtype of First Recurrent Stroke According to Pathological Subtype of Index Stroke

	Recurrent Stroke			
Index Stroke	CI	PICH	Undetermined	Total
CI (n=250)	33	1	4	38
Large-artery occlusion (n=170)	24	1	2	27
Lacunar (n=25)	5	...	...	5
Cardioembolic (n=43)	3	...	1	4
Boundary zone (n=12)	1	...	1	2
PICH (n=36)	3	3	4	10
Subarachnoid hemorrhage (n=13)	...	...	...	...
Undetermined (n=44)	1	...	3	4
Total (n=343)	37	4	11	52

CI indicates cerebral infarction.

by backward elimination, each variable was entered separately into the model to look for further effects.

Ethical Considerations

The protocol for the study was approved by the Committee for Human Rights at the University of Western Australia and by the Confidentiality of Health Information Committee of the Health Department of Western Australia. Patients or their next of kin gave permission for review of medical records pertaining to suspected vascular events occurring during follow-up.

Results

Study Population

The study initially registered 492 patients with acute stroke during the study period, among whom 370 patients (75%; 95% CL, 71%, 79%) had an acute first-ever stroke. Nineteen of these patients died within the first 2 days, and of the remaining 351, follow-up data at 5 years were available for 343 (98%). The present report focuses on this cohort of 343 patients with first-ever stroke for whom there was complete follow-up (and thus no censoring due to loss to follow-up). The mean age of these patients was 73±13 years, with a median of 76 years; 53% (181) were male, and 47% (162) female. The median age was 73 years for men and 78 years for women. Fifty-four percent of patients were Australian, 18% from the United Kingdom/Ireland, 18% from Europe, and 9% from other countries. Forty-eight percent of patients were living with spouse or partner at time of initial stroke (66% of men and 27% of women), and 52% were living with no partner (34% of men and 72% of women). Most patients were retired from work because of age (81%) or ill-health (6%); 8% were working full time or part time, 1% were unemployed, and 1% were receiving sickness benefits.

One in 5 patients was managed entirely outside the hospital during the acute phase (19%; 95% CL, 15%, 23%). The pathology of the index stroke was identified in 87% of index events. Cerebral infarction accounted for 73% of all strokes (95% CL, 68%, 78%), primary intracerebral hemorrhage (PICH) 10.5% (95% CL, 7%, 14%), and subarachnoid hemorrhage 3.8% (95% CL, 2%, 6%). Surviving patients contributed a minimum of 3.8 years and a maximum of 5.3 years of follow-up time.

Outcome at 5 Years

Five years after a first stroke, 199 patients (58%) had died and 52 (15%) had suffered a first recurrent stroke, of which 12 (23%) were fatal within 28 days. There were 164 patients who were censored because of death (ie, death occurred before a recurrent stroke) of the total of 199 deaths. Thirty-two of the 52 recurrent strokes were registered during the 1989–1990 incidence study, in which patients were recruited over 18 months and then followed up at 4 months and 12 months. The other 20 recurrent strokes were recorded at the time of the follow-up study in 1994–1995. Forty-three of the 52 recurrent strokes were detected by review of autopsy and medical records (all 32 in 1989–1990 and 11 in 1994–1995), and 9 were detected by the structured interview in 1994–1995.

Pathological Subtype of Recurrent Stroke

The majority (n=37, 71%) of recurrent strokes were due to cerebral infarction, and 89% (33/37) of new ischemic strokes occurred in patients with cerebral infarction as the index stroke. Among the 4 patients with new PICH, 3 occurred in patients with prior PICH (Table 1). In 88% (36) of the 41 patients in whom the pathological basis of both the index and recurrent event was known, these were identical.

Risk of Recurrent Stroke

The 5-year cumulative risk of first recurrent stroke was 22.5% (95% CL, 16.8%, 28.1%). The risk of recurrent stroke was greatest in the first 6 months after stroke, at 8.8% (95% CL, 5.4 to 12.1%) (Table 2 and Figure 1). The 5-year cumulative risk of surviving free of recurrent stroke was 77.6% (95% CL, 71.9%, 83.2%), as shown in Figure 1.

Table 3 shows the number of first recurrent strokes in each calendar year after the index stroke compared with the expected number of strokes in the general population of the same age and sex.

TABLE 2. Kaplan-Meier Estimates of Risk of Occurrence of a First Recurrent Stroke Within Defined Time Intervals After Index Stroke

	0–6 mo	6–12 mo	1–2 y	2–3 y	3–4 y	4–5 y
% Risk	8.8	4.1	1.0	4.9	3.9	2.0
95% CL	5.4, 12.1	1.5, 6.7	0.0, 2.4	1.8, 8.1	0.8, 6.9	0.0, 4.8
% Cumulative risk	8.8	12.5	13.4	17.7	20.8	22.4
95% CL	5.4, 12.1	8.5, 16.6	9.2, 17.5	12.9, 22.5	15.6, 26.1	16.8, 28.1
No. at risk	343	232	211	192	166	135

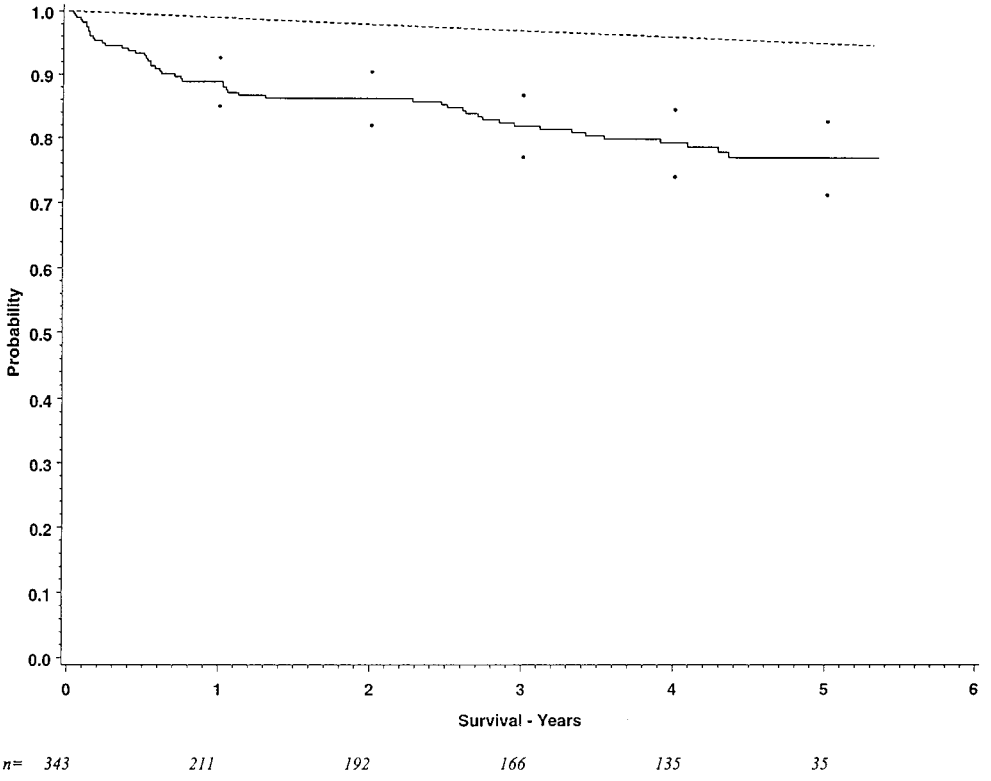

Figure 1. Kaplan-Meier survival curve showing the probability that, given survival, a patient with a stroke will remain free of a recurrent stroke (solid line) compared with the expected probability of people in the same general population remaining free from a first stroke (dotted line), derived from PCSS incidence data 1989–1990. Stipples indicate 95% CL; *n*, number at risk at the beginning of each year.

Predictors of First Recurrent Stroke Over 5 Years

Table 4 shows the associations of baseline prognostic variables with recurrent stroke in the 343 patients with a first-ever stroke. When all index hemorrhagic strokes, that is, cases of PICH plus those of subarachnoid hemorrhage, were considered as a single group, none of the relationships examined was statistically significant at the 5% level.

Figures 2, 3, and 4 show Kaplan-Meier survival curves for first recurrent stroke, stratified by the age of the patient, clinical syndrome, and pathology of the first stroke, respectively.

The multivariate prediction model for first recurrent stroke was based on 47 events in 337 patients (Table 5). After adjustment for sex, the prognostic factors for recurrent stroke were an index stroke that was hemorrhagic (hazard ratio [HR], 2.1; 95% CL, 0.98, 4.4) and diabetes mellitus (HR, 2.1; 95% CL, 0.95, 4.4), although neither of these was statistically significant at the 5% level. Patients aged 75 to 84 years at the time of their index stroke were significantly more likely than those aged <65 years to suffer a recurrent stroke.

Discussion

The risk of a recurrent stroke in the community of Perth, Western Australia, is similar to that reported in other community-based studies, particularly during the first year after stroke.[5,13] As was the case in the Oxfordshire Community Stroke Project (OCSP), we found that the risk of a recurrent stroke within the first 6 months after a first-ever stroke was ≈9% (8.8% in PCSS and 8.6% in OCSP), and after 1 year it was ≈13% (12.5% in PCSS and 13.2% in OCSP).[13] The risk of another stroke occurring in the 12 months after a first stroke was 8.5 (95% CL, 5.4, 11.6) times greater than the risk of first stroke in the general population

TABLE 3. Number of First Recurrent Strokes in Each Calendar Year After Index Stroke Compared With Expected Number of Strokes in the General Population of the Same Age and Sex

Year	No. at Risk	Observed	Expected	Observed/Expected	95% CL of Observed/Expected
0	343	...	...	...	...
1	211	29	3.4	8.5	5.4, 11.6
2	192	6	3.3	1.8	0.4, 3.3
3	166	9	3.3	2.7	0.9, 4.5
4	135	5	3.3	1.5	0.2, 2.8
5	35	3	3.4	0.9	0.0, 1.9

of the same age and sex, an estimate that is significantly less than the figure of 15.4 (95% CL, 12.1, 19.0) reported in the OCSP.[13] The reasons for this difference are unclear, but the 2 studies were conducted almost a decade apart, during which time it became much clearer that low-dose aspirin is a simple, inexpensive, and safe treatment for the secondary prevention of stroke.[35] We collected data concerning secondary prevention treatments at registration (baseline) and at follow-up at 4 and 12 months but not at discharge from hospital. Thus, we do not have a complete picture of medical management after

TABLE 4. Univariate Analysis of Prognostic Variables Associated With First Stroke Recurrence in 343 Patients With a First-Ever Index Stroke

Feature of Index Stroke (No. With Complete Data)	Prevalence, %	HR for Recurrent Stroke	95% CL
Age, y (343)			
0–64	21	1.0	...
65–74	24	1.5	0.66, 3.3
75–84	38	1.9	0.89, 3.9
≥85	16	0.8	0.22, 3.0
Sex (343)			
Male	53	1.0	...
Female	47	1.0	0.56, 1.7
Marital status (342)			
Partner	48	1.0	...
No partner	52	0.9	0.53, 1.6
Residential living arrangements (333)			
Own home, flat, or elderly unit	83	1.0	...
Lodge, hostel, or nursing home	14	0.8	0.25, 2.6
Social living arrangements (339)			
With spouse, family, or others	63	1.0	...
Alone	29	1.1	0.59, 2.0
Nursing home	7	2.2	0.54, 9.4
Pre-event Barthel score (340)			
Independent	73	1.0	...
Some dependency	27	1.4	0.70, 2.9
Pre-event Rankin score (341)			
No assistance	74	1.0	...
Requires assistance	25	1.0	0.44, 2.2
Cigarette smoking (339)			
Never smoked	43	1.0	...
Ex-smoker	33	0.8	0.43, 1.6
Current smoker	23	0.9	0.46, 1.8
Alcohol consumption (326)			
Lifelong nondrinker	25	1.0	...
Former drinker	11	0.8	0.29, 2.3
Drinks occasionally now	16	0.9	0.34, 2.2
Drinks daily or almost daily now	43	0.9	0.44, 1.7
History of hypertension (341)	62	1.3	0.71, 2.3
History of angina (340)	31	0.8	0.40, 1.5
History of myocardial infarction (340)	19	0.7	0.31, 1.6
Diabetes mellitus (337)	14	1.6	0.77, 3.3
Intermittent claudication (325)	16	1.1	0.50, 2.5
History of transient ischemic attack (300)	13	1.2	0.56, 2.5
Pathological subtype of initial stroke (343)			
Cerebral infarction	73	1.0	...
PICH	11	1.4*	0.71, 2.9
Subarachnoid hemorrhage	4		
Undetermined	13	2.7	0.96, 7.7

TABLE 4. Continued

Feature of Index Stroke (No. With Complete Data)	Prevalence, %	HR for Recurrent Stroke	95% CL
Etiologic subtype of initial stroke (343)			
Large-artery occlusion	50	1.0	...
Cardioembolic stroke	13	0.7	0.26, 2.1
Lacunar infarction	8	1.2	0.48, 3.2
Boundary zone infarction	4	0.9	0.21, 3.7
All other	27	1.6	0.85, 3.1
Clinical syndrome of initial stroke (298)			
Total anterior circulation	26	1.0	...
Partial anterior circulation	27	1.7	0.66, 4.2
Lacunar	22	1.3	0.50, 3.5
Posterior circulation	11	1.1	0.30, 3.8
Glasgow Coma Scale (310)			
No impairment	53	1.0	...
Mild impairment	25	1.2	0.60, 2.4
Severe impairment	13	0.5	0.07, 3.8
Motricity score (230)†			
None or mild impairment	27	1.0	...
Moderate impairment	25	1.0	0.50, 2.1
Severe impairment	16	0.5	0.12, 2.2
Barthel score at baseline (316)†			
Independent	19	1.0	...
Some dependency	73	1.3	0.62, 2.8
Incontinent at baseline (324)	42	0.9	0.45, 1.8
Cardiac failure at baseline (295)	8	0.8	0.19, 3.2
Atrial fibrillation at baseline (294)	73	0.8	0.25, 2.6
Clinical hypertension at baseline (257)‡	42	1.3	0.68, 2.5

*Comparison for PICH and subarachnoid hemorrhage combined, there being no recurrent strokes in patients with an index subarachnoid hemorrhage.

†Data not available for patients first seen late after the index event.

‡Either diastolic blood pressure ≥160 mm Hg or systolic blood pressure ≥160 mm Hg or both at baseline examination.

the index stroke and cannot judge whether this might explain the different relative survivals observed in the PCSS and the OCSP.

After the first year, the average annual risk of recurrent stroke for the next 4 years fell to ≈3%, which is again lower than the figures of 4% to 6% reported in most other population-based studies.[2–4,8,13] This is mainly because of the low frequency of stroke in the second year after an index event (1.0%), which is inconsistent with other years in our study (and other studies) and may reflect some incompleteness of ascertainment of recurrent events. Our patients were not followed up between 12 months and 5 years after their index events. Rather, recurrent strokes treated in the hospital were ascertained by linking identifying information from the inception cohort to the Hospital Morbidity Data System, an electronic file that includes all inpatient separations in Western Australia, while fatal recurrent strokes were detected by linkage of the cohort to the official death register. Our vulnerable area is therefore recurrent strokes occurring in patients who survived these events and were not treated in the hospital. We suspect that the recall of patients surviving to 5 years of the occurrence, up to 3 years earlier, of nonfatal, nondisabling recurrent strokes that were not severe enough to require admission to the hospital may have been incomplete. Similarly, it was impossible for us to detect mild events of this kind in patients who subsequently died of other causes.

The high rate of a recurrent stroke within the first year, and particularly the first few months, of first stroke is well recognized and consistent with the hypothesis that atheroma (the cause of most strokes) is an acute-on-chronic disease, causing recurrent episodes of thromboembolism before settling down as the endothelium of the ulcerated plaque heals. In the OCSP, the cumulative incidence of recurrent stroke over the year after cerebral infarction varied among the 4 clinical subtypes of cerebral infarction: from 6% in total anterior circulation infarction, 9% in lacunar infarction, 17% in partial anterior circulation infarction, to 20% in posterior circulation infarction.[36] There were 3 different patterns of recurrence: patients with partial anterior circulation infarction have a high risk of early recurrence (suggesting an active source of recurrent embolism); patients with posterior circu-

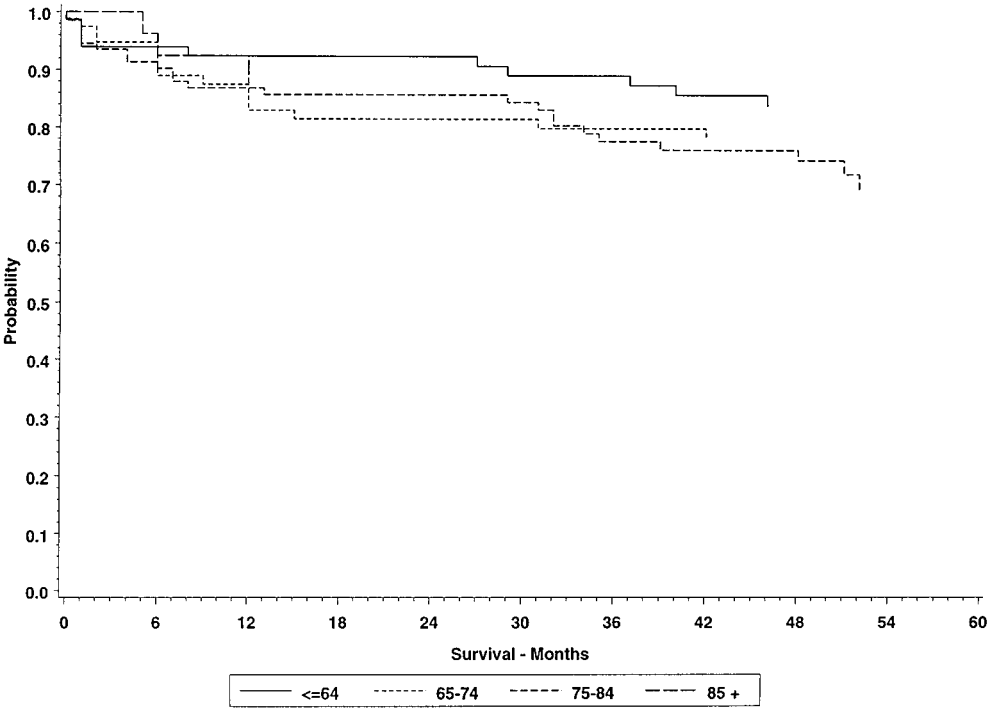

Figure 2. Kaplan-Meier survival curve showing the probability that, given survival, a patient with a stroke will remain free of a recurrent stroke, stratified by the age of the patient.

lation infarction have a moderately high risk early, with further episodes throughout the first year; and those with lacunar infarction have a low and fairly constant rate of recurrence, supporting the notion that lacunar infarcts occur as a result of occlusion of a single perforating artery and are not usually due to an active source of recurrent embolism.[37] Our results are consistent with these findings in that partial anterior circulation infarction was associated with the highest rate of recurrent stroke, although the association was not statistically significant (Table 4).

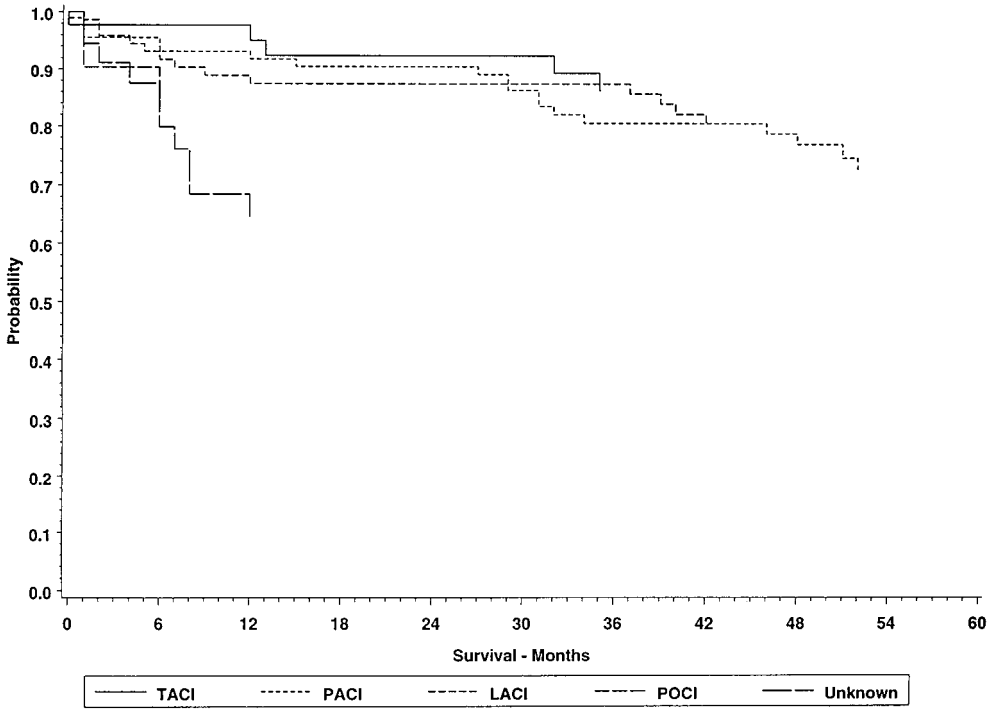

Figure 3. Kaplan-Meier survival curve showing the probability that, given survival, a patient with a stroke will remain free of a recurrent stroke, stratified by the clinical syndrome of first-ever stroke. TACI indicates total anterior circulation infarction; PACI, partial anterior circulation infarction; LACI, lacunar infarction; and POCI, posterior circulation infarction.

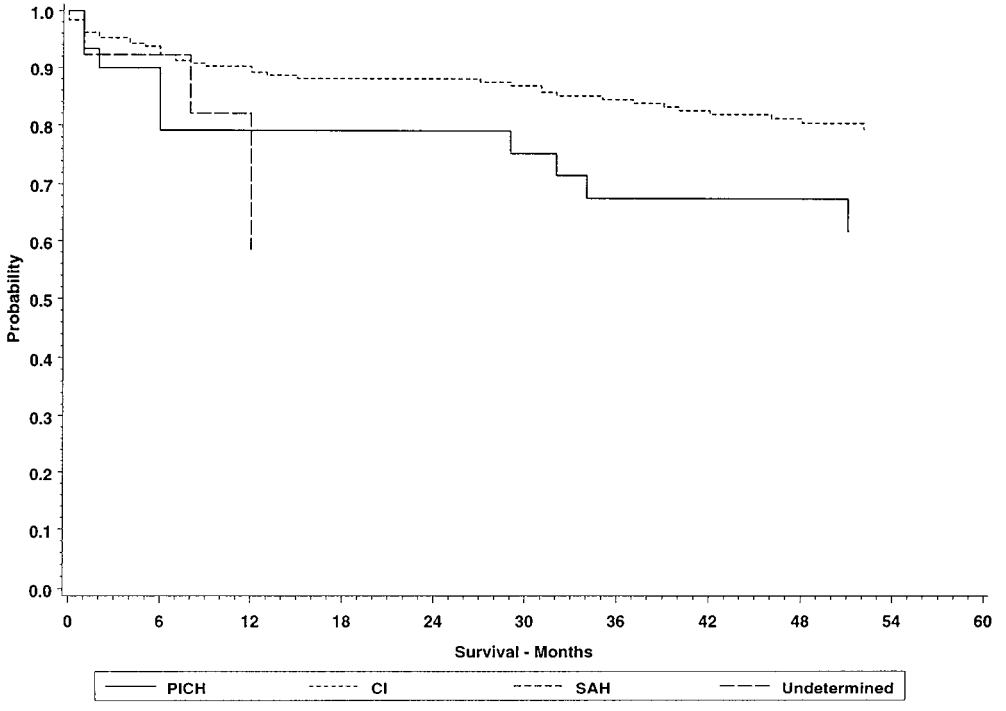

Figure 4. Kaplan-Meier survival curve showing the probability that, given survival, a patient with a stroke will remain free of a recurrent stroke, stratified by the pathological type of the index stroke. CI indicates cerebral infarction; SAH, subarachnoid hemorrhage.

We were unable to classify recurrent strokes into clinical subtypes. Previous studies provide some evidence that recurrent infarcts in patients with lacunar infarction are predominantly lacunar, supporting the hypothesis that lacunar infarctions are usually caused by intracranial obstruction of small vessels, but other studies have found that recurrent lacunar infarctions account for no more than ≈25% of recurrences (which is similar to the proportion of patients with first-ever ischemic stroke who are found to have a lacunar infarction).[38–40]

TABLE 5. Final Multivariate Prediction Model for First Recurrent Stroke Within 5 Years of Stroke (n=337)

Variable	HR	95% CL	*P*
Age, y			
0–64	1.0	...	...
65–74	2.0	0.8, 4.9	0.14
75–84	2.6	1.1, 6.2	0.02
≥85	1.2	0.3, 4.9	0.81
Sex			
Male	1.0	...	...
Female	0.8	0.5, 1.5	0.52
Pathological subtype of initial stroke			
Cerebral infarction	1.0	...	...
Hemorrhage*	2.1	0.98, 4.4†	0.06
Undetermined	2.7	0.8, 9.4	0.12
Diabetes mellitus			
No history at baseline	1.0	...	...
Present at baseline	2.1	0.95, 4.4†	0.07

*PICH or subarachnoid hemorrhage.
†Significant at 0.10 level only.

Factors that increase the risk of a first-ever stroke may not necessarily be as important in predicting a recurrent stroke. We identified advanced (but not extreme) age, hemorrhagic stroke, and diabetes mellitus as the independent predictors of recurrent stroke. We were surprised to identify diabetes as the single most important modifiable risk factor for recurrence (ahead of hypertension and heart disease, for example), but we note that several other studies, including the Rochester population study,[5] the Lehigh Valley study,[10] and the Stroke Data Bank,[16] also found diabetes to be an independent predictor of recurrence.[5,10,16,17] Although our statistical model is unstable because of the modest number of recurrent strokes on which it is based, these studies collectively support the increasing body of evidence that diabetes has widespread effects on vascular, hemorheologic, and coagulation systems. Furthermore, they emphasize that diabetes should be recognized as an important risk factor for recurrent stroke that is amenable to intervention. Similarly, patients with hemorrhagic stroke should also be considered at increased risk of recurrent stroke and investigated to identify an underlying treatable cause, such as poorly controlled hypertension or an arteriovenous malformation. Among populations with reasonable blood pressure control, lobar hemorrhages in particular appear to confer an increased risk of recurrent hemorrhagic stroke, presumably because they reflect a persistent underlying cause such as a small angioma (which tends to cause recurrent hemorrhage in the same site) or cerebral amyloid angiopathy (which tends to cause recurrent lobar hemorrhage in different sites).[40]

The high rate of early stroke recurrence that we and others have identified emphasizes the importance of early secondary prevention for those at increased risk. There is now evidence

from the International Stroke Trial and Chinese Aspirin Stroke Trial that early treatment with aspirin, within 48 hours of onset of acute ischemic stroke, prevents ≈5 recurrent strokes (7 fewer recurrent ischemic strokes but 2 more hemorrhagic strokes) and 9 nonfatal strokes or deaths in the first few weeks per 1000 patients treated ($2P<0.001$).[41,42] Early aspirin therapy is also associated with ≈13 (SD 5) fewer patients who are dead or dependent after some weeks or months of follow-up per 1000 treated ($2P<0.01$).[41,42] There have been no long-term prognostic studies beyond 5 years to indicate whether risks of stroke recurrence and the need for long-term treatments continue.

Conclusions

In conclusion, ≈1 in 6 survivors (15%) of a first-ever stroke experience a recurrent stroke over the next 5 years, and ≈25% of these first recurrent strokes are fatal within 28 days. The risk of recurrent stroke is highest (9%) in the first 6 months after the index stroke. The pathological subtype of the recurrent stroke is the same as that of the index stroke in 88% of cases. The predictors of recurrent stroke are advanced age, hemorrhagic stroke, and diabetes mellitus. Although diabetes is increasingly recognized as an important risk factor that is amenable to therapy, there is no single factor that has consistently been associated with an increased or decreased risk of recurrence in the literature. This may reflect differences between reports in the types of recurrent strokes studied (eg, first or multiple recurrence; pathological subtype [ischemic or hemorrhagic], etiologic subtype, severity [fatal, disabling, nondisabling], and timing [early or late]) but more probably reflects the interplay of several factors in determining the risk of recurrent stroke and the statistical instability of the prediction models because of the small numbers of recurrent strokes included. Larger community-based studies of recurrent stroke are required to resolve these uncertainties and to determine unambiguously the balance of benefits and risks associated with use of various secondary preventive treatments in particular subsets of patients.

Acknowledgments

The PCSS was originally funded by the National Health and Medical Research Council (NHMRC) of Australia. This follow-up study was supported by an additional grant from the Public Health Research and Development Committee of the NHMRC and by a grant from Healthway, Health Promotion in Western Australia. The study would not have been possible without the help of the patients and their families and the generous cooperation of doctors, nursing homes, hospitals, the Health Department, the Registrar General, and the Australian Bureau of Statistics in Western Australia and the Perth Coroner.

References

1. Ricci S, Celano MG, Guercini G, Rucireta P, Vitali R, La Rosa F, Duca E, Ferraguzzi R, Paolotti M, Seppoloni D, et al. First year results of a community-based study of stroke incidence in Umbria, Italy. *Stroke*. 1989;7:853–857.
2. Matsumoto N, Whisnant JP, Kurland LT, Okazaki H. Natural history of stroke in Rochester, Minnesota 1955–1969: an extension of a previous study 1945–1954. *Stroke*. 1973;4:20–29.
3. Dombovy M, Basford J, Whisnant J, Bergstrahl E. Disability and use of rehabilitation services following stroke in Rochester, Minnesota, 1975–1979. *Stroke*. 1987;18:830–836.
4. Meissner I, Whisnant JP, Garraway WM. Hypertension management and stroke recurrence in a community (Rochester, Minnesota, 1950–1979). *Stroke*. 1988;19:459–463.
5. Petty G, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. *Neurology*. 1998;50:208–216.
6. Sacco RL, Wolf PA, Kannel WB, McNamara PM. Survival and recurrence following stroke: the Framingham Study. *Stroke*. 1982;13: 290–295.
7. Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalised cerebral infarction in an urban community: the Northern Manhattan Stroke Study. *Neurology*. 1994;44: 626–634.
8. Schmidt EV, Smirnov VE, Ryabova VS. Results of the seven year prospective study of stroke patients. *Stroke*. 1988;19:942–949.
9. Viitanen M, Eriksson S, Asplund K. Risk of recurrent stroke, myocardial infarction and epilepsy during long-term follow-up after stroke. *Eur Neurol*. 1988;28:227–231.
10. Alter M, Sobel E, McCoy RL, Francis ME, Davanipour Z, Shofer F, Levitt LP, Meehan EF. Stroke in the Lehigh Valley: risk factors for recurrent stroke. *Neurology*. 1987;37:503–507.
11. Alter M, Friday G, Min Lai S, O'Connell J, Sobel E. Hypertension and risk of stroke recurrence. *Stroke*. 1994;25:1605–1610.
12. Min Lai S, Alter M, Friday G, Sobel E. A multifactorial analysis of risk factors for recurrence of ischemic stroke. *Stroke*. 1994;25:958–962.
13. Burn J, Dennis MS, Bamford J, Sandercock PAG, Wade D, Warlow CP. Long-term risk of recurrent stroke after a first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. 1994;25:333–337.
14. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. *Cerebrovasc Dis*. 1996; 6(suppl 2):11. Abstract.
15. Petty Moroney JT, Bagiella E, Tatemichi TK, Paik MC, Stern Y, Desmond DW. Dementia after stroke increases the risk of long-term stroke recurrence. *Neurology*. 1997;48:1317–1325.
16. Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR. Determinants of early recurrence of cerebral infarction: the Stroke Data Bank. *Stroke*. 1989;20:983–989.
17. Hier DB, Foulkes MA, Swiontoniowski M, Sacco RL, Gorelick PB, Mohr JP, Price TR, Wolf PA. Stroke recurrence within 2 years after ischemic infarction. *Stroke*. 1991;22:155–161.
18. Irie K, Yamaguchi T, Minematsu K, Omae T. The J-curve phenomenon in stroke recurrence. *Stroke*. 1993;24:1844–1849.
19. Broderick JP, Phillips SJ, O'Fallon WM, Frye RL, Whisnant JP. Relationship of cardiac disease to stroke occurrence, recurrence, and mortality. *Stroke*. 1992;23:1250–1256.
20. The French Study of Aortic Plaques in Stroke Group. Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. *N Engl J Med*. 1996;334:1216–1221.
21. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet*. 1991;337:1235–1243.
22. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445–453.
23. Anderson CS, Jamrozik KD, Burvill PW, Chakera TMH, Johnson GA, Stewart-Wynne EG. Ascertaining the true incidence of stroke: experience from the Perth Community Stroke Study, 1989–1990. *Med J Aust*. 1993;158:80–84.
24. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for one year among different subtypes of strokes: results from the Perth Community Stroke Study. *Stroke*. 1994;25:1935–1944.
25. Teasdale G, Murray G, Parker L, Jennett B. Adding up the Glasgow Coma Scale. *Acta Neurochir Suppl (Wien)*. 1979;28:13–16.
26. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. *Eur Neurol*. 1980;19:382–389.
27. Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *Int Disabil Stud*. 1988;10:64–67.
28. Collin C, Wade DT. The Barthel ADL Index: a reliability study. *Int Disabil Stud*. 1988;10:61–63.
29. WHO MONICA Project (prepared by Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A). Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. *Circulation*. 1994;90:583–612.
30. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ*. 1980;58:113–130.

31. Statistical Analysis System Institute. *SAS Version 6.0*. Cary, NC: SAS Inc; 1997.
32. Therneau T, Sicks R, Bergstralh E, Offord J. *Expected Survival Based on Hazard Rates*. Rochester, Minn: Section of Biostatistics, Mayo Clinic; 1994. Technical Report No. 52.
33. Machin D, Gardner MJ. Calculating confidence intervals for survival time analyses. In: Gardner MJ, Altman DG, eds. *Statistics with Confidence*. London, England: British Medical Journal; 1989:64–70.
34. Statistics and Epidemiological Research Corporation. *EGRET Epidemiological Computer Package*. Seattle, Wash: SERC; 1991.
35. Antiplatelet Trialists Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet therapy. *BMJ*. 1988;296:320–331.
36. Bamford J, Sandercock PAG, Dennis MS, Burn J, Warlow CP. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337:1521–1526.
37. Bamford J, Warlow CP. Evolution and testing of the lacunar hypothesis. *Stroke*. 1988;19:1074–1082.
38. Yamamoto H, Bogousslavsky J. Pathophysiological patterns of stroke recurrence. *Cerebrovasc Dis*. 1997;7(suppl 1):5–9.
39. Samuelsson M, Lindell D, Norrving B. Presumed pathogenetic mechanisms of recurrent stroke after lacunar infarction. *Cerebrovasc Dis*. 1996;6:128–136.
40. Yamamoto H, Bogousslavsky J. Mechanisms of second and further strokes. *J Neurol Neurosurg Psychiatry*. 1998;64:771–776.
41. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischemic stroke. *Lancet*. 1997; 349:1569–1581.
42. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: a randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischemic stroke. *Lancet*. 1997;349:1641–1649.