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

Karsten Bruins Slot, clinical research fellow, Eivind Berge, senior consultant, Paul Dorman, consultant neurologist, Steff Lewis, medical statistician, Martin Dennis, professor, Peter Sandercock, professor, on behalf of the Oxfordshire Community Stroke Project, the International Stroke Trial (UK), and the Lothian Stroke Register

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

The global burden of stroke is large, yet there are still gaps in our knowledge. 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. This lack of information is important for many reasons. If, for example, functional status several months after a stroke has a major influence on long term survival, this will affect clinical practice (including our communication with patients), our estimates of the future global burden and costs of stroke, and the planning of health care and research.

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 the UK patients enrolled in the first international stroke trial.

Initial data collection and clinical follow-up

Oxfordshire community stroke project—This project was a community based incidence study of stroke and transient ischaemic attacks. Patients were registered from 1981 to 1986. Details on the study population, clinical definitions, methods of assessment, and investigations have been described in detail elsewhere. A study neurologist assessed all patients as soon as possible after the onset of symptoms. Baseline characteristics were recorded in a standardised form. Trained 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. The 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. A total of 19,435 patients were enrolled from 1991 to 1997, of whom 6,257 (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 NHS central register of the Office for National Statistics (ONS). On the death of a cohort participant, ONS forwarded notification of the death and a copy of the death certificate to the study office. Patients who were not reported to have died before the close of follow-up on 16 November 2000 were assumed to be alive.

Classification of ischaemic strokes
In all three cohorts, ischaemic stroke was diagnosed with a combination of clinical criteria and brain imaging or autopsy. As these examinations excluded intracerebral haemorrhages and conditions mimicking stroke (for example, subdural haematoma or cerebral tumour), the presence of visible infarction on imaging (or autopsy) was not necessary for the diagnosis of ischaemic stroke. According to criteria from the Oxfordshire community stroke project classification, we used the clinical features to subdivide diagnosis into total anterior circulation infarct, partial anterior circulation infarct, lacunar infarct, posterior circulation infarct, or, when no clinical subtype could be assigned, cerebral infarct of indeterminate clinical subtype.

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. 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. The patients (directly or through relatives) were asked if they had needed help from another person to perform everyday activities within the past two weeks (such as bathing, feeding, walking, dressing, or use of the toilet). The Rankin score and the two simple questions are methods that both 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 as means are hugely influenced by the length of follow-up (which varied in the three cohorts). We performed univariate and multivariate analyses of risk factors with Cox’s proportional hazards models. Data from patients who were dead at six months after stroke onset were not entered in the models as we were interested only in the impact of functional status at six months on subsequent survival. We entered age and systolic blood pressure as continuous variables. The proportionality assumption was verified with the Schoenfeld test and did not seem to be violated. We used SPSS software (version 13.0 for Mac OS X) for the statistical analysis.

RESULTS
Oxfordshire cohort
This study registered 675 patients with first ever stroke. We excluded 136 (20%). Of these, 130 did not have a diagnosis of ischaemic stroke (33 had a subarachnoid haemorrhage, 65 a primary intracerebral haemorrhage, and 32 a stroke of undefined pathological type). We excluded six other patients in whom there was an apparent error in the recording of the date of death. The 539 remaining patients had a definite (n=434) or probable (n=105) ischaemic stroke.

Table 1 shows the baseline characteristics and vital and dependency status at six months. Patients were followed up for a maximum of 19 years. Figure 1 shows...
survival curves for patients stratified by Rankin score 0-5 at six months. 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 in table 1 and functional status at six months after stroke onset into a univariate and multivariate Cox’s regression model (table 2). 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. We used a similar model to analyse the impact of the Rankin scores at one month after stroke onset. This gave generally the same results as those of the Rankin scores at six months (data not shown).

Lothian cohort
In all, 4435 patients with a stroke, transient ischaemic attack, retinal artery occlusion, or other diagnosis were entered on the register in 1990-9. We sought patients with relevant clinical features and computed tomography or magnetic resonance imaging at baseline indicating an ischaemic infarct (n=1547) or patients with normal results on computed tomography or magnetic resonance imaging at baseline and a clinical diagnosis of a probable (n=320) or definite stroke (n=629). We excluded 442 (18%) of these patients from our final analysis; 414 patients whose first follow-up occurred (for organisational reasons) at 12 months or later (hence functional status at six months was not known), seven patients who were lost to follow-up by six months, one patient in whom there was an apparent error in the recording of the date of death (P=0.4%) patients from the final analysis as we did not know their dependency status at six months (n=20) or there was an error in the recording of the date of death (n=2). Table 1 shows the survival curves for patients who were followed up for a maximum of 9.7 years. Figure 2 shows survival curves. 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 in table 1 and the functional status at six months after stroke onset into a univariate and multivariate Cox’s regression model (table 3). 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. We excluded 22 (0.4%) patients from the final analysis as we did not know their dependency status at six months (n=20) or there was an error in the recording of the date of death (n=2). Table 1 shows the baseline characteristics. Among the patients with probable or definite ischaemic stroke, 49% underwent computed tomography before randomisation into the trial; in the remainder the diagnosis was confirmed either by computed tomography after randomisation or by autopsy. Figure 3 shows the survival curves for patients who were...
Table 2 | Univariate and multivariate Cox’s regression analyses of baseline variables for patients alive at six months after stroke onset in Oxfordshire community stroke project. Figures are hazard ratios (95% confidence intervals)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (1.04 to 1.07)***** 1.04 (1.03 to 1.06)*****</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>0.99 (0.80 to 1.24) 1.22 (0.98 to 1.54)</td>
<td></td>
</tr>
<tr>
<td>Mean systolic BP</td>
<td>1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.94 (1.43 to 2.65)***** 1.85 (1.33 to 2.58)*****</td>
<td></td>
</tr>
<tr>
<td>Visible infarct on CT</td>
<td>1.19 (0.96 to 1.49) 1.13 (0.89 to 1.43)</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet use before stroke</td>
<td>1.08 (0.60 to 1.92) 0.95 (0.52 to 1.73)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulant use before stroke</td>
<td>0.62 (0.20 to 1.93) 0.64 (0.19 to 2.14)</td>
<td></td>
</tr>
</tbody>
</table>

**P<0.05 ***P<0.001

Independent and dependent at six months after randomisation. There was a significant effect [log rank test, P<0.001] of the level of dependency on survival. We entered all baseline variables in table 1 and the functional status at six months after stroke onset in a Cox’s regression model (table 4). 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).

Pool estimate of median survival

Table 5 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 5 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

We compared survival in all three cohorts among independent and dependent patients who were enrolled during three different time periods (1981-6, 1990-4, and 1995-2000). 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. No accurate estimations can be given for the period 1995-2000, as over half of both dependent and independent patients were alive at the end of follow-up.

We also analysed the influence of year of recruitment on two year survival in the Lothian and international stroke trial cohorts. We compared the proportions of patients who were alive at two years. 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.

We also entered the date of stroke onset (or date of randomisation in the international stroke trial cohort) as a variable in the multivariate Cox’s regression analyses of each cohort. Date of stroke onset was not a significant variable 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. A multivariate Cox’s regression analysis in the international stroke trial cohort showed that, 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.

We were surprised to see the poor survival of patients with a Rankin score of 4-5. The five year survival for
Table 3 | Univariate and multivariate Cox’s regression analyses of baseline variables for patients alive at six months after stroke onset in Lothian stroke register. Figures are hazard ratios (95% confidence intervals)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (1.05 to 1.07)***</td>
<td>1.05 (1.04 to 1.06)***</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.05 (0.87 to 1.26)</td>
<td>1.33 (1.08 to 1.64)*</td>
</tr>
<tr>
<td>Mean systolic BP</td>
<td>1.00 (0.99 to 1.01)</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.00 (2.37 to 3.80)***</td>
<td>1.65 (1.25 to 2.17)*</td>
</tr>
<tr>
<td>Visible infarct on CT</td>
<td>1.22 (1.01 to 1.47)*</td>
<td>1.09 (0.89 to 1.35)</td>
</tr>
<tr>
<td>Antiplatelet use before stroke</td>
<td>1.48 (1.22 to 1.80)***</td>
<td>1.31 (1.07 to 1.62)*</td>
</tr>
<tr>
<td>Anticoagulant use before stroke</td>
<td>1.07 (0.63 to 1.82)</td>
<td>0.91 (0.51 to 1.60)</td>
</tr>
</tbody>
</table>

Stroke syndrome:

- LACI
- PACI 1.57 (1.24 to 2.00)*** 1.32 (1.02 to 1.72)*
- POCI 1.01 (0.74 to 1.39) 1.16 (0.83 to 1.62)
- TACI 2.25 (1.63 to 3.11)*** 1.22 (0.83 to 1.79)
- Indeterminate subtype 1.25 (0.77 to 2.04) 1.14 (0.68 to 1.92)

Rankin score (at six months):§

<table>
<thead>
<tr>
<th>Rankin score</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.01 (0.66 to 1.56)</td>
<td>0.98 (0.63 to 1.54)</td>
</tr>
<tr>
<td>1</td>
<td>1.66 (1.12 to 2.46)*</td>
<td>1.74 (1.16 to 2.61)*</td>
</tr>
<tr>
<td>2</td>
<td>2.86 (1.95 to 4.20)***</td>
<td>2.58 (1.73 to 3.87)***</td>
</tr>
<tr>
<td>3</td>
<td>4.11 (2.69 to 6.30)***</td>
<td>3.89 (2.48 to 6.12)***</td>
</tr>
<tr>
<td>4</td>
<td>6.41 (4.23 to 9.73)***</td>
<td>4.98 (3.15 to 8.88)***</td>
</tr>
<tr>
<td>5</td>
<td>2.87 (2.38 to 3.64)***</td>
<td>2.43 (1.96 to 3.01)***</td>
</tr>
</tbody>
</table>

CT=computed tomography; LACI=lacunar infarct; PACI=partial anterior circulation infarct; POCI=posterior circulation infarct; TACI=total anterior circulation infarct.

*P<0.05, ***P<0.001

†Overall P values of stroke syndrome: univariate analysis P<0.01 and multivariate analysis P<0.001.

‡Overall P values of Rankin score (at six months): univariate and multivariate analysis P<0.001.

§Separate multivariate analysis without variable “Rankin score (at six months).”

Table 4 | Univariate and multivariate Cox regression analyses of baseline variables for patients alive at six months after randomisation into the first international stroke trial. Figures are hazard ratios (95% confidence intervals)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07 (1.06 to 1.07)***</td>
<td>1.07 (1.06 to 1.07)***</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.97 (0.88 to 1.07)</td>
<td>1.42 (1.28 to 1.58)***</td>
</tr>
<tr>
<td>Mean systolic BP</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.64 (1.45 to 1.86)***</td>
<td>1.16 (1.02 to 1.32)*</td>
</tr>
<tr>
<td>Visible infarct on CT</td>
<td>0.95 (0.85 to 1.06)</td>
<td>1.05 (0.94 to 1.17)</td>
</tr>
<tr>
<td>Antiplatelet use before stroke</td>
<td>1.21 (1.08 to 1.35)*</td>
<td>1.17 (1.04 to 1.31)*</td>
</tr>
<tr>
<td>Anticoagulant use before stroke</td>
<td>0.71 (0.35 to 1.42)</td>
<td>0.62 (0.31 to 1.24)</td>
</tr>
</tbody>
</table>

Stroke syndrome:

- LACI
- PACI 1.25 (1.09 to 1.42)* 1.15 (1.01 to 1.33)*
- POCI 0.98 (0.81 to 1.19) 1.04 (0.86 to 1.26)
- TACI 1.44 (1.24 to 1.66)*** 1.23 (1.06 to 1.43)*
- Indeterminate subtype 0.28 (0.07 to 1.14) 0.36 (0.09 to 1.43)
- Functionally dependent (at six months) 1.91 (1.68 to 2.16)*** 1.63 (1.43 to 1.85)***

CT=computed tomography; LACI=lacunar infarct; PACI=partial anterior circulation infarct; POCI=posterior circulation infarct; TACI=total anterior circulation infarct.

*P<0.05, ***P<0.001

†Overall P values of stroke syndrome: univariate analysis P<0.01 and multivariate analysis P<0.03.

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 much the same, the differences are due to the patient characteristics and data collected.
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.
Lille 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.

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.16–22 The proportions of stroke subtypes according to the Oxfordshire community stroke project classification in our cohorts were similar to those found in other studies (though there were fewer total anterior circulation infarcts in the Lothian and Oxfordshire cohorts), as were the outcomes in terms of early case fatality and the proportion of patients who were dead or dependent at six months.16–22 These cohorts, however, were assembled at a time when secondary prevention in stroke survivors was much less intensive than now. Our analyses of survival during different time periods showed, as one might expect, that survival did indeed slightly improve over time. Hence, when we apply these estimates to current average, at a given level of dependency, median survival would be somewhat better than portrayed here.26

We believe that these data have several implications for clinical practice. They can be used to inform patients and their relatives about the prognosis after an ischaemic stroke. They have implications for the estimation of the impact and costs of stroke and for the planning of health care and research. Estimates of global disease burden and costs have so far relied on 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.


27 Spieler JF, Lane N, Amarendo P. Costs of stroke care according to handicap levels and stroke subtypes. Cerebrovasc Dis 2004;17:134-42.


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