Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies

Karsten Bruins Slot,[1] Eivind Berge,[1] Paul Dorman,[2] Steff Lewis,[3] Martin Dennis,[3] Peter Sandercock,[3] on behalf of the Oxfordshire Community Stroke Project, the International Stroke Trial (UK), and the Lothian Stroke Register

EDITORIAL by Rodgers and Thomson

[1]Department of Internal Medicine, Ullevaal University Hospital, NO-0407 Oslo, Norway
[2]Department of Neurology, Newcastle General Hospital, Newcastle upon Tyne
[3]Department of Clinical Neurosciences, Western General Hospital, Edinburgh
Correspondence to: K Bruins Slot karsten.bruins.slot@medisin.uio.no

BMJ 2008;336:376-9
doi:10.1136/bmj.39456.688333.BE

ABSTRACT

Objective To estimate the impact on long term survival of functional status at six months after ischaemic stroke.

Design Prospective cohort study.

Settings Three cohorts: Oxfordshire community stroke project, Lothian stroke register, and the first international stroke trial (in the United Kingdom).

Participants 7710 patients with ischaemic stroke registered between 1981 and 2000 and followed up for a maximum of 19 years.

Main outcome measures Functional status at six months after stroke assessed with modified Rankin scale or "two simple questions." Mortality during follow-up. Survival analysis with Kaplan-Meier curves, log rank test, and Cox's regression model.

Results In a combined analysis of all three cohorts, among patients who survived to assessment six months after the index stroke, the subsequent median length of survival among those independent in daily living and those dependent was 9.7 years (95% confidence interval 8.9 to 10.6) and 6.0 years (5.7 to 6.4), respectively. In a combined analysis of the Oxfordshire and Lothian cohorts, subsequent median survival fell progressively from 12.9 years (10.0 to 15.9) for patients with a Rankin score of 0-1 at six months after the stroke to 2.5 years (1.4 to 3.5) for patients with a Rankin score of 5. All previously stated differences in median survival were significant (log rank test $P<0.001$). The influence of functional outcome on survival remained significant ($P<0.05$) in each cohort after adjustment for relevant covariates (such as age, presence of atrial fibrillation, visible infarct on computed tomography, subtype of stroke) in a Cox's regression model.

Conclusion Functional status six months after an ischaemic stroke is associated with long term survival. Early interventions that reduce dependency at six months might have positive effects on long term survival.

INTRODUCTION

Although there are now reliable estimates on outcome in the early months and years after an ischaemic stroke, we know much less on long term survival and what influences it.[1] We estimated the relative and absolute effects of the level of functional status at six months on long term survival in three large prospective cohorts of patients with ischaemic stroke.

METHODS

We sought data from three cohorts of patients with an ischaemic stroke recruited in the United Kingdom: the Oxfordshire community stroke project, the Lothian stroke register, and UK patients enrolled in the first international stroke trial. In all three cohorts, ischaemic stroke was diagnosed with a combination of clinical criteria and brain imaging or autopsy.

Initial data collection and clinical follow-up

Oxfordshire community stroke project—This was a community based incidence study of stroke and transient ischaemic attacks. Patients were registered from 1981 to 1986.[2] A study neurologist assessed all patients as soon as possible after the onset of symptoms. Study nurses followed up surviving patients at one, six, and 12 months from the date of stroke onset and then annually for up to five years. When possible, a study physician assessed survivors at the end of clinical follow-up.

Lothian stroke register—The register was established to collect data on patients with suspected stroke, transient ischaemic attacks, or retinal artery occlusion from those attending outpatient clinics and admitted to one hospital in Edinburgh. Registration began in 1990 and continued to 2000. One of the study's stroke physicians examined the patient and collected baseline data as soon as possible after symptom onset. Patients were followed up at 6, 12, 24, and 36 months from the date of symptom onset. Follow-up data were obtained either by telephone interview, postal questionnaire, or home or clinic visits.

First international stroke trial—This was a randomised trial of aspirin, subcutaneous heparin, both, or neither, started within 48 hours of onset of ischaemic stroke.[3] A total of 19 435 patients were enrolled from 1991 to 1997, of whom 6257 (32%) were enrolled by hospitals in the UK. Baseline data were collected before randomisation in the trial. Final clinical follow-up at six months was by postal questionnaire or telephone interview or, in a few cases, during a clinic visit.

Collection of long term survival data

At the end of planned clinical follow-up in each of the three cohorts, notes of patients who were still alive were "flagged" at the central register of the Office for National Statistics (ONS). On the death of a cohort participant, ONS notified the study office. Patients who

This article is an abridged version of a paper that was published on bmj.com on 29 January 2008. Cite this article as: *BMJ* 29 January 2008, doi: 10.1136/bmj.39456.688333.BE

Table 1 | Baseline characteristics and status of patients at six months after stroke onset in three cohorts. Figures are numbers (percentages) of patients unless stated otherwise

	OCSP (n=539)	LSR (n=2054)	IST-1 (n=5117)	All cohorts (n= 7710)
Mean (SD) age (years)	73 (12)	68 (13)	73 (11)	72 (12)
Men	269 (50)	1087 (53)	2683 (52)	4039 (52)
Mean (SD) systolic BP (mm Hg)	162 (33)	157 (30)	158 (27)	158 (28)
Atrial fibrillation on baseline ECG	84 (16)*	259 (13)†	1012 (20)‡	1355 (18)
CT performed at baseline	472 (88)	2054 (100)	2499 (49)§	5025 (65)
Visible infarct on baseline CT	263 (56)	1245 (61)	1639 (66)§	3147 (63)
Medication before stroke:				
Antiplatelet	17 (4)	641 (31)	1281 (25)¶	1939 (25)
Anticoagulant	6 (1)	84 (4)	39 (1)**	129 (2)
Stroke syndrome:				
TACI	92 (17)	246 (12)	1437 (28)	1775 (23)
PACI	182 (34)	811 (39)	2072 (40)	3065 (40)
LACI	137 (25)	546 (27)	1042 (20)	1725 (22)
POCI	128 (24)	342 (17)	551 (11)	1021 (13)
Indeterminate subtype	—	109 (5)	15 (0.3)	124 (2)
Status at six months:				
Independent	285 (53)	1142 (56)	1098 (22)	2525 (33)
Dependent	154 (29)	604 (29)	2678 (52)	3436 (45)
Dead	100 (18)	308 (15)	1341 (26)	1749 (23)

OCSP=Oxfordshire community stroke project; LSR=Lothian stroke register; IST-1=first international stroke trial; ECG=electrocardiogram; CT=computed tomography; TACI=total anterior circulation infarct; PACI=partial anterior circulation infarct; LACI=lacunar infarct; POCI=posterior circulation infarct.
*Missing data in 11 patients.
†Not recorded in 288 patients.
‡Not recorded in 348 patients during pilot phase of trial.
§Diagnosis confirmed in remainder by CT after randomisation or by autopsy. "Visible infarct on CT" refers only to those scans performed before randomisation.
¶Not recorded in 348 patients during pilot phase and subsequently recorded only if aspirin was used.
**Not recorded in 153 patients during pilot phase and use subsequently recorded only if heparin was used.

were not reported to have died before the close of follow-up on 16 November 2000 were assumed to be alive.

Definition of outcomes

In the Oxfordshire and Lothian cohorts the level of function at six months after stroke onset was assessed by the modified Rankin scale.[4] In the international stroke trial this was done by means of the "two simple questions" that were developed to assess functional outcome after stroke in large scale trials.[5] Both the Rankin score and the two simple questions have good validity and reliability between observers and correspond well with each other. We defined an independent state as Rankin score of 0-2 and a dependent state as score of 3-5. The international stroke trial classified patients who reported not needing any help to perform everyday activities within the past two weeks as independent.

Statistical analysis

We estimated survival curves in the three cohorts with the Kaplan-Meier product limit technique. We used median rather than mean to describe and compare survival from the six month assessment of functional outcome in each cohort. We performed univariate and multivariate analyses of risk factors with Cox's proportional hazards models. See bmj.com for details.

RESULTS

Oxfordshire cohort—This study registered 675 patients with first ever stroke. We excluded 136 (20%) leaving 539 patients with a definite (n=434) or probable (n=105) ischaemic stroke (table 1). Patients were followed up for a maximum of 19 years. There was a significant trend (log rank test, $P<0.001$) of decreasing survival with increasing Rankin score at six months. We entered all baseline variables and functional status at six months after stroke onset into a univariate and multivariate Cox's regression model. Both the separate Rankin scores and level of dependency at six months had a significant effect ($P<0.05$) on subsequent survival in the multivariate analyses. The more dependent a patient was at six months, the shorter their subsequent survival. Age and the presence of atrial fibrillation on examination also had a significant negative effect ($P<0.001$) on survival.

Lothian cohort—In all, 4455 patients were entered on the register in 1990-9. We sought patients with relevant clinical features and imaging at baseline indicating an ischaemic infarct or no pathology. After exclusions we had data on 2054 patients (table 1). Patients were followed up for a maximum of 9.7 years. There was a significant trend (log rank test, $P<0.001$) of a decrease in survival with an increase in Rankin score at six months. We entered the baseline variables and the functional status at six months after stroke onset in a univariate and multivariate Cox's regression model.

Both the separate Rankin scores and the level of dependency had a significant effect (P<0.001) on survival in multivariate analyses. Age, sex, and the presence of atrial fibrillation also had significant negative effects (P<0.05) on survival.

International stroke trial cohort—A probable or definite ischaemic stroke was diagnosed in 5139 patients recruited in the UK. After exclusions we had data on 5117 patients (table 1). There was a significant effect (log rank test, P<0.001) of the level of dependency on survival. We entered all baseline variables and the functional status at six months after stroke onset in a Cox's regression model. The level of dependency at six months had a significant effect (P<0.001) on survival in the multivariate analysis. Age, sex, presence of atrial fibrillation on baseline examination, use of aspirin before the stroke, and stroke subtype were also significant (P<0.05).

Pooled estimate of median survival

Table 2 shows estimates of the median survival time, subdivided by Rankin score, based on the combined dataset of the Lothian and Oxfordshire cohorts. There was a significant trend (log rank test P<0.001) of decreasing median survival with increasing Rankin score. Table 2 also gives estimates of median survival for independent and dependent patients based on data from all three cohorts combined. This difference was highly significant (log rank test, P<0.001).

Survival among cohorts recruited in different time periods

Estimated median survival for patients who were dependent at six months after stroke onset was 4.2 years among those recruited during 1981-6 and 6.5 years among those recruited during 1990-4. In the Lothian and international stroke trial cohorts, among patients recruited in 1990-4 and 1995-2000 who were independent at the six month assessment, the proportions alive at two years were 90% and 93%, respectively. Among those recruited in the same years who were dependent at the six month assessment the proportions alive at two years were 80% and 81%. These differences were not significant.

Date of stroke onset was not a significant variable in the multivariate Cox's regression analyses in the Oxfordshire (P=0.45) and Lothian (P=0.083) cohorts. The date of randomisation was a significant variable (P<0.001) in the international stroke trial cohort; among patients recruited in 1995-7, survival was significantly greater than among those recruited in 1991-4 (P<0.001; hazard ratio 0.82, 95% confidence interval 0.73 to 0.91).

DISCUSSION

This study provides robust estimates of the relative and absolute effects that the level of dependency six months after an ischaemic stroke has on subsequent long term survival. The impact of functional status on median survival was substantial and remained significant after adjustment for baseline variables known to influence prognosis. The findings were consistent in size and direction across these three, somewhat different, cohorts of ischaemic stroke patients.

The five year survival for patients with a Rankin score of 4-5 was about 45%, which is worse than for many malignancies. Median survival was negatively influenced by age at onset of stroke in all cohorts. The presence of atrial fibrillation on the first examination also significantly influenced long term survival in the three cohorts, as shown in previous studies.[6,7]

Strengths and weaknesses

The cohorts were large and well characterised, the baseline data were generally complete, and follow-up was prospective and prolonged, with minimal loss to six month and prolonged follow-up. The scope for selection bias in the assembly of these cohorts was least for the community based Oxfordshire cohort and greatest for the randomised international stroke trial. Our analyses are based on the assumption that patients not reported as dead were alive and that official statistics are accurate. We think that the effect of independent survivors moving abroad would be small because emigration, especially among elderly people, is relatively uncommon.

Relevance of findings

The consistency across the three cohorts of the effect of the patient's level of dependency on subsequent survival suggests that the relative effects are generalisable. A graded effect was evident in the three cohorts, even though there were variations in case mix, time period, and location. Also, the demographics of the three studies suggest that the results are generalisable. The mean age of patients in the three cohorts (ranging from 68 to 73 years) was similar to that in large community and hospital based studies of ischaemic stroke patients. The proportions of stroke subtypes in our cohorts were similar to those found in other studies, as were the outcomes in terms of early case fatality and the proportion of patients who were dead or dependent at six months. Our analyses of survival during different time periods showed that survival slightly improved over time. It may be reasonable to assume that on

Table 2 | Combined analysis estimating effect of functional status at six months on subsequent median survival

Functional status	Median survival (years) (95% CI)
Rankin score in Oxfordshire and Lothian cohorts (No of patients):	
0 (311)	>15*
1 (540)	11.7 (8.4 to 14.9)
2 (576)	8.4 (7.6 to 9.3)
3 (433)	6.0 (5.2 to 6.8)
4 (189)	3.7 (2.9 to 4.6)
5 (136)	2.5 (1.4 to 3.5)
All three cohorts (No of patients):	
Independent (2525)	9.7 (8.9 to 10.6)
Dependent (3436)	6.0 (5.7 to 6.4)

*Exact median not given as less than half of patients died during follow-up. Median survival 12.9 years (95% CI 10.0 to 15.9) for Rankin 0 and 1 combined.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Several factors influence the outcome of patients with ischaemic stroke and their survival in the early months and years after stroke onset

Little is known on the impact of functional outcome shortly after ischaemic stroke on long term survival

WHAT THIS STUDY ADDS

Functional status of patients six months after onset of an ischaemic stroke has a significant and substantial effect on their long term survival

Less than half those alive with severe disability at six months will survive five years; a survival statistic comparable with that of several malignancies

Our findings have implications for the estimation of the global burden and costs of stroke, for the planning of health care and research, and in clinical practice

average, at a given level of dependency, median survival would be somewhat better than portrayed here.[8]

We believe that these data have implications for clinical practice. They can be used to inform patients and their relatives about the prognosis after an ischaemic stroke, for the estimation of the impact and costs of stroke, and for the planning of health care and research. Previous studies have shown that the costs of long term care account for about half of the total costs of stroke care.[9-11] A health economics model has suggested that treatments that reduce dependency in survivors by only a modest amount might, none the less, have a substantial effect on long term survival free of dependency and hence prove highly cost effective.[12 13] Our data strongly support this hypothesis.

We thank the patients who participated in all the studies. We are grateful to Mike McDowall, who has looked after the Lothian and Oxfordshire datasets, and to Sheila Grant, who collated and entered the data on deaths from the three cohorts.

Contributors: See bmj.com.

Funding: The Oxfordshire community stroke project and the international stroke trial were funded by the UK Medical Research Council. Some of the costs of collection of the long term survival data were supported by an unrestricted educational grant from Boehringer Ingelheim.

Competing interests: None declared.

Ethical approval: All studies were approved by relevant local ethical committees.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol* 2003;2:43-53.
2 Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire community stroke project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry* 1988;51:1373-80.
3 International Stroke Trial Collaborative Group. International stroke trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet* 1997;349:1569-81.
4 Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-7.
5 Lindley RI, Waddel IF, Livingstone M. Can simple questions assess outcome after stroke? *Cerebrovasc Dis* 1994;4:314-24.
6 Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen stroke study. *Stroke* 1996;27:1765-9.
7 Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation. The Framingham study. *Stroke* 1996;27:1760-4.
8 Carter KN, Anderson CS, Hackett ML, Barber PA, Bonita R. Improved survival after stroke: is admission to hospital the major explanation? Trend analyses of the Auckland regional community stroke studies. *Cerebrovasc Dis* 2007;23:162-8.
9 Spieler JF, Lanoe JL, Amarenco P. Costs of stroke care according to handicap levels and stroke subtypes. *Cerebrovasc Dis* 2004;17:134-42.
10 Gerzeli S, Tarricone R, Zolo P, Colangelo I, Busca MR, Gandolfo C. The economic burden of stroke in Italy. The EcLIPSE study: economic longitudinal incidence-based project for stroke evaluation. *Neurol Sci* 2005;26:72-80.
11 Kolominsky-Rabas PL, Heuschmann PU, Marschall D, Emmert M, Baltzer N, Neundörfer B, et al. Lifetime cost of ischemic stroke in Germany: results and national projections from a population-based stroke registry: the Erlangen stroke project. *Stroke* 2006;37:1179-83.
12 Samsa GP, Matchar DB. Have randomized controlled trials of neuroprotective drugs been underpowered? An illustration of three statistical principles. *Stroke* 2001;32:669-74.
13 Samsa GP, Reutter RA, Parmigiani G, Ancukiewicz M, Abrahamse P, Lipscomb J, et al. Performing cost-effectiveness analysis by integrating randomized trial data with a comprehensive decision model: application to treatment of acute ischemic stroke. *J Clin Epidemiol* 1999;52:259-71.

Accepted: 21 November 2007

Tale of the unexpected

"Hello again, sir. How's your breathing now then?" I cheerily boom, pulling back the blue curtain. But he is not breathing at all. I am stunned, quite stunned. I have to force back every inclination to urge him to put the oxygen mask back on, to restart the nitrate infusion, or to call in the nurses for help in getting him sitting up in a better breathing position.

Yet why am I so surprised? Hadn't I, in documenting "impression—severe pulmonary oedema," registered that it has a 90% mortality? Hadn't I, in requesting senior review an hour earlier, suggested that a "do not attempt resuscitation" order might be appropriate? Hadn't I heard the medical registrar prepare the family for the worst?

Yes. But neither statistics nor protocols can really prepare you for that moment when your role as doctor changes; when both your lifesaving inclinations and your drug armoury are helpless in the presence of someone already dead; when, contrary to every other clinical encounter, your diagnosis rests not on the particular pitch of a wheeze or the variant waveform of a pulse but on the complete absence of any signs of life.

Often, as junior doctors at least, our confrontation with death is buffered. We either fend it off (successful medicine?) or we are prepared for it (called up by the nurses to come and certify a death that they have already discovered).

On this occasion the nurses had found the elderly man dead five minutes earlier but hadn't told me because I had been with another patient in the next bay. It made me realise how harrowing their job can be—always opening the blue curtain on to the unexpected.

Elizabeth Ingall foundation year 1 trainee, Addenbrooke's Hospital, Cambridge lizzieingall@hotmail.com