Twenty-Year Trends in Long-term Mortality Risk in 17 149 Survivors of Ischemic Stroke Less Than 55 Years of Age

Kok Wai Giang, MSc; Lena Björck, PhD; Susanne Nielsen, MSc; Masuma Novak, PhD; Tatiana Zverkova Sandström, BSc; Christina Jern, MD; Kjell Torén, MD; Annika Rosengren, MD

Background and Purpose—The purpose of the present study was to investigate the 4-year mortality risk among patients <55 years with a first ischemic stroke during 1987–2006.

Methods—A total of 17 149 cases (37.4% women) aged 18 to 54 years who survived ≥28 days after a first ischemic stroke were identified in the Swedish Inpatient Register from 1987 to 2006. All patients were followed for 4 years or until death. The standardized mortality ratio was calculated by comparing the mortality rates with those of the general population of equivalent age, sex, and calendar year.

Results—During the period, there were 1265 deaths. Long-term survival improved over time in both men and women. Among men, the mortality risk decreased by 32% (hazard ratio=0.68 [95% confidence interval, 0.56–0.82]) from the first 5-year period to the last 5-year period (1987–1991 versus 2002–2006), and among women, the mortality risk decreased by 45% (0.55 [0.41–0.75]). Despite an overall decrease in mortality, the standardized mortality ratios for the last 5-year period remained high: 5.88 (95% confidence interval, 5.10–6.71) for men and 5.91 (4.68–7.29) for women with an absolute excess risk of 1.60 and 0.97 per 100 person-years, respectively, with nearly half of all deaths related to cardiovascular disease.

Conclusions—During the 20-year period, 4-year mortality decreased by one third but was still 6-fold higher than that of the general population in the most recent period, emphasizing the importance of secondary prevention in young persons who have had a stroke.

Key Words: age factors ■ epidemiology ■ ischemic ■ mortality ■ stroke ■ survival ■ trends

During the past few decades, mortality from ischemic stroke (IS) has decreased in several parts of Europe, and survival after a stroke is improving. Nevertheless, it is still one of the leading causes of death and morbidity. Despite recent favorable trends in mortality, the incidence of stroke among younger adults in Sweden and elsewhere is increasing.

The risk of stroke increases with age, and accordingly, the majority of all events occur among the elderly. Stroke survivors are known to have a poorer prognosis and a higher risk of death compared with a healthy population. Because most persons who have had a stroke are elderly, the majority of studies on risk factors, outcome, incidence, and mortality have been focused on older patients. However, given the recent trend of an increasing incidence of stroke among younger adults, a substantial proportion of stroke survivors are now <55 years of age. Knowledge about the prognosis of these patients is therefore essential because outcomes may be different from those in older patients and younger patients stand to lose more of their lifetime. To our knowledge, few studies with sufficiently large data sets have investigated trends in survival and the risk of death after a first IS among younger adults aged <55 years. The aim of the present study was to investigate trends in long-term mortality among men and women aged 18 to 54 years who were hospitalized with a first IS during 1987–2006. All patients were followed up for 4 years, and mortality rates were compared with those of the general population.

Methods

Study Population

Sweden has a publicly financed healthcare system, which offers healthcare to all citizens at comparatively low cost. The Inpatient Register (IPR) was first established in 1964, and it has been operating on a nationwide basis since 1987. Hospitals are required to report principal and contributory discharge diagnoses of all patients to the IPR. For the purpose of the present study, data from the IPR and the Cause of Death Registers were linked through the Swedish unique 10-digit personal identifier number.

The present study included all men (10 677) and women (6 373) aged 18 to 54 years who survived ≥28 days after hospitalization with a principal discharge diagnosis of IS. We used a time frame of 7 years for any event to be considered as a first-time event in order to ensure that all cases were treated as uniformly as possible. A total of 17 149 IS cases (99 recurrent after >7 years) were identified during 1987–2006. Hemorrhagic strokes were excluded in the analysis because a proportion of cases among younger adults resulted from...
vascular malformations and had a different pathogenesis. Patients were stratified according to age (18–44 and 45–54 years) and admission period (1987–1991, 1992–1996, 1997–2001, and 2002–2006) and then followed for 4 years with respect to all-cause mortality.

The International Classification of Diseases (ICD), Ninth Revision (ICD-9) was used from 1987 to 1996, and the ICD-10 was used from 1997 onward. IS was identified using ICD-9 codes 434 and 436 and ICD-10 codes I63 and I64.

Comorbidities were defined by the following discharge codes (diagnoses 7 years before index hospitalization and during the index hospitalization are included): atrial fibrillation: 427D (ICD-9), I48 (ICD-10); acute myocardial infarction: 410 (ICD-10); heart failure: 428 (ICD-9), I50 (ICD-10); hypertension: 401–405 (ICD-9), I10–I15 (ICD-10); diabetes mellitus: 250 (ICD-9), E10–E14 (ICD-10); cardiomyopathy: 425 (ICD-9), I42 (ICD-10); and chronic respiratory disease: 490–496 (ICD-9), J40–J47 (ICD-10). Surgical treatment was defined by the following surgical codes: coronary artery bypass grafting: 3066, 3067, 3105, 3127, FNA, FNB, FNE, FNC; and percutaneous coronary intervention: 3080, FNG 00, FNG 02, FNG 05.

The following codes were used for cause of death: subarachnoid hemorrhage: 430 (ICD-9), I60 (ICD-10); IS: 434 (ICD-9), I64 (ICD-10); hemorrhagic stroke: 431, 432 (ICD-9), I61, 162 (ICD-10); any other stroke diagnosis: 433, 436–438 (ICD-9), I64–I68 (ICD-10); coronary heart disease (CHD): 410–414 (ICD-9), I20–I25 (ICD-10); cardiovascular disease: 390–459 (ICD-9), I00–I99 (ICD-10); malignancy: 140–208 (ICD-9), C00–C97 (ICD-10).

**Ethics**

For anonymity, all personal identifiers were removed and replaced with a code in the final data set. The protocol was approved by the regional Ethics Board of Gothenburg.

**Statistical Analysis**

All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC), and graphs were produced using R version 2.15.1. The \( \chi^2 \) test was used to compare differences in comorbidities between men and women. A \( P \) value \( \leq 0.05 \) was considered significant. To compare mortality rates in patients with a first IS with those in the general population, standardized mortality ratios (SMRs) with 2-sided 95% confidence intervals (CIs) were calculated as the ratio of the observed number of deaths to the expected number of deaths. The expected mortality in the general population was calculated on the basis of age, sex, and calendar year from the mortality rates from the Official Statistics of Sweden (SCB). The absolute excess risk (AER) was estimated by subtracting the expected number of deaths from the number observed, dividing by the number of person-years at risk, and multiplying by 100. The AER is useful to determine the absolute additional mortality or the excess risk of death in a population with a disease.

To calculate age- and sex-specific changes in mortality over time, a Cox proportional hazard regression analysis was used, yielding hazard ratios with 2-sided 95% CI. The period 1987–1991 was used as the reference period; all final models were adjusted for age and diabetes mellitus (because diabetes mellitus prevalence increased over time) and tested for proportionality by interaction of covariates, age, diabetes mellitus, and time, to adjust for nonproportionality. Survival probabilities were estimated according to the Kaplan–Meier method. The log-rank test was used to study any changes in survival between different time periods.

**Results**

From 1987 to 2006, a total of 17,149 men and women were identified with a first-time IS; of these, 4,520 (26.4%) were 18 to 44 years old and 12,629 (73.6%) were 44 to 54 years old. Overall, previous heart conditions and procedures (acute myocardial infarction, atrial fibrillation, heart failure, percutaneous coronary intervention, and coronary artery bypass grafting), as well as diabetes mellitus and hypertension, were more common in men, whereas malignancy and chronic respiratory disease were more common in women (Table 1).

**Table 1. Baseline Characteristics in Men and Women With a First IS**

<table>
<thead>
<tr>
<th>No. of IS events</th>
<th>All, n (%)</th>
<th>Men, n (%)</th>
<th>Women, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of IS events</td>
<td>17,149</td>
<td>10,739</td>
<td>6,410</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age 18–44</td>
<td>4,520 (26.4)</td>
<td>2,522 (23.5)</td>
<td>1,998 (31.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age 44–54</td>
<td>12,629 (73.6)</td>
<td>8,217 (76.5)</td>
<td>4,412 (68.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2,190 (12.8)</td>
<td>1,452 (13.5)</td>
<td>738 (11.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3,811 (22.2)</td>
<td>2,544 (23.7)</td>
<td>1,267 (19.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>256 (1.5)</td>
<td>158 (1.4)</td>
<td>98 (1.5)</td>
<td>0.7635</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>197 (1.15)</td>
<td>113 (1.05)</td>
<td>84 (1.31)</td>
<td>0.1247</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>654 (3.81)</td>
<td>522 (4.86)</td>
<td>132 (2.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>574 (3.35)</td>
<td>423 (3.94)</td>
<td>151 (2.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>417 (2.43)</td>
<td>304 (2.83)</td>
<td>113 (1.76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>197 (1.15)</td>
<td>154 (1.43)</td>
<td>43 (0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>414 (2.41)</td>
<td>179 (1.67)</td>
<td>235 (3.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>363 (2.12)</td>
<td>172 (1.60)</td>
<td>191 (2.98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCI</td>
<td>108 (0.63)</td>
<td>87 (0.81)</td>
<td>21 (0.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABB</td>
<td>273 (1.59)</td>
<td>226 (2.10)</td>
<td>47 (0.73)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; CABB, coronary artery bypass grafting; IS, ischemic stroke; and PCI, percutaneous coronary intervention.

**Standardized Mortality Ratio**

Table 2 shows SMRs by age and sex. In survivors of IS, a total of 1265 deaths occurred within 4 years. For both men and women, the SMR was highest in the youngest age group (18–44 years). In men, there was a 9-fold higher risk of death (SMR=9.15 [95% CI, 7.71–10.71]) compared with the corresponding general male population, and the AER was 1.31 per 100 person-years. The SMR for women in the same age group was 12.12 (9.60–14.94) with an AER of 0.93 per 100 person-years. In the age group of 45 to 54 years, the mortality risk when compared with the general population was 5-fold higher (5.11 [4.75–5.49]) for men and 6-fold higher (6.37 [5.68–7.10]) for women, with AERs of 1.89 and 1.54 per 100 person-years, respectively. In general terms, therefore, the excess mortality in IS survivors was between 0.93 and 1.89 per 100 person-years, corresponding to an approximate absolute risk rate of dying between 1.47 and 2.35 per 100 person-years.

Table 3 shows SMRs by time period and sex. For the last period (2002–2006), the mortality ratio for men (5.88 [5.10–6.71]) and women (5.91 [4.68–7.29]) was more or less similar when compared with the general population but with a slightly higher excess mortality for men compared with women (AER=1.60 for men and 0.97 per 100 person-years for women).

**Long-term Survival After a First IS**

From 1987 to 2006 the overall survival improved for both men and women. However, notably, there was no improvement between the third and the fourth period among men (Figure).
From the first to the last period, the 4-year mortality risk decreased by 32% in men (hazard ratio=0.68 [0.56–0.82]) and 45% in women (0.55 [0.41–0.75]). Again, there was no improvement in men from the third to the fourth period (Table 4).

Table 5 shows sex-specific causes of death for the 1265 deaths that occurred. For men, half of all deaths were related to cardiovascular disease (50.3%), with the majority from CHD (23.5%). The rest resulted from malignancies (15.3%) or other causes (34.4%). Among women, <40% of all deaths were related to cardiovascular disease (36.4%; 11.1% from CHD). In women, more than half of all deaths resulted from malignancies (28.4%) or other causes (35.1%).

Discussion
In the present study, we found that the 4-year mortality in young survivors of a first IS decreased substantially during a 20-year period, with a significant improvement in survival for both men and women. However, compared with the general population, these younger IS patients still had ≈6-fold increased risk of dying.

The incidence of IS has increased among younger adults in both Sweden and the United States.6 In Finland, a 5-year cumulative mortality risk of 10.7% was found in 731 stroke survivors aged <50 years,16 which is similar to our findings and to other studies in Europe.13,17 Our study adds that the mortality risk over time decreased by 32% in men and 45% in women. The positive survival trend in Sweden might be explained by improvements in treatment and changes in cardiovascular risk factors during recent decades. For example, during the study period, both blood pressure and smoking rates, 2 well-known risk factors of stroke, have decreased.18 Lower blood pressure levels could be explained by dietary changes (eg, less salt intake) and better antihypertensive treatment in the population, whereas lower smoking rates could partly be explained by improved knowledge and interventions against smoking but also by increasing use of moist snuff (snus) in Sweden.19–22 Diabetes mellitus, which is a major risk factor for stroke, had high prevalence in our population.21 However, with better treatment and management, the survival rates among patients with diabetes mellitus have improved during the past number of years.23 In addition, total cholesterol levels have declined during recent years, which explained most of the decrease in CHD in Sweden.24,25 Although elevated cholesterol is not a strong risk factor for stroke, lower levels could be an indicator of changes in diet. In addition, improved management in specialized stroke care units and secondary prevention could lead to better survival, especially among those <65 years old.26–28

Despite favorable trends in survival during the past few decades, mortality remains high among patients with stroke when compared with the general population. Today, studies on mortality rates in stroke are mostly focused on older patients. In a recent study by Rutten-Jacobs et al,12 long-term mortality among younger patients with stroke (18–50 years) was ≈4-fold that of the general population in The Netherlands. We observed similar results among IS patients aged 18 to 54 years during the last period 2002–2006 but with higher SMRs of 5.88 for men and 5.91 for women.
Stroke among younger adults leads not only to potential loss of function and working capacity, but also to mortality rates that are much higher than those for people of similar age. Similar to previous studies, we found cardiovascular disease to be the most common cause of death among younger IS survivors. However, in contrast to other studies, death from CHD was more common than death from stroke or malignancy. In Sweden, Glader et al. showed that the use of secondary treatment, such as antihypertensive medication, statins, antiplatelet, and warfarin, declined substantially during the first 2 years among patients with stroke, and these medications are important for prevention of future CHD and stroke events.

Table 4. Four-Year Mortality HRs (95% CI) in Men and Women Aged 18 to 54 y Hospitalized With a First IS From 1987 to 2006 by Period

<table>
<thead>
<tr>
<th>Period</th>
<th>No. of Deaths</th>
<th>HR (95% CI)*</th>
<th>Annual Decrease, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–1991</td>
<td>222</td>
<td>1.00 (ref)</td>
<td>2.55 (1.38–3.71)</td>
</tr>
<tr>
<td>1992–1996</td>
<td>224</td>
<td>0.74 (0.62–0.89)</td>
<td></td>
</tr>
<tr>
<td>1997–2001</td>
<td>229</td>
<td>0.69 (0.57–0.83)</td>
<td></td>
</tr>
<tr>
<td>2002–2006</td>
<td>203</td>
<td>0.68 (0.56–0.82)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–1991</td>
<td>83</td>
<td>1.00 (ref)</td>
<td>3.33 (1.54–5.08)</td>
</tr>
<tr>
<td>1992–1996</td>
<td>117</td>
<td>0.86 (0.65–1.15)</td>
<td></td>
</tr>
<tr>
<td>1997–2001</td>
<td>108</td>
<td>0.67 (0.50–0.89)</td>
<td></td>
</tr>
<tr>
<td>2002–2006</td>
<td>79</td>
<td>0.55 (0.41–0.75)</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and IS, ischemic stroke.

*Adjusted for age, diabetes mellitus, and interactions of age, diabetes mellitus, and time.

Table 5. Causes of Death in Men and Women Aged 18 to 54 y Hospitalized With a First IS From 1987 to 2006

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Total, n (%)</th>
<th>Men, n (%)</th>
<th>Women, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deaths</td>
<td>1265</td>
<td>878</td>
<td>387</td>
<td></td>
</tr>
<tr>
<td>All CVD</td>
<td>583 (46.1)</td>
<td>442 (50.3)</td>
<td>141 (36.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAH</td>
<td>8 (0.63)</td>
<td>6 (0.68)</td>
<td>2 (0.52)</td>
<td>0.731</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>88 (6.96)</td>
<td>63 (7.18)</td>
<td>25 (6.46)</td>
<td>0.645</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>66 (5.22)</td>
<td>53 (6.04)</td>
<td>13 (3.36)</td>
<td>0.049</td>
</tr>
<tr>
<td>Other stroke diagnosis</td>
<td>47 (3.72)</td>
<td>22 (2.51)</td>
<td>25 (6.46)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>249 (19.7)</td>
<td>206 (23.5)</td>
<td>43 (11.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other CVD</td>
<td>125 (9.88)</td>
<td>92 (10.5)</td>
<td>33 (8.53)</td>
<td>0.284</td>
</tr>
<tr>
<td>Malignancies</td>
<td>244 (19.3)</td>
<td>134 (15.3)</td>
<td>110 (28.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other causes</td>
<td>438 (34.6)</td>
<td>302 (34.4)</td>
<td>136 (35.1)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; IS, ischemic stroke; and SAH, subarachnoid hemorrhage.
Therefore, to further reduce the mortality and improve the health status among IS patients, more intensive and persistent secondary interventions are warranted, including both medication and lifestyle changes.28,29,36

Limitations
There are some limitations as well as several strengths to our study. Strengths include a large, representative population, with virtually no loss to follow-up. Because stroke is uncommon among younger adults, large populations are needed to identify a sufficient number of young patients. Therefore, a major strength of our study is the use of IPR, which has a near-complete coverage of all hospitalized stroke cases for an extended time period in Sweden. Limitations of the IPR lie in the variations in current stroke diagnosis from earlier data and in the varying judgments on the validation of stroke cases.37 Differentiation of IS from other stroke subtypes may have changed over time; however, IS is the most common form among younger adults, large populations are needed to identify a sufficient number of young patients. Therefore, a major strength of our study is the use of IPR, which has a near-complete coverage of all hospitalized stroke cases for an extended time period in Sweden. Limitations of the IPR lie in the variations in current stroke diagnosis from earlier data and in the varying judgments on the validation of stroke cases.37

Conclusions
This large national study of younger patients with IS found that the survival probability improved significantly in both men and women during the past 20 years. Possible explanations for this trend could be attributed to better secondary prevention, improved treatment of cardiovascular risk factors, and the introduction of specialized stroke care units. However, the mortality risk remained high among these patients compared with the same-age group in the general population. It is possible that risk varies substantially between groups of patients with stroke, and further work should attempt to identify subgroups at particularly high risk. Meanwhile, implementation of the use of validated secondary preventive measures, which is now substANDARD, should be a high priority.

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Disclosures
None.

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