Causes of Death by Level of Dependency at 6 Months After Ischemic Stroke in 3 Large Cohorts

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Background and Purpose—We assessed the influence of functional status at 6 months after ischemic stroke on cause of death during long-term follow-up in 3 prospective cohorts.

Methods—The cohorts were 7710 patients from the Oxfordshire Community Stroke Project, Lothian Stroke Register, and International Stroke Trial. Functional status was assessed at 6 months after stroke onset. Causes of death were identified from death certificates, and were also classified into “stroke-related” or “other” causes. We calculated the relative risk with 95% CI to assess the association between dependency level and cause of death. We also performed a multivariable regression analysis to adjust for other relevant factors.

Results—Six months after stroke onset 5961 (78%) patients were still alive. At the end of follow-up period, 1620 (47%) patients who were functionally dependent at 6 months after stroke onset had died vs 711 (28%) independent patients. Dependent patients had a relative risk of dying from stroke of 1.70 (95% CI, 1.44–2.00) compared to independent patients. Overall, dependent patients had a relative risk of 1.68 (95% CI, 1.49–1.91) of dying from stroke-related causes. Dependency remained significantly (P<0.01) associated with stroke-related causes of death in a multivariable regression analysis.

Conclusion—Stroke-related deaths continue to be a problem during the years after an ischemic stroke, especially in patients who are functionally dependent at 6 months after onset. Better acute treatments to reduce dependency and adequate secondary prevention remain high priorities. (Stroke. 2009;40:00-00.)

Key Words: cerebral infarct ■ epidemiology ■ mortality ■ outcome

The global burden of stroke is large and projected to increase during the coming decades.1 In many Western countries stroke is the third leading cause of death in adults. Case fatality is high in the acute phase of a stroke and remains high in surviving patients during the subsequent months and years after stroke onset.2–10 Important causes of death in stroke patients are the index stroke or a recurrent stroke, stroke-related complications (eg, pneumonia, pulmonary embolism), and cardiac diseases. More knowledge about the causes of death that occur after ischemic stroke might be useful to optimize secondary prevention and avoid deaths from stroke-related complications. However, little is known about the impact of a patient’s functional status several months after stroke onset on the cause of death during long-term follow-up. In a previous study we have shown that the functional status at 6 months after an ischemic stroke is strongly associated with long-term survival.11 In the present study, we sought to assess the influence of functional status at 6 months after ischemic stroke onset on the cause of death during long-term follow-up in 3 large prospective cohorts.

Subjects and Methods
We used data from 3 large cohorts of patients with an ischemic stroke recruited in the UK: the Oxfordshire Community Stroke Project (OCSP), the Lothian Stroke Register, and patients enrolled in the First International Stroke Trial in the UK.

Cohorts and 6-Month Follow-Up
The OCSP was a community-based incidence study of stroke and TIA.12 Patients were registered between 1981 and 1986. Baseline characteristics were recorded in a standardized form by a study neurologist as soon as possible after stroke onset. Trained study nurses assessed functional status in all surviving patients at 6 months after stroke onset using the modified Rankin scale (mRS).13 The Lothian Stroke Register was a register at the Western General Hospital in Edinburgh, UK, in which data were collected on patients admitted with a suspected stroke, TIA, or retinal artery occlusion. Baseline data were collected as soon as possible after symptom onset by 1 of the study’s stroke physicians. Registration began in 1990 and continued to 2000. In most patients functional status was assessed by the mRS at 6 months after stroke onset. Follow-up data were obtained by telephone interview, postal questionnaire, or visits in the patients’ homes or in the hospital. The First International Stroke Trial was a randomized trial of aspirin, subcutaneous heparin, both, or neither, started within 48 hours of ischemic stroke onset.14 Approximately one-third (n=6257)
of all patients were recruited by hospitals in the UK between 1991 and 1997. Baseline data were collected before randomization. Follow-up at 6 months was by postal questionnaire, telephone interview, or, in a few cases, during a clinic visit. Functional status was assessed by means of the “2 simple questions” that were developed for use in large clinical trials.13

Diagnosis of Ischemic Stroke
In the present study we were only interested in patients with an index event of ischemic stroke. In all 3 cohorts, ischemic stroke was diagnosed with a combination of clinical criteria and brain imaging. We thus excluded intracerebral hemorrhages and conditions mimicking stroke. The presence of a visible infarct was not necessary for the diagnosis of ischemic stroke. In 18 patients (1%), the diagnosis of ischemic stroke was based on clinical examination only. All strokes were graded according to the OCSP classification.16

Assessment of Level of Dependency
In the OCSP and Lothian Stroke Register cohorts, we defined a functionally independent state at 6 months after stroke onset as mRS score 0 to 2 and a functionally dependent state as mRS score 3 to 5. In patients in the First International Stroke Trial in the UK cohort, no mRS scores were available, because functional status was only assessed by the “2 simple questions.” In this cohort, we classified patients who reported to have needed help to perform everyday activities within the past 2 weeks as functionally dependent. The mRS and “2 simple questions” are assessment tools that both have good validity and reliability between observers and correspond well with each other.13,17

Collection of Mortality Data and Classification of Causes of Death
All patients who survived beyond 6 months after stroke onset were “flagged” at the NHS central register of the Office for National Statistics. On the death of a patient, Office for National Statistics forwarded a copy of the death certificate to the central study office. Follow-up closed on November 16, 2000; all patients who were not reported to have died by then were assumed to be alive. The maximum time of follow-up was 17 years.

The 9th version of the International Classification of Diseases (ICD-9) was used to classify the cause of death in nearly all death certificates. In the remainder, the ICD-10 version was used. Although the cause of death recorded on the death certificates may have been based on autopsy findings, we had no information on this. We also used a simple classification of the causes of death that was partially based on one that was recently proposed by Halkes.18 We categorized all causes of death into 2 groups: “stroke-related cause of death” and “other causes of death.” If the ICD codes for cerebrovascular diseases (ICD-9 430-438; ICD-10 I60-I69) were mentioned in the death certificate as either a primary cause of death or a contributing factor (ie, secondary, tertiary, or quaternary cause of death), we categorized the diagnosis of ischemic stroke as mimicking stroke. The presence of a visible infarct was not necessary for the diagnosis of ischemic stroke. In 18 patients (1%), the diagnosis of ischemic stroke was based on clinical examination only. All strokes were graded according to the OCSP classification.16

Statistical Analysis
Data on the causes of death and functional status at 6 months after stroke were analyzed in 2 × 2 contingency tables. We calculated the relative risk (RR) with 95% CI and performed a multivariable regression analysis to adjust for baseline variables at stroke onset. Age and systolic blood pressure were entered as continuous variables. We used SPSS software (version 14.0 for Mac OS X; SPSS Inc) for all statistical analyses.

Ethical Approval
All studies were approved by relevant local ethical committees.

Results
Survival and Dependency Status
Overall, 7710 patients with an ischemic stroke were enrolled in the 3 cohorts. After stroke onset, 5961 (78%) patients were still alive. Table 1 shows the baseline characteristics of the 2331 (30%) patients who were alive at 6 months after stroke onset and died during the subsequent follow-up period.

Primary Causes of Death
Table 2 shows the primary causes of death categorized by the functional status at 6 months after the index stroke. Overall, functionally dependent patients had RR of dying from stroke of 1.70 (95% CI, 1.44–2.00), from pneumonia RR of 1.72 (1.33–2.23), from pulmonary embolism RR of 0.53 (0.16–1.72), from cardiac diseases RR of 0.53 (0.47–0.59), from cancer RR of 0.61 (0.48–0.78), and from miscellaneous causes RR of 0.90 (0.76 to 1.07) compared to functionally independent patients.

Stroke-Related Causes of Death
Stroke-related causes of death were present in 794 (49%) of the functionally dependent patients vs 207 (29%) of the independent patients in all 3 cohorts combined. Dependent
patients had RR of dying from a stroke-related cause of 1.61 (95% CI, 1.21–2.14) in the OCSP cohort, 1.99 (1.52–2.60) in the Lothian Stroke Register cohort, and 1.57 (1.32–1.87) in the First International Stroke Trial in the UK cohort. Overall, the RR was 1.68 (95% CI, 1.49–1.91) for dependent patients of dying from a stroke-related cause.

As a sensitivity analysis we also calculated the RR of dying from stroke-related causes after having categorized all patients who had cancer as a primary cause of death as having died from “other causes.” This did not alter the results (overall RR, 1.90; 95% CI, 1.66–2.17). Table 3 shows the primary cause of death that was stated in the death certificates for all patients (n = 1001) who were categorized as having died from “stroke-related” causes.

As another sensitivity analysis, we assessed the risk of dying from stroke-related causes by mRS score at 6 months after stroke onset in the Lothian Stroke Register and OCSP cohorts (Table 4). The RR of dying from stroke-related causes significantly increased with an increasing mRS score.

Table 5 shows the RR for dependent vs independent patients of dying from a stroke-related cause during different time intervals after the 6 months of follow-up. During subsequent time intervals, the risk of dying from stroke-related causes was significantly higher for dependent patients compared to independent patients and did not appear to change much over time.

Table 2. Primary Cause of Death Categorized by Functional Status at 6 Months After Stroke Onset in Each Cohort and in All Cohorts Combined

<table>
<thead>
<tr>
<th>Primary Cause of Death</th>
<th>OCSP Independent</th>
<th>OCSP Dependent</th>
<th>LSR Independent</th>
<th>LSR Dependent</th>
<th>IST-1 UK Independent</th>
<th>IST-1 UK Dependent</th>
<th>All cohorts Independent</th>
<th>All cohorts Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>30 (15)</td>
<td>17 (13)</td>
<td>36 (18)</td>
<td>96 (38)</td>
<td>71 (22)</td>
<td>417 (33)</td>
<td>137 (19)</td>
<td>530 (33)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>30 (15)</td>
<td>40 (32)</td>
<td>18 (9)</td>
<td>38 (15)</td>
<td>16 (5)</td>
<td>173 (14)</td>
<td>64 (9)</td>
<td>251 (15)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>5 (1)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>5 (0)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>Cardiac diseases</td>
<td>80 (41)</td>
<td>42 (34)</td>
<td>61 (31)</td>
<td>38 (15)</td>
<td>109 (34)</td>
<td>300 (24)</td>
<td>250 (35)</td>
<td>380 (23)</td>
</tr>
<tr>
<td>Cancer</td>
<td>36 (18)</td>
<td>20 (16)</td>
<td>34 (17)</td>
<td>27 (11)</td>
<td>53 (17)</td>
<td>115 (9)</td>
<td>105 (15)</td>
<td>146 (9)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>36 (18)</td>
<td>20 (16)</td>
<td>45 (23)</td>
<td>53 (21)</td>
<td>69 (22)</td>
<td>234 (19)</td>
<td>150 (21)</td>
<td>307 (19)</td>
</tr>
</tbody>
</table>

Figures are numbers (percentages) of patients.

Multivariable Regression Analyses

Results of the multivariable regression analysis in all 3 cohorts combined are shown in Table 6. Dependent patients were significantly (P < 0.01) more likely to die of stroke-related causes than independent patients, both in the separate analyses for each cohort (data not shown) and in the pooled analysis. The pooled analysis also showed that the variables male gender and total anterior circulation infarct were significantly (P < 0.01) associated with stroke-related causes of death.

Cause of Death During Different Time Periods

We compared the cause of death among patients who were enrolled during 3 different time periods (1981–1986, 1990–1994, and 1995–2000). The RR of dying from stroke-related causes was significantly increased during each of these time periods and did not seem to diminish over time (data not shown). We also entered the date of stroke onset (or date of randomization in the First International Stroke Trial in the UK cohort) as a variable in the multivariable regression analysis of each cohort and for all cohorts combined. This variable was not significant in the analyses for any of the cohorts (P > 0.05) or in a combined analysis (P = 0.42). Dependent patients remained significantly (P < 0.01) more likely of dying from stroke-related causes.

Discussion

This study shows that patients who are dependent at 6 months after an ischemic stroke are more likely to die of stroke-related causes during long-term follow-up than are independent patients. The impact of functional status on the cause of death.

Table 3. Primary Cause of Death for All Patients Who Are Categorized as Having Died From Stroke-Related Causes

<table>
<thead>
<tr>
<th>Primary Cause of Death</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>33 (3)</td>
<td>33 (3)</td>
<td>33 (3)</td>
<td>33 (3)</td>
<td>33 (3)</td>
</tr>
<tr>
<td>Cardiac diseases*</td>
<td>86 (9)</td>
<td>86 (9)</td>
<td>86 (9)</td>
<td>86 (9)</td>
<td>86 (9)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>667 (67)</td>
<td>667 (67)</td>
<td>667 (67)</td>
<td>667 (67)</td>
<td>667 (67)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>124 (12)</td>
<td>124 (12)</td>
<td>124 (12)</td>
<td>124 (12)</td>
<td>124 (12)</td>
</tr>
<tr>
<td>Miscellaneous†</td>
<td>89 (8)</td>
<td>89 (8)</td>
<td>89 (8)</td>
<td>89 (8)</td>
<td>89 (8)</td>
</tr>
</tbody>
</table>

*No myocardial infarctions were stated as primary cause of death.
†The most common primary causes of death in this category were chronic airway obstruction/chronic obstructive pulmonary disease (25%), vascular disease (15%), diabetes (15%), and traumatic injuries (3%).

Table 4. RR and 95% CI of Dying From Stroke-Related Cause by mRS Score at 6 Months After Stroke Onset

<table>
<thead>
<tr>
<th>mRS Score</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>1.00 (baseline)</td>
</tr>
<tr>
<td>2</td>
<td>1.12 (0.82–1.56)</td>
</tr>
<tr>
<td>3</td>
<td>1.66 (1.24–2.23)</td>
</tr>
<tr>
<td>4</td>
<td>1.92 (1.41–2.61)</td>
</tr>
<tr>
<td>5</td>
<td>2.57 (1.92–3.43)</td>
</tr>
</tbody>
</table>

OCSP and LSR Cohorts Combined.
death remained significant after adjustment for several baseline variables and was consistent in size and direction in three large cohorts of ischemic stroke patients.

We found that 43% of all patients who were alive at 6 months after stroke onset died of stroke-related causes during the follow-up period. This is consistent with the results of other studies. A Danish study of stroke patients who survived the initial 4 weeks after stroke onset showed that cerebrovascular diseases accounted for 32% of all causes of death during long-term follow-up. Similar studies with extended follow-up periods found that 22% to 48% of all deaths after stroke onset were attributable to cerebrovascular diseases. However, it is difficult to compare the results of these studies with ours, because we analyzed data from patients with ischemic strokes only and excluded all patients who died within 6 months after stroke onset. Furthermore, different methods for assessing the cause of death than ours were used and none of the studies provided data on functional outcome after stroke onset.

To the best of our knowledge, only 1 study has thus far assessed the impact of functional status after ischemic stroke on the cause of death. This Japanese study of 10 981 patients with ischemic stroke and TIA evaluated functional status at the time of their hospital discharge using the mRS. During a median follow-up period of 272 days, there were significant differences in the causes of death between functionally independent (mRS, 0–2) and dependent (mRS, 3 to 5) patients. Pneumonia was the major cause of death (26%) in dependent patients and malignancies (23%) were the major cause of death in independent patients. Cerebrovascular diseases accounted for approximately 22% of all deaths in independent patients vs 25% in dependent patients. Still, it is difficult to compare these findings with ours, because functional outcome was not assessed at a fixed moment in time after stroke onset, causes of death were not based on death certificates, and follow-up was much shorter than in our cohorts.

The main strength of this study is that the findings are based on 3 large and well-characterized community and hospital-based cohorts of ischemic stroke patients, with long follow-up and minimal loss of follow-up. The small differences in functional outcome at 6 months between the 3 cohorts are probably attributable to variations in case mix, because the studies were performed at different times and used different criteria for selection of patients. Still, functional status at 6 months after stroke onset had a significant impact on the cause of death in all 3 cohorts. This suggests that the results are generalizable.

The study also has some limitations. One limitation is that we relied on only death certificates to assess the cause of death. Causes of death stated in death certificates can be inaccurate, especially when no autopsy has been performed. Therefore, there is a risk that we have misclassified the causes of death in some cases. The effect of such “random” misclassifications would weaken the results and bring the RR closer to 1, not the opposite. Furthermore, to standardize the way death causes were classified, we used the method developed by Halkes. Obviously, none of the physicians who completed death certificates used this specific classification.

One potential nonrandom (systematic) source of error is that physicians may have classified stroke as the cause of death more often in patients who were functionally dependent than in those who are independent, because they may have been reminded of the previous stroke by the patient’s functional status. Furthermore, our analyses were based on the assumption that patients who were not reported as dead at the end of follow-up were indeed alive. Patients who have died abroad might not have been recorded if their death certificate was not sent to the UK. We believe, however, that this effect is small, because emigration among the elderly is relatively uncommon in the UK.

Finally, the 3 cohorts were assembled at a time when secondary prevention was much less intense than now. At present, stroke-related deaths are likely to occur less often in both dependent and independent patients. Our previous analyses of these cohorts did show that survival improved over time. A recent study from the Oxford region, UK, also showed that stroke mortality halved between 1979 and 2004. Improvements in stroke prevention and stroke care appeared to be largely responsible for this substantial decrease.

Our findings emphasize the need for effective and widely applicable acute treatments and adequate secondary prevention after ischemic stroke onset. Such measures have the potential of improving functional status and reducing the risk
of subsequent stroke-related deaths in a large number of patients.

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**Disclosures**
None.

**References**
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