Causes of Death and Predictors of 5-Year Mortality in Young Adults After First-Ever Ischemic Stroke
The Helsinki Young Stroke Registry

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Background and Purpose—Data on mortality and its prognostic factors after an acute ischemic stroke in young adults are scarce and based on relatively small heterogeneous patient series.

Methods—We analyzed 5-year mortality data of all consecutive patients aged 15 to 49 with first-ever ischemic stroke treated at the Department of Neurology, Helsinki University Central Hospital, from January 1994 to September 2003. We followed up the patients using data from the mortality registry of Statistics Finland. We used life table analyses for calculating mortality risks. Kaplan–Meier method allowed comparisons of survival between clinical subgroups. We used the Cox proportional hazard model for identifying predictors of mortality. Stroke severity was measured using the National Institutes of Health Stroke Scale and the Glasgow Coma Scale.

Results—Among the 731 patients (mean age, 41.5 ± 7.4 years; 62.8% males) followed, 78 died. Cumulative mortality risks were 2.7% (95% CI, 1.5% to 3.9%) at 1 month, 4.7% (3.1% to 6.3%) at 1 year, and 10.7% (9.9% to 11.5%) at 5 years with no gender difference. Those ≥45 years of age had lower probabilities of survival. Among the 30-day survivors (n = 711), stroke caused 21%, cardioaortic and other vascular causes 36%, malignancies 12%, and infections 9% of the deaths. Malignancy, heart failure, heavy drinking, preceding infection, type 1 diabetes, increasing age, and large artery atherosclerosis causing the index stroke independently predicted 5-year mortality adjusted for age, gender, relevant risk factors, stroke severity, and etiologic subtype.

Conclusions—Despite the overall low mortality after an ischemic stroke in young adults, several recognizable subgroups had substantially increased risk of death in the long term. (Stroke. 2009;40:2698-2703.)

Key Words: cerebral infarct ■ mortality ■ prognosis ■ risk factors ■ stroke in young adults

Ischemic stroke is the second leading cause of death worldwide.1 Although mortality rates in young adults with ischemic stroke are low compared with similar older patients, they still sustain clearly more deaths than the young in the general population.2 Giving the potentially disastrous impact of a stroke in a young adult, it is important that the treating physician will be able to give as accurate prognostic information as possible early in the course of the disease. In addition, information on long-term outcome and factors associated with mortality help in optimizing secondary prevention strategies.

Earlier studies on long-term mortality in young adults after an ischemic stroke have involved rather modest numbers of patients, may have had incomplete follow-up, may have been unpowered for multivariate analyses, or have not analyzed all relevant factors affecting mortality risk.2–7 Models for predicting outcome after stroke have been developed,8 but because young patients typically are underrepresented in randomized trials and data sets—and because stroke characteristics between younger and older patients differ—such models may not apply to those of younger ages. Therefore, we decided to analyze death rates, causes of death, and predictors of 5-year mortality in a large, consecutive, hospital-based defined cohort of young patients with first-ever ischemic stroke.

Patients and Methods

This study was approved by the Ethics Committee and carried out at the Department of Neurology, Helsinki University Central Hospital. Our hospital has the only neurological emergency room for a defined population of 1.5 million. In Finland, practically all patients with stroke are treated in the hospital regardless of symptom severity. In the present study, we included all consecutive patients aged 15 to 49 years with first-ever ischemic stroke from January 1994 to September 2003 entered into the Helsinki Young Stroke Registry according to previously published, clearly defined inclusion and exclusion criteria.9

All patients underwent a routine range of laboratory and other diagnostic testing, which are described in detail elsewhere.9 Risk factor information was obtained from the medical records. We
defined family history of any stroke as a history of ischemic or hemorrhagic stroke, or transient ischemic attack, in a first-degree relative. Dyslipidemia was defined as on lipid-lowering medication or total cholesterol level ≥5.0 mmol/L (193 mg/dL), low-density lipoprotein level ≥3.0 mmol/L (116 mg/dL), or high-density lipoprotein level <1.0 mmol/L (39 mg/dL). A patient was defined as a smoker if smoking regularly ≥1 cigarettes per day within the year before stroke. Hypertension was defined as treated with antihypertensive medication or a history, or present diagnosis, of hypertension according to the 2003 World Health Organization criteria as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. We defined obesity as body mass index ≥30 kg/m² or patient clearly stated as heavily obese in case body mass index data were not available. Recorded cardiovascular diseases included coronary heart disease, heart failure (ejection fraction <55%), previous myocardial infarction, and peripheral arterial disease. We recorded separately diabetes mellitus Types 1 and 2 and defined them as treated or presently diagnosed according to the 1990 World Health Organization criteria as fasting plasma glucose ≥7.0 mmol/L (126 mg/dL). Patients drinking an estimated amount of >200 g of pure alcohol per week regularly were considered heavy drinkers. We defined preceding infection as documented symptoms of any infection or diagnosis of infectious disease within 1 month before stroke. Obstructive sleep apnea was defined as apnea–hypopnea index ≥5 with clinical symptoms. In addition, we recorded a history of transient ischemic attack, presence of chronic or paroxysmal atrial fibrillation, and migraine. The latter was defined according to the International Headache Society criteria.10 We measured stroke severity at admission for each patient by using the National Institutes of Stroke Scale Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS). If a NIHSS score was not available from the medical records, it was assessed by a single investigator (J.P.) based on documented patient examination using a previously published algorithm.11 Retrospective assessment of NIHSS score has been validated and suggested to be reliable and unbiased.12 Based on NIHSS, stroke severity was classified as follows: mild (NIHSS score 0 to 6), moderate (7 to 14), or severe (≥15). Impaired consciousness was defined as GCS score <15.

Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria.13 Stroke subtype was assigned to each patient by pairs of investigators and in case of discrepancy, the patient records were reviewed by a senior investigator and the final categorization was based on a consensus agreement of all these.

We followed up the patients using data from the mortality registry at Statistics Finland, the central statistical office of the country. Each death, its certificate, and the corresponding personal information in the computerized population register are crosschecked. Thus, due to legislation and death certification practices, Finnish mortality data have been assessed to be exceptionally reliable.14 Onset of stroke symptoms was considered the starting point for follow-up. If the exact date of onset was unknown, we used the first day of the month when the stroke was known to occur as the date of onset.

Deaths in the mortality register are classified according to the Finnish Edition of the International Classification of Diseases, 9th Revision from 1994 to 1996 and the 10th Revision since 1997. In addition to primary cause of death, we recorded the contributory causes on the death certificate. We categorized causes of deaths into ischemic or hemorrhagic strokes, cardioaortic causes, other vascular causes (eg, pulmonary embolism), malignancies, infections, and miscellaneous causes.

We estimated cumulative mortality risks and 95% Cs with Kaplan–Meier analysis. Actual annual risks were calculated from Kaplan–Meier data with the Life Tables function. Average annual rate was calculated using the formula 1−[(1−L)1/n], where L is cumulative mortality rate at n years. Only patients who survived the first 30 days after the index stroke were included in the subsequent analyses. χ² and Fisher exact tests allowed comparisons of proportions of causes of death. We used the Cox proportional hazards model for univariate and multivariate risk factor analyses. A prediction model using a backward stepwise method was constructed by selecting significant or relevant variables from the univariate analyses.

Table 1 shows the baseline data of the 731 consecutive patients with complete 5-year follow-up. Of these, 78 had died. During the first 30 days, 20 patients died giving a case-fatality rate of 2.7% (95% CI, 1.5% to 3.9%). One-year cumulative mortality risk was 4.7% (95% CI, 3.1% to 6.3%), but annual mortality fell to a level ranging from 1.4% to 1.9%.
in the subsequent years. Average annual mortality was 2.2%. Cumulative 5-year mortality risk was 10.7% (95% CI, 9.9% to 11.5%) in the study population. In contrast to roughly 2 times higher risk of death in those aged 45 to 49 compared with those <45 (cumulative 5-year risk 14.7% [95% CI, 13.1% to 16.3%] versus 7.0% [6.4% to 7.6%]), mortality curves showed no gender difference (Figure 1). Those with large artery atherosclerosis or cardioembolism had overall higher risks of death compared with patients with small vessel disease, undetermined etiology, or other determined etiology (Figure 2).

Proportions of causes of death in those surviving the first 30 days, but who died within the 5-year observation (n=58), are shown in Figure 3. Ischemic (n=9) or hemorrhagic (n=3) strokes caused more than one fifth of the deaths, 18 died from cardioaortic causes, and 3 from other vascular causes (2 pulmonary embolisms, one intestinal necrosis). Overall, acute or chronic alcohol-related condition, or an alcohol-attributable disease, was present in 14 (18%) deaths. All patients dying of malignancies were ≥45 years of age. Otherwise, we found no significant differences in the spectrums of causes of death between males and females and between those aged 15 to 44 and ≥45 years (data not shown).

Previous myocardial infarct and severe index stroke were factors associated with death within 5 years only in the crude univariate analysis. After adjustment for age and gender, the strongest predictor of death in the long-term was malignancy, followed by heart failure, large artery atherosclerosis under-lying the index stroke, peripheral arterial disease, heavy drinking preceding infection, and age ≥45 years (Table 2).

Malignancy, heart failure, large artery atherosclerosis, Type 1 diabetes, heavy drinking, preceding infection, and increasing age were all independent factors in the Cox proportional hazards model associated with risk of death within 5 years from the index stroke (Table 3).

**Discussion**

The overall risk of long-term death after an acute ischemic stroke in young adults is low. However, apart from patients with malignancies, several subgroups are at notably higher risk of death and therefore need special attention. Multifactorial assessment, including demographics, risk factors, stroke severity as well as stroke subtype, is a key role in identifying those young adults who have a high risk of death after their first ischemic stroke.

The 30-day case-fatality rates in young adults with ischemic stroke ranged from 2.3% to 3.4% in prior studies from the last 2 decades.3,6,15,16 The first-year mortality rates varied from 4.5% to 6.3%,2,5–7 and the average rates were between 0.8% and 1.8% during the subsequent years.2,5–7 These figures are closely similar to ours despite the variation in the chosen upper age limit between the studies or whether patients with earlier stroke were included. The overall risk of death is clearly highest during the first month and year after ischemic stroke in young adults but reduces considerably thereafter.

In earlier studies, which included sufficient information on causes of death during long-term follow-up in young adults, recurrent strokes caused 0% to 33% of deaths, 13% to 55% died due to cardiac causes and 23% to 33% due to malignancies.4,6,7 The variability in the proportions of vascular causes in these studies is perhaps related to referral bias, small sample sizes, or incomplete data on causes of death. Based on our consecutive patient series and reliable mortality data,
more than one fifth of the deaths in 30-day survivors were caused by recurrent stroke, nearly one third by cardiac or aortic cause, and in total 58% by a vascular cause within the first 5 years from the index stroke.

In young patients with ischemic stroke, aged 15 to 45 years, age >35 years was reported as a predictive variable for increased risk of death,2,6 whereas a Norwegian study, which included patients aged 15 to 49 years, did not find an association between age and mortality.7 In our study, the risk of death was clearly higher in those >45 years compared with younger patients. In addition, increasing age independently predicted death after adjusting for gender and other relevant factors, akin to general knowledge. Higher mortality in patients ≥45 years likely also reflects their higher prevalence of well-defined vascular risk factors.9 We did not find an association between male gender and higher mortality within

Table 2. Cumulative 5-Year Mortality Rates (From Kaplan-Meier Functions) Stratified by Presence or Absence of Demographic Factors, Selected Risk Factors, Stroke Severity, Thrombolysis, and Etiology in 30-Day Survivors With Complete 5-Year Follow-Up (n=711) and Respective Univariate Hazard Ratios (From Cox Proportional Hazard Functions)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Cumulative Mortality Rate</th>
<th>Crude Univariate Hazard Ratio (95% CI)</th>
<th>Adjusted Univariate Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥45 years</td>
<td>12%</td>
<td>2.56 (1.47–4.47)*</td>
<td>2.47 (1.41–4.33)*</td>
</tr>
<tr>
<td>Male gender</td>
<td>9%</td>
<td>1.55 (0.87–2.76)</td>
<td>1.36 (0.76–2.44)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of any stroke</td>
<td>6%</td>
<td>0.63 (0.25–1.58)</td>
<td>0.57 (0.23–1.43)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>9%</td>
<td>1.33 (0.76–2.34)</td>
<td>1.09 (0.61–1.95)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>10%</td>
<td>1.47 (0.87–2.46)</td>
<td>1.38 (0.82–2.33)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11%</td>
<td>1.61 (0.96–2.69)</td>
<td>1.27 (0.75–2.16)</td>
</tr>
<tr>
<td>Obesity</td>
<td>12%</td>
<td>1.56 (0.77–3.18)</td>
<td>1.41 (0.69–2.87)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>16%</td>
<td>2.10 (0.90–4.88)</td>
<td>1.68 (0.72–3.95)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>32%</td>
<td>5.22 (2.64–10.32)*</td>
<td>5.25 (2.63–10.49)*</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21%</td>
<td>2.84 (1.13–7.10)*</td>
<td>2.27 (0.90–5.74)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>27%</td>
<td>4.03 (1.46–11.14)*</td>
<td>2.96 (1.06–8.30)*</td>
</tr>
<tr>
<td>History of transient ischemic attack</td>
<td>13%</td>
<td>1.72 (0.87–3.40)</td>
<td>1.65 (0.83–3.26)</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 2</td>
<td>12%</td>
<td>1.57 (0.68–3.66)</td>
<td>1.23 (0.52–2.90)</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 1</td>
<td>17%</td>
<td>2.27 (0.91–5.69)</td>
<td>2.19 (0.88–5.48)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>13%</td>
<td>1.68 (0.52–5.36)</td>
<td>1.48 (0.46–4.73)</td>
</tr>
<tr>
<td>History of migraine</td>
<td>4%</td>
<td>0.42 (0.17–1.04)</td>
<td>0.51 (0.20–1.30)</td>
</tr>
<tr>
<td>Heavy drinking</td>
<td>19%</td>
<td>3.34 (1.97–5.68)*</td>
<td>2.65 (1.64–4.98)*</td>
</tr>
<tr>
<td>Preceding infection</td>
<td>18%</td>
<td>2.70 (1.48–4.93)*</td>
<td>2.95 (1.61–5.41)*</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>6%</td>
<td>0.78 (0.19–3.17)</td>
<td>0.63 (0.15–2.59)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>56%</td>
<td>13.81 (5.51–34.62)*</td>
<td>20.54 (7.41–56.92)*</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, NIHSS score 0–6</td>
<td>7%</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Moderate, NIHSS score 7–14</td>
<td>9%</td>
<td>NA</td>
<td>1.25 (0.61–2.57)</td>
</tr>
<tr>
<td>Severe, NIHSS score ≥15</td>
<td>13%</td>
<td>NA</td>
<td>1.85 (0.87–3.94)</td>
</tr>
<tr>
<td>GCS score ≤15</td>
<td>13%</td>
<td>NA</td>
<td>1.77 (0.84–3.73)</td>
</tr>
<tr>
<td>Acute treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous alteplase</td>
<td>6%</td>
<td>NA</td>
<td>0.72 (0.18–2.96)</td>
</tr>
<tr>
<td>Stroke etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>21%</td>
<td>NA</td>
<td>4.60 (1.62–13.04)*</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>11%</td>
<td>NA</td>
<td>2.20 (0.79–6.18)</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>5%</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Other determined etiology</td>
<td>7%</td>
<td>NA</td>
<td>1.47 (0.52–4.12)</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>6%</td>
<td>NA</td>
<td>1.18 (0.43–3.24)</td>
</tr>
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*P<0.05.
†Adjusted for age and gender.
‡Females.
NA indicates not applicable.

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long-term death after stroke independently associated with long-term death after infection during the week before stroke compared with those without infection. Long-term outcome or mortality were not affected by the occurrence of preceding infection within the first 30 days. However, due to methodological limitations of our study, the association between infection preceding stroke and long-term risk of death—and particularly whether the risk could be modified—should be further investigated in large-scale prospective trials.

NIHSS score is widely used and rapid to assess and strongly predicts functional outcome and death after stroke at 3 months. In young adults, high NIHSS score predicted combined unfavorable outcome or death at 3 months. In older patients, severe index stroke predicts long-term mortality, but this issue has not been analyzed in young patients, who generally have better likelihood to survive. In our analysis, stroke severity measured with the NIHSS or GCS had no impact on long-term mortality in patients who survived the first 30 days. According to prior literature and our results, severe stroke thus affects survival in young adults merely during the very early phase after the stroke.

In our study, patients with large artery atherosclerosis and cardioembolism underlying the index stroke were at clearly higher risk of long-term death compared with those with index strokes of other etiologic subtypes (Figure 2). The former was also observed in an earlier study on young patients with stroke. After adjustment for age, gender, and clinical variables, large artery atherosclerosis was a strong independent predictor of long-term mortality in our study. In contrast, cardioembolism lacked such predictive value, probably because more deaths attributable to cardioembolic index stroke occurred within the first 30 days. In older patients with stroke, both cardioembolism and large vessel disease were associated with low probability of survival during the first years after the stroke compared with that of small vessel disease. These differences most likely arise from the overall higher prevalence of atrial fibrillation and other high-risk cardiac sources among the elderly versus relatively larger proportion of low-risk cardiac causes, eg, patent foramen ovale, in the young. In addition, our data suggest that mortality rates are generally low in the young with stroke attributable not only to small vessel disease, but also to undetermined and other determined etiologies. Moreover, our mortality data apply in part also to patients with cervicocebral artery dissection, because they comprised 59% of those with other determined etiologies.

Our nonselected consecutive patients came from a well-defined population, nearly all patients in the studied age groups were treated in our hospital, and complete mortality data were obtained from a reliable national crosschecked register. Yet, our study has potential limitations. Baseline data were obtained retrospectively and we included patients from a very long time period. We may have underestimated the prevalence of risk factors that are often based on self-reporting such as family history of stroke, drinking, or smoking. Because of overall low mortality in our young patients, we could not perform reliable subgroup analyses on deaths due to vascular causes. We also could not analyze the effect of secondary prevention with respect to risk of death due to lacking data of medication used. Furthermore, stroke severity measured with the NIHSS or GCS had no impact on long-term mortality in patients who survived the first 30 days. According to prior literature and our results, severe stroke thus affects survival in young adults merely during the very early phase after the stroke.

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therapy has made considerable advances during the last 2 decades, which might have improved the survival along the years. These problems are common to most longitudinal observational studies on patients with stroke, however.

**Conclusions**

Despite the overall low risk of death in the young after the first-ever ischemic stroke, several easily recognizable factors associate independently with the long-term mortality. Regarding young adults with a long expected lifespan ahead, detecting these factors are important, because in most patients, they can be modified by lifestyle changes, strictly controlled medication, or invasive interventions, when indicated.

**Acknowledgments**

We are indebted to Marja Metso, RN, and Jaana Valkeapää, RN, for their dedication and technical support.

**Source of Funding**

This work was supported by the Helsinki University Central Hospital (TYH2008253).

**Disclosures**

None.

**References**


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Stroke. 2009;40:2698-2703; originally published online July 9, 2009;
doi: 10.1161/STROKEAHA.109.554998

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