Predictors of Early and Late Case-Fatality in a Nationwide Danish Study of 26 818 Patients With First-Ever Ischemic Stroke

Klaus Kaae Andersen, MS, PhD; Zorana Jovanovic Andersen, MS, PhD; Tom Skyhøj Olsen, MD, PhD

**Background and Purpose**—Predictors of early case-fatality (3-day, 7-day, and 30-day) in first-ever ischemic stroke were identified and compared with predictors of late case-fatality (90-day and 1-year).

**Methods**—A registry designed to register hospitalized patients with stroke in Denmark 2000 to 2007 holds 26 818 patients with first-ever ischemic stroke with information on stroke severity (Scandinavian Stroke Scale), CT scan, cardiovascular risk factors, marital status, and fatality within 1 year. Multiple logistic regression was used in identifying predictors.

**Results**—Mean age was 71.2 years; 48.5% were women; mean Scandinavian Stroke Scale score was 43.9. Early case-fatality showed stroke severity and age were significant predictors of 3-day, 7-day, and 30-day case-fatality (nonlinear effect). In addition, atrial fibrillation (OR, 1.56) predicted 30-day case-fatality. For late case-fatality, significant predictors of 90-day and 1-year case-fatality were age, stroke severity (nonlinear effect), atrial fibrillation (OR, 1.37 and 1.57), and diabetes (OR, 1.35 and 1.33), respectively. Male gender (OR, 1.28), previous myocardial infarction (OR, 1.40), and smoking (OR, 1.21) were also associated with 1-year case-fatality. Alcohol consumption, hypertension, intermittent arterial claudication, and marital state had no influence. All case-fatality rates accelerated with increasing age, but 3-day and 7-day case-fatality rates tended to level off or decline at the highest ages.

**Conclusions**—Age and stroke severity were the only significant predictors of fatality within the first poststroke week; they were associated with late case-fatality as well. Cardiovascular risk factors were associated with late case-fatality; with the exception of atrial fibrillation, they were not significantly associated with early case-fatality rates. *(Stroke. 2011;42:00-00.)*

**Key Words:** acute stroke ■ brain infarction ■ case-fatality ■ epidemiology ■ outcome

The approach to stroke has changed. From being rather conservative, the attitude to treatment is now very active. As a result, treatment in the very acute state has come into focus. Risk of death is high in the first weeks1 and treatment aimed at ensuring survival in this critical period has high priority. Knowledge about predictors of early fatality is essential for optimizing stroke survival strategies. Information on predictors of early fatality is, however, sparse, in part due to the lack of large study populations with sufficient numbers of stroke events needed for statistically reliable predictor identification. Studies on predictors of survival within the first week after stroke are few and address only some of the potential factors associated with early fatality.2 A larger evidence base exists on the predictors of 30-day case-fatality but with inconsistent results and with few studies based on large populations.3-7

Death within the first month after a stroke is mainly caused by the index stroke, whereas deaths occurring later are mainly caused by other diseases, including recurrent stroke, cardiovascular events, complications of immobility, etc.5 Factors influencing early case-fatality are, therefore, more likely related to death caused by the index stroke, whereas factors associated with late case-fatality are more likely related to death caused by diseases other than the index stroke.

Based on a Danish nationwide registry of 26 818 patients with first-ever ischemic stroke, the present study aims at identifying predictors of early case-fatality (3-day, 7-day, and 30-day). Furthermore, predictors of late case-fatality (90-day and 1-year) were identified to examine whether predictors of early case-fatality might also influence the late case-fatality.

**Methods**

The study is based on data from the Danish National Indicator Project described in detail elsewhere.8,9 All Danish hospitals are committed to reporting a predefined set of data into the National Indicator Project database on all patients admitted to the hospital with acute stroke, including age, gender, marital status, admission stroke severity measured by the Scandinavian Stroke Scale (SSS),10 stroke subtype, and a predefined cardiovascular profile.

The SSS is a validated neurological stroke scale that evaluates stroke severity on a score from 0 to 58 with lower scores indicating more severe strokes.10 The distinction between ischemic and hemorrhagic stroke was determined after a CT/MR scan. The cardiovascular profile included information on: alcohol consumption (≤14/21/>14/21) U per week for women and men, respectively, representing under/over the limit values set by the Danish National...
Board of Health), current daily smoking, diabetes mellitus (DM), atrial fibrillation (AF; chronic or paroxysmal), arterial hypertension, previous myocardial infarction, previous stroke, and intermittent arterial claudication. Diagnosis of DM, AF, arterial hypertension, previous myocardial infarction, previous stroke, and intermittent arterial claudication was made on current Danish standards9 and was either known before onset of a stroke or diagnosed during hospitalization. A stroke was defined according to the World Health Organization criteria.11

This study included only patients with first-ever ischemic stroke admissions by excluding those who had been hospitalized for a stroke before May 8, 2000. For patients with >=1 stroke hospitalization, after May 8, 2000, only the first event was included in the analysis. Patients with hemorrhagic stroke, transient ischemic attacks, or patients <18 years were excluded from the study as well as patients in whom a CT/MR scan was not performed (0.4%) or unavailable (0.7%). The time origin for the analysis was the date of hospital admission.

The National Indicater Project registry coverage was by professionals consensus estimated to be approximately 80% of all stroke admissions in Denmark.12 The very high proportion of patients with stroke are admitted to hospital (90%) due to free hospital care in Denmark.13 Survival of the patients included in the Danish National Indicater Project database was followed through the Danish Central Person Registry with information on the date of death or emigration. We studied all-cause mortality only. Inclusion of patients started on May 8, 2000, and end of the study follow-up was on January 16, 2007. Less than 0.2% of the patients were lost to follow-up. The study was approved by the board of the Danish National Indicater Project and the Danish Data Protection Agency.

Statistical Analyses

First, 3-day, 7-day, 30-day, 90-day, and 1-year case-fatality was calculated by each of the following cardiovascular risk factors: DM, previous myocardial infarction, AF, hypertension, intermittent claudication, smoking (current smoker/ex- or never smoker), alcohol consumption (over limit: >14/21; under limit: ≤14/21 U per week for women and men, respectively) as well as gender, and marital status (single/married or cohabiting). A generalized additive logistic regression model was used to estimate the odds of dying when controlling for gender, cardiovascular risk factors, marital status, age, and stroke severity. Both age and stroke severity were modeled as continuous variables using penalized cubic regression splines with 4 degrees of freedom to allow for the nonlinear effects. Given the large data set size, results were presented as ORs and 99% CIs.

The nonlinear effect of age and stroke severity on case-fatality was illustrated graphically by predicting specific patient profiles using the fitted generalized additive logistic regression models. We quantify the excess risk by OR and 99% CI. For late case-fatality, death is common and thus OR may overestimate the effect size if interpreted as relative risks.

We applied the generalized coefficient of determination proposed by Nagelkerke14 to evaluate how well the models fit data. The generalized coefficient of determination should be interpreted as the proportion of the variation explained by the model. Possible values are between 0% and 100% with 0 denoting that the model does not explain any variation and 100% denoting that it perfectly explains the observed variation. Mathematically, it is defined as $R^2 = 1 - (L_0/ L_1)^{2n}$ in which $L_0$ is the likelihood of the model with only the intercept, $L_1$ is the likelihood of the estimated model, and n is the sample size. However, in the case of a logistic model in which $L_1$ cannot be greater than 1, $R^2$ is between 0 and $R^2_{max} = 1 - (L_0)^{2n}$. Thus, we apply maxed-rescaled $R^2_m = R^2/R^2_{max}$.

Results

Of the 26,818 patients, 13,007 (48.5%) were women. Mean age was 71.2 (13.4) years and mean SSS score was 43.9 (15.2). SSS scores were missing for 3622 (13.5%) patients. Other clinical characteristics including marital status (single/married or cohabiting) and cardiovascular risk factors appear in Table 1.

Mean time from symptom onset to hospitalization was 0.88 days and was known in 81.1% of all cases. The vast majority (96%) of the patients received treatment in a stroke unit.

Three-day, 7-day, 30-day, 90-day, and 1-year case-fatality were 1.9%, 3.3%, 6.8%, 10.2% and 16.0%, respectively. Case-fatality rates were strongly influenced by age and stroke severity as seen in Figure 1. Case-fatality rates were significantly negatively associated with increasing SSS (decreasing stroke severity). Thirty-day, 90-day, and 1-year case-fatality increased with increasing age. This was also observed for 3-day and 7-day case-fatality but at ages >70 years, 3-day case-fatality and 7-day case-fatality appeared to level off and 3-day case-fatality even declined in patients aged >85 years. The effect of age on case-fatality was not modified by stroke severity (Figure 1). The Nagelkerke coefficients of determination for the models for 3-day, 7-day, 30-day, 90-day, and 1-year case-fatality are in Table 2.

Predictors of Early Case-Fatality

In our multiple logistic regression analysis including age, stroke severity, sex, marital status, and the cardiovascular risk factors, age and stroke severity emerged as significant predictors of 3-day, 7-day, and 30-day case-fatality (Table 2; Figures 2 and 3). Furthermore, AF (OR, 1.56) was a significant predictor of 30-day mortality (Table 2). The remaining variables included in the analysis had no significant predictive power.

Predictors of Late Case-Fatality

Age and stroke severity significantly predicted 90-day and 1-year case-fatality (Figures 1 and 2). The association between age and SSS and case-fatalities was enhanced with increasing follow-up time (90-day, 1-year; Figures 2 and 3). DM (OR, 1.35 and 1.33) and AF (OR, 1.37 and 1.57) significantly predicted 90-day and 1-year fatality, respectively. Male gender (OR, 1.28), previous myocardial infarction (OR, 1.40), and smoking (OR, 1.27) significantly predicted 1-year case-fatality. Alcohol consumption, intermittent arterial claudication, hypertension, and marital status had no predictive power (Table 2).

Discussion

The main findings in this study were that only age and stroke severity were associated with very early case-fatality, whereas cardiovascular risk factors mainly were associated with late case-fatality. Interestingly, we found that very early case-fatality rates tend to level off after the age of approximately 70 years, and age >85 years, 3-day case-fatality rates even declined.

We consider our study population to be representative of the Danish hospital stroke population. Our study is nationwide, covering approximately 80% of all hospitalized patients with stroke in Denmark,12 and data completeness was high exceeding 85% for all individual variables.
Most patients with acute stroke are hospitalized in Denmark. However, a minority is not hospitalized. It should be stressed, therefore, that our observations apply to hospitalized patients with stroke only.

**Case-Fatality**

Knowledge on early case-fatality rates is limited. In hospital-based studies on all ischemic strokes, 7-day case-fatality was 6.9% in Canada and 8% in Holland, whereas in our study on first-ever ischemic stroke, 3-day and 7-day case-fatality were 1.9% and 3.3%, respectively. Thirty-day to 1-year case-fatality rates are comparable to that of another large nationwide Scandinavian hospital-based study.

Stroke severity was closely related to case-fatality: 3-day as well as 1-year case-fatality. Thirty-day, 90-day, and 1-year case-fatality continuously increased with increasing age. Interestingly, however, 3-day and 7-day case-fatality rates leveled off above the age of approximately 70 years, and 3-day case-fatality rates even declined above the age of 85 years. Due to wide confidence levels, interpretations of our observation should be made with caution. We recently suggested heterogeneity in regard to survival as a possible explanation of the phenomenon. Some individuals may be frailer than others and the frail die first. Hence, individuals alive at old ages would be the most resilient. Presumably, individuals who live longest are superior in keeping disease at bay, but our finding may indicate that long life is also associated with superiority in surviving disease (at least stroke) when it turns up. Most deaths within the first week after stroke occur in patients with severe strokes and are considered to be due to the stroke lesion itself. Some patients who survive severe stroke lesions die, however, within weeks or months of hospitalization because disabilities resulting from the stroke lesion promote complications from which the patients die at a later stage after stroke. This may explain why the leveling off/decline phenomenon is only seen when studying early case-fatality but not when studying case-fatality at a later time after stroke. Moreover, late case-fatality as demonstrated in this study is dominated by deaths due to diseases other than the index stroke. Prevalence of these diseases increases in frequency with age and explains the continuous acceleration of 30-day, 90-day, and 1-year case-fatality rates.

<table>
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<th>3-D</th>
<th>7-D</th>
<th>30-D</th>
<th>90-D</th>
<th>1-Y</th>
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<td>3.3</td>
<td>6.8</td>
<td>10.2</td>
<td>16.0</td>
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<td>11.9</td>
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<tr>
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<td>3346 (12.5)</td>
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<td>No</td>
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<td>Yes</td>
<td>952 (3.5)</td>
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<td>7.7</td>
<td>12.1</td>
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<tr>
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<td>14.4</td>
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<td>Current daily smoking</td>
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<td>4.9</td>
<td>6.5</td>
<td>10.5</td>
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<tr>
<td>Under</td>
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<td>5.2</td>
<td>8.4</td>
<td>13.4</td>
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<td>Marital status</td>
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<td>3611 (13.5)</td>
<td>5.5</td>
<td>9.3</td>
<td>17.5</td>
<td>23.3</td>
<td>31.4</td>
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<td>Married/cohabiting</td>
<td>14 465 (54.0)</td>
<td>1.5</td>
<td>4.1</td>
<td>4.8</td>
<td>6.9</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>702 (2.5)</td>
<td>3.1</td>
<td>5.5</td>
<td>13.0</td>
<td>16.5</td>
<td>24.8</td>
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</table>

Table 1. Distribution of Risk Factors and Case-Fatality (Overall and by Risk Factors) in 26 818 Patients With First-Ever Ischemic Stroke
It could be argued that the levelling off/decline phenomenon reflects that elderly stroke patients with severe strokes and poor prognosis more often remain at home. Indeed, patients with stroke dying out of the hospital in Denmark are older than patients dying in the hospital. It should be stressed, therefore, that our observations pertain to hospitalized patients with stroke only and not to the entire stroke population. However, stroke severity increases with age in our cohort, arguing against the possibility that poor outcome (more severe strokes) kept more elderly patients with stroke from hospitalization. Furthermore, our findings were not modified by stroke severity and applied equally to mild and severe strokes.

**Predictors of Early Case-Fatality**

Only age and stroke severity emerged as significant predictors of 3-day and/or 7-day survival. In the Registry of the Canadian Stroke Network, stroke severity but not age or sex significantly predicted 7-day survival. Stroke severity is the single most important predictor of case-fatality, especially for

| Table 2. Association Between Risk Factors and Mortality in 26818 Patients With First-Ever Ischemic Stroke* |
|---|---|---|---|---|---|
| Factor | 3-D (OR [99% CI]) | 7-D (OR [99% CI]) | 30-D (OR [99% CI]) | 90-D (OR [99% CI]) | 1-Y (OR [99% CI]) |
| Male gender | 1.12 (0.66–1.88) | 1.35 (0.91–2.00) | 1.15 (0.87–1.51) | 1.19 (0.96–1.49) | 1.28 (1.08–1.51) |
| Diabetes mellitus | 1.06 (0.50–2.24) | 0.97 (0.55–1.71) | 1.29 (0.90–1.87) | 1.35 (1.01–1.81) | 1.33 (1.06–1.69) |
| Intermittent arterial claudication | 1.32 (0.48–3.61) | 1.13 (0.50–2.53) | 1.12 (0.63–1.99) | 1.21 (0.76–1.92) | 1.20 (0.82–1.74) |
| Atrial fibrillation | 0.69 (0.36–1.31) | 1.04 (0.66–1.63) | 1.56 (1.15–2.09) | 1.37 (1.08–1.74) | 1.57 (1.29–1.91) |
| Previous myocardial infarction | 1.30 (0.62–2.72) | 1.33 (0.77–2.29) | 1.21 (0.81–1.81) | 1.35 (0.98–1.86) | 1.40 (1.09–1.79) |
| Hypertension | 0.89 (0.54–1.47) | 1.16 (0.81–1.67) | 1.08 (0.85–1.40) | 1.07 (0.87–1.31) | 0.98 (0.84–1.15) |
| Current daily smoking | 1.06 (0.61–1.81) | 1.22 (0.82–1.82) | 1.23 (0.92–1.64) | 1.21 (0.97–1.52) | 1.27 (1.06–1.52) |
| Over limit alcohol consumption | 1.59 (0.67–3.78) | 1.12 (0.55–2.29) | 1.26 (0.74–2.04) | 0.95 (0.59–1.52) | 1.06 (0.74–1.51) |
| Single/living with someone | 1.36 (0.79–2.26) | 1.09 (0.74–1.62) | 1.02 (0.78–1.35) | 1.13 (0.90–1.40) | 1.14 (0.96–1.34) |

*OR indicates odds ratio; CI, confidence interval.

*Age and Scandinavian Stroke Scale were included nonlinearly as restricted cubic splines in the analysis, both being significant predictors of 3-d to 1-y case-fatality (Figures 2 and 3).
early case-fatality. In predicting 3-day case-fatality, the Nagelkerke coefficient of determination is 25.9% but is only 2.4% if stroke severity is left out of the model. This indicates that stroke severity is the all important predictor for short-term case-fatality. The lower number of patients included in the Canadian study (n=3631) may explain why age did not come out as a significant predictor. The influence of individual cardiovascular risk factors on 7-day case-fatality was not examined in that study. Usually, death within the first week after stroke is considered to be caused by the stroke lesion.5 Our finding that none of the diseases in our cardiovascular risk factor panel had a predictive impact is in agreement with this notion. Reducing early stroke survival, according to this study, thus rests on reduction of stroke severity as the only modifiable risk factor for early stroke death.

AF was associated with the increased risk of dying within 30 days by 56%. Recurrent strokes in patients in whom prevention by warfarin was omitted because of the severity of the stroke may explain the excess mortality in these patients.

Predictors of Late Case-Fatality

Age and stroke severity were also significantly associated with 90-day and 1-year case-fatality. In comparison to the effect of these 2 factors on early case-fatality, their influence on 90-day and 1-year case-fatality was enhanced, indicating that severity of stroke (although to a lesser degree) still has an independent effect on the risk of death as long as 1 year after the stroke. Because stroke severity is potentially modifiable, this means that also treatment directed toward patients with strokes at the milder end of the stroke spectrum may improve longer-term outcome. For 1-year case-fatality, the Nagelkerke coefficient of determination is 25.8% and drops to 15.1% when stroke severity is left out of the model, supporting that also other risk factors are significant predictors of late case-fatality.

Ischemic heart disease, AF, DM, and smoking are well-known risk factors for stroke.19 Expectedly, they are also associated with the increased risk of death after stroke. Consequences of stroke such as immobilization in combination with ≥1 of these risk factors may be the cause of some poststroke deaths. The effect of these factors was, however, independent of stroke severity and thus also a manifestation of the excess mortality related to each of the cardiovascular risk factors. Recurrent cardiovascular disease (stroke, myocardial infarction) and respiratory disease related to smoking may account for the major part of these deaths.

Hypertension being a major risk factor for stroke19 was not associated with the increased risk of poststroke death in this study. Hypertension was not associated with case-fatality in studies of 5-year and 10-year stroke survival.7 In our study, we adjusted for the presence of previous myocardial infarction, AF, and intermittent arterial claudication, all associated with hypertension. The lack of association between hypertension and case-fatality most probably reflects that it is the consequence of hypertension that accounts for poststroke death, whereas hypertension as such is of minor importance. Moreover, hypertension in our study also includes patients in treatment for hypertension. Data on patients receiving anti-hypertensive treatment are not available in this data set, but patients discharged from Danish hospitals with a stroke are
generally expected to receive antihypertensive treatment in the event of hypertension.\textsuperscript{20}

Alcohol consumption did not significantly associate with case-fatality. Moderate alcohol consumption is known to give some protection against recurrent cardiovascular attacks.\textsuperscript{19} A higher cardiovascular recurrence rate in nondrinkers may counterbalance a higher recurrence rate in patients with high or excessive alcohol consumption, hence explaining the lack of association between alcohol and case-fatality in this study.

Most studies on survival after a stroke do not show significant differences between sexes.\textsuperscript{21} Recently, however, studies including large numbers (\textgtr20,000) do report better survival of females as also seen in this study.\textsuperscript{9,15,22,23} in which gender is significantly associated with 1-year case-fatality. The association was independent of the cardiovascular risk factor variables included in the analysis, indicating that the lower case-fatality rate observed in women\textsuperscript{24} is not only a consequence of less frequent occurrence of cardiovascular disease in women. A female-specific superiority in stroke survival may also play a role.

**Conclusions**

Case-fatality rates generally increase with increasing age. However, very early case-fatality rates tended to level off and even declined at the highest ages, as a likely indication of heterogeneity in regard to survival and survival of the fit test. The all dominating risk factors for early stroke death were age and stroke severity, whereas cardiovascular risk factors for stroke such as AF, smoking, DM, and ischemic heart disease were mainly associated with late case-fatality through deaths not directly caused by the index stroke such as recurrent cardiovascular events, smoking-related disease, etc.

**Disclosures**

None.

**References**


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Stroke. published online August 4, 2011;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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