Intracranial Hemorrhage After Ischemic Stroke
Incidence, Time Trends, and Predictors in a Swedish Nationwide Cohort of 196,765 Patients

Joachim Ögren, MD; Anna-Lotta Irewall, MD; Lisa Bergström, MD; Thomas Mooe, MD, PhD

Background—Epidemiological data on the risk of intracranial hemorrhage (ICrH) after ischemic stroke are sparse. The aims of this study were to describe incidence, trends over time, and predictors of ICrH within 1 year after ischemic stroke.

Methods and Results—All patients registered in the Swedish stroke register Riksstroke for 1998 to 2009 were included (n=196,765), and data were combined with the National Patient Register to identify ICrH occurrence. A matched reference population was obtained. Incidence rates and cumulative incidences were calculated. Multivariable regression analyses were used to identify predictors. Analyses were performed separately for the first 30 days and days 31 to 365 after ischemic stroke. The incidence rate was 1.97% per year at risk for the first year (0.13% in the reference population) and 0.85% excluding the first 30 days. Over time, the cumulative incidence increased the first 30 days but decreased over days 31 to 365. Thrombolysis, previous ICrH, atrial fibrillation, and male sex were associated with increased risk of ICrH during the first 30 days. Previous ICrH, increasing age, and male sex were associated with increased risk during days 31 to 365. Statins and antithrombotic treatment did not independently predict ICrH occurrence.

Conclusions—The incidence of ICrH within 1 year after ischemic stroke was ≈2% per year at risk, about 15 times higher compared with the reference population. Over the study period, ICrH risk increased within the first 30 days but decreased thereafter. Previous ICrH, thrombolysis, and male sex affected the risk, whereas an increased use of antithrombotic treatments and statins did not. (Circ Cardiovasc Qual Outcomes. 2015;8:00-00. DOI: 10.1161/CIRCOUTCOMES.114.001606.)

Key Words: epidemiology ■ intracerebral hemorrhage ■ intracranial hemorrhage ■ regression analysis ■ risk ■ stroke

Approximately 30,000 patients in Sweden have stroke annually, including ≈85% brain infarction, ≈10% intracerebral hemorrhage (ICH), and 5% subarachnoid hemorrhage.1 It is well known that stroke survivors are at high risk of stroke recurrence and that the risk is the greatest within the first year2–4; in Sweden, recurrent events constitute ≈23% of the annual stroke events.5 Recurrent stroke subtypes differ in many cases from the previous stroke and may therefore be hemorrhagic after an ischemic index stroke.5,6 Although primary ICH is a serious disease with high mortality and morbidity,7 there are no large studies focusing on the risk of ICH or intracranial hemorrhage (ICH) after ischemic stroke (IS).

The evidence supporting the use of oral anticoagulant (OAC) therapy or antiplatelet therapy in secondary prevention after IS of cardioembolic or arterial origin, respectively, is substantial,8–10 and today, the majority of patients with IS are discharged with either antiplatelet or OAC therapy. It is also well known from randomized, controlled trials that these treatments are associated with an increased risk of ICrH.11,12 However, the subjects included in randomized, controlled trials are younger and have fewer comorbidities than the average patient with stroke, and risk may therefore be underestimated.

In addition, previous observational studies varied in design and size and included only a few cases of ICrH.13,14 Thrombolytic treatment is becoming more common and is also associated with an increased risk of bleeding.14

In this study, we investigated a Swedish nationwide cohort of fairly unselected patients with IS. Our objectives were to study the risk of ICrH during 1 year of follow-up to examine trends over time in ICrH incidence during the 12-year inclusion period and to identify predictors associated with increased risk of ICrH.

Methods

Gathering Patient Data From National Registers
In this cohort study, patient data were obtained from all patients registered with an IS in the Swedish Stroke Register (Riksstroke) between 1998 and 2009. Riksstroke is a national quality register in which all patients admitted to hospital with an acute stroke are registered. The register was initiated in 1994 and underwent increasing coverage during the 1990s; since 1998, all hospitals in Sweden have reported their patients to this register. In 2000, the estimated coverage was 75% to 80%, and in 2009, 85% of all acute stroke events were covered.1

Riksstroke provides information about demographics, discharge

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WHAT IS KNOWN
• The risk of a new stroke and other cardiovascular events is increased after an ischemic stroke.
• A majority of patients with ischemic stroke is discharged with antithrombotic treatment, which increases the risk of hemorrhage, including intracranial hemorrhage.

WHAT THE STUDY ADDS
• The risk of intracranial hemorrhage is the greatest the first 30 days after an ischemic stroke.
• The risk of intracranial hemorrhage the first 30 days has increased during the study period. More frequent use of thrombolysis can probably explain some of the increase.
• The risk of intracranial hemorrhage days 31 to 365 after an ischemic stroke has decreased during the study period despite an increased use of antithrombotic treatment.

diagnosis, medications at admission and discharge, smoking, diabetes mellitus, and atrial fibrillation at admission.10–12 Using each patient’s unique social security number, Riksstroke was combined with the National Patient Register (NPR), which includes dates for admission and discharge, as well as diagnoses at discharge for all hospital stays in Sweden. The NPR has been validated, and a diagnosis of first-ever stroke has a positive predictive value of 94% to 98%.16,17 Both Riksstroke and the NPR are based on the entire population in Sweden.

There were no exclusion criteria for the current investigation. The NPR was searched for any ICH within 365 days of an ischemic index stroke in Riksstroke, as well as for the date of the event. During the hospital stay, the time interval between the index event and a diagnosed ICH was not recorded. ICH was defined as an occurrence of a subarachnoid hemorrhage (I60), an ICH (I61), or other ICrH (I62), according to The International Classification of Diseases 10th Revision. When results on ICH are presented separately, this type of event is defined as an I61 diagnosis and described as an ICH. We also searched the NPR for myocardial infarction (I21), IS (I63), or ICrH before the index stroke. This project was approved by the ethics committee at Umeå University (2010-167-31).

To compare the incidence of ICrH in the study group with that in a population representative for the general population in Sweden, a reference population was obtained from the governmental agency: Statistics Sweden. The reference subjects were randomly selected 1:1 after matching by age, sex, and county with the stroke subjects and then linked to the NPR by the same algorithm as the study population.

Between January 1, 1998 and December 31, 2009, 235820 patients with stroke were admitted to hospital and registered in Riksstroke. A total of 196765 cases remained after excluding hemorrhagic and unidentified strokes as index events; another 35 cases were excluded because of invalid data. Because reference subjects were identified at the beginning of each year, 5763 of them had died before the date of the index stroke, leading to their exclusion from subsequent analysis. Furthermore, matched reference subjects could not be identified for 845 cases. Thus, the reference population contained 190157 subjects. The patients with stroke and the reference subjects were followed up for 365 days from the date of the index stroke until death because of any cause or until an ICrH, whichever occurred first.

OAC therapy during the study period was synonymous with warfarin administration, and lipid-lowering therapy was synonymous with statins administration. Antiplatelet therapy was defined as treatment with aspirin, clopidogrel, or dipyridamol. Antihypertensive treatment was defined as treatment with drugs with antihypertensive effect. Information about medication was collected from Riksstroke. Diabetes mellitus included both diabetes mellitus type 1 and type 2.

Missing Data
The Riksstroke registry does not contain data on smoking habits, diabetes mellitus, and antiplatelet or OAC therapy at discharge between 1998 and 2000 because these variables were not compulsory during that period. For 2001 to 2009, data were missing for smoking habits, diabetes mellitus, antiplatelet therapy at admission and discharge, and OAC therapy at admission and discharge in 12.8%, 1.1%, 2.7%, 4.5%, 3.0%, and 4.8% of cases, respectively. For 1998 to 2009, data for atrial fibrillation were missing in 3.1% of patients. For 2004 to 2009, data for antihypertensive medication were missing in 1.4% of the patients at admission and in 5.8% at discharge. For lipid-lowering medications, there were missing data in 5.9% of the patients at discharge. Data about medication and some comorbidities (ie, hypertension, atrial fibrillation, and diabetes mellitus) were not collected in the reference group.

Statistical Analysis
Results are presented as mean values with SD for continuous variables and as percentages for categorical variables. Kaplan–Meier analysis, using the Log-rank test for group comparisons, was performed to assess the cumulative incidence of ICrH. The cumulative incidence was calculated separately for the period within 30 days and for 31 to 365 days after the index stroke to describe the acute and long-term risks, respectively, of ICrH. Incidence rates, expressed as % per year at risk, were also calculated for comparison with published data. The ICrH incidence rate for the subgroup undergoing OAC treatment was only calculated for days 31 to 365 because we do not have data to determine whether the hemorrhage occurred before or after starting OAC treatment during the first 30 days. The overall study period was divided into 4 subperiods (1998–2000, 2001–2003, 2004–2006, and 2007–2009) before the analyses, and the cumulative incidence of ICrH within 30 days and for days 31 to 365 was calculated for each subperiod to study changes over time. The same calculations of cumulative incidences were made for the reference group and for the subgroup having ICH.

To explore predictors of ICrH for short-term and long-term follow-ups, separate analyses were performed for a follow-up period of 30 days and for 31 to 365 days within IS. Univariable and multivariable logistic regression analyses were performed for the first 30 days and corresponding Cox-regression analyses for days 31 to 365. To obtain a fairly recent and complete data set, we did not include data before 2004. Patients with an ICrH during the first 30 days were excluded in the analysis of predictors for days 31 to 365. In the multivariable model, previously established predictors of risk were considered together with significant variables from the univariable analysis. Smoking was excluded from the analyses because the status was unknown in >10% of the cases. Values of ≤0.05 were considered significant. All statistical analyses were performed using SPSS 20.0 software.

Results
This study included 196765 patients who had an IS between 1998 and 2009. The mean patient age was 76.0 (SD, 64.6–87.4) years, and 50.0% were women. Patient characteristics are shown in Tables 1 and 2. The reference population of 190157 subjects had a mean age of 75.8 (SD, 64.4–87.1) years, and 49.8% were women. Reference subjects had fewer comorbidities than patients with stroke: previous myocardial infarction, 7.7% versus 12.3%, respectively; previous IS, 3.6% versus 14.6%, respectively; and previous ICrH, 0.9% versus 1.7%, respectively.
ICrH Incidence

During the study period, 3186 patients had an ICrH within the first 365 days from the index stroke, an incidence rate of 1.97% (95% confidence interval [CI]: 1.91–2.03) per year at risk. The incidence rate was 12.90% (95% CI, 12.75–13.05; n=1932) per year at risk within the first 30 days and 0.85% (95% CI, 0.81–0.89; n=1254) per year at risk between days 31 and 365. The incidence rate for days 31 to 365 in patients discharged with OAC therapy was 1.04% (95% CI, 0.88–1.20; n=144) per year at risk and 0.75% (95% CI, 0.70–0.80; n=657) per year at risk in patients discharged with antiplatelet therapy.

Of the 3186 patients with ICrH, 2177 patients had an ICH, an incidence rate of 1.34% (95% CI: 1.29–1.39) per year at risk. The incidence rates within 30 days and for days 31 to 365 were 8.67% (95% CI, 8.55–8.79; n=1303) and 0.59% (95% CI, 0.55–0.63; n=874), respectively, per year at risk.

In the reference group, the incidence rate of ICrH within 365 days was 0.13% (95% CI, 0.11–0.15; n=231) per year at risk. The corresponding percentage for ICH was 0.04% (95% CI, 0.03–0.05, n=74). The cumulative incidences of ICrH and ICH are given in Table 3.

Trends Over Time

During the study period, the cumulative incidence of ICrH increased during the first 30 days ($P \leq 0.001$) after IS but decreased between days 31 and 365 ($P=0.021$; Table 3). The cumulative incidence in the reference group remained fairly steady over the study period and was considerably lower than that of the patients (Figure 1). The cumulative incidence of ICrH the entire year after IS, stratified by consecutive time intervals, as well as the cumulative incidence in the reference group, is presented in Figure I in the Data Supplement. The cumulative incidence increased significantly over time among the patients with stroke ($P<0.001$).

OAC or antiplatelet treatment became more common between 2001 and 2009 (Figure 2); in 2001, 70.9% of patients were discharged with antiplatelet therapy, and in 2009, the number increased to 80.7%. OAC therapy increased from 11.1% of patients to 13.6% of patients during the same period and discharge with neither OAC nor antiplatelet decreased from 19.6% to 7.4% of patients. Between 2004 and 2009, statin treatment increased each year, from 29.2% to 60.3%. All trends over time were significant ($P<0.001$).

### Table 1. Characteristics of Study Patients With Ischemic Stroke With and Without Subsequent ICrH Within 1 y

<table>
<thead>
<tr>
<th></th>
<th>Total, n=196765</th>
<th>No ICH, n=193579</th>
<th>ICH, n=3186</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>76.0 (64.6–87.4)</td>
<td>76.0 (64.7–87.4)</td>
<td>74.7 (63.1–86.4)</td>
</tr>
<tr>
<td>Women, %</td>
<td>50.0</td>
<td>50.1</td>
<td>43.2</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>27.4</td>
<td>27.3</td>
<td>29.7</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>20.5</td>
<td>20.5</td>
<td>18.2</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>16.2</td>
<td>16.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Event before index stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>12.3</td>
<td>12.3</td>
<td>11.2</td>
</tr>
<tr>
<td>Ischemic stroke, %</td>
<td>14.6</td>
<td>14.6</td>
<td>13.8</td>
</tr>
<tr>
<td>ICrH, %</td>
<td>1.7</td>
<td>1.6</td>
<td>8.5</td>
</tr>
</tbody>
</table>

ICrH indicates intracranial hemorrhage.

### Table 2. Characteristics of Study Patients With Ischemic Stroke Stratified by Time Period and by Subsequent ICrH Within 1 y

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n=45125</td>
<td>n=576</td>
<td>n=47577</td>
<td>n=706</td>
<td>n=706</td>
<td>n=50780</td>
<td>n=803</td>
<td>n=5097</td>
<td>n=910</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>75.7 (65.0–86.4)</td>
<td>74.7 (64.0–85.4)</td>
<td>76.1 (65.0–87.2)</td>
<td>74.5 (63.0–86.1)</td>
<td>76.2 (64.7–87.7)</td>
<td>74.7 (62.6–86.8)</td>
<td>76.1 (64.1–88.1)</td>
<td>74.9 (62.9–87.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, %</td>
<td>49.3</td>
<td>42.6</td>
<td>50.6</td>
<td>43.8</td>
<td>50.5</td>
<td>43.2</td>
<td>50.0</td>
<td>43.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>26.8</td>
<td>26.7</td>
<td>26.3</td>
<td>29.4</td>
<td>27.8</td>
<td>31.1</td>
<td>28.3</td>
<td>31.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>n/a</td>
<td>n/a</td>
<td>21.2</td>
<td>16.2</td>
<td>20.2</td>
<td>19.8</td>
<td>20.2</td>
<td>18.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker, %</td>
<td>n/a</td>
<td>n/a</td>
<td>16.7</td>
<td>16.1</td>
<td>16.0</td>
<td>19.1</td>
<td>15.8</td>
<td>14.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event before index stroke</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>11.2</td>
<td>9.4</td>
<td>12.0</td>
<td>10.8</td>
<td>12.9</td>
<td>11.0</td>
<td>13.1</td>
<td>13.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke, %</td>
<td>19.7</td>
<td>19.2</td>
<td>16.1</td>
<td>13.7</td>
<td>12.8</td>
<td>13.1</td>
<td>10.5</td>
<td>9.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICrH, %</td>
<td>1.9</td>
<td>8.6</td>
<td>1.6</td>
<td>9.9</td>
<td>1.4</td>
<td>7.2</td>
<td>1.5</td>
<td>8.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICrH indicates intracranial hemorrhage; and n/a, not available.
In 2009, 5.7% of all patients with an IS received intravenous thrombolysis.

Predictors of ICrH After IS

Predictors of ICrH within 30 days and during days 31 to 365 after an ischemic index stroke are shown in Tables 4 and 5, respectively. Previous ICrH and thrombolytic treatment were strongly associated with ICrH within 30 days of the index stroke. Atrial fibrillation at admission was also associated with significantly increased risk, whereas female sex, increasing age, and antihypertensive treatment before admission were associated with decreased risk.

As for the first 30 days after IS, previous ICrH was strongly associated with a new hemorrhage 31 to 365 days after stroke. Increasing age was also associated with increased risk, whereas female sex was associated with decreased risk.

In contrast, thrombolytic predicted a decreased risk of ICrH during days 31 to 365. Antiplatelet, OAC, antihypertensive, and lipid-lowering treatments at discharge were not independently predictive of ICrH.

When the risk of ICH was analyzed separately, previous ICH thrombolytic treatment and male sex remained associated with an increased risk within 30 days, whereas the same was true for previous ICrH and male sex during days 31 to 365.

Discussion

Incidence

The incidence rate of ICrH in our study was 1.97% per year at risk within 1 year and 0.85% per year at risk for days 31 to 365. In a previous Swedish study based on a population derived from Riksstroke entries for 2001 to 2005, the incidence of major hemorrhages (including ICrH, gastrointestinal bleeding, and other major bleedings) after IS was investigated with a focus on patients with a previous major hemorrhage. After a mean follow-up of 720 days, the rates of major hemorrhage (all locations) and ICrH in the entire cohort were 2.55% and 0.89% per year at risk, respectively. As in our study (Table 3; Figure 1), previous hemorrhage was associated with increased risk of hemorrhage after IS. However, ICrH was not consistently studied separately, and the 1-year risk was not reported in that previous investigation.

These and other methodological differences preclude direct comparison between our study and the previous one. Other observational studies investigating the risk of ICrH in patients with previous IS were based on fairly few outcome events. We detected an increased risk of ICrH during the first 30 days after stroke compared with days 31 to 365. This observation may be explained by thrombolytic treatment and a hemorrhagic transformation of the IS itself; thrombolytic treatment was identified as an independent predictor of ICrH in a multivariable logistic regression model.

Even when the first 30 days were excluded from the analysis, the risk of ICrH or ICH was substantially greater after IS than in the reference population. In a previously published meta-analysis, the risk of ICH in the general population was 24.6 per 100,000 person years at risk, a risk that was stable over >20 years. We uncovered a similar incidence in our reference population, and consistent with the meta-analysis, this incidence was essentially stable during the study period. The higher risk in the study population may be because of not only
more comorbidities but also recent IS. The latter hypothesis is supported by data from the REACH study, in which patients with myocardial infarction had an increased risk of ICH if they had a history of IS, especially within the first year after stroke.19

The incidence rate of ICrH for days 31 to 365 in patients discharged with OACs was 1.04% per year at risk (n=144). The randomized, controlled trials that examined warfarin versus placebo use in patients with nonvalvular atrial fibrillation9,10 and observational studies12,13 included only a few patients with ICrH, rendering comparisons impossible. In substudies of patients with IS and atrial fibrillation in trials of new OACs, the incidence rates of ICrH in the warfarin groups were 0.63% to 1.49% per year at risk (similar to our result) versus 0.25% to 0.59% per year at risk in the new OAC groups.20–22

Trends Over Time
The trends over time of the cumulative incidences of ICrH differed between the acute phase and the later phase. We detected an increased risk of ICrH during the first 30 days after stroke and a decreased risk of ICrH during days 31 to 365 (Table 3; Figure 2). Increased risk during the acute phase was associated with intravenous thrombolysis which increased during the study period, whereas the decreased risk for days 31 to 365 (Figure 2) occurred despite more patients being discharged with OACs or antiplatelets. The size of the increased risk the first 30 days resulted in a significantly increased overall risk despite the decrease seen days 31 to 365 (Figure 1). It is difficult to speculate about the importance of individual risk factors, but thrombolytic treatment is one contributing factor.

Blood pressure is a risk factor for ICH,23,24 and lowering blood pressure is an important strategy to reduce recurrent IS25 and to decrease the risk of ICH after IS.26 Unfortunately, we lack data on blood-pressure levels or trends in this study, but during the investigated period, more patients received antihypertensive treatment before their stroke27 and at discharge,28 which may have been beneficial.

Predictors of ICrH After IS
Intravenous thrombolysis and previous ICrH were strongly associated with increased risk of ICrH within 30 days. It is

Table 4. Univariable and Multivariable Logistic Regression Analyses of Predictors of ICrH Within 30 d of Ischemic Stroke (Index Stroke, 2004–2009)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Multivariable Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.99 (0.99–1.00)</td>
<td>&lt;0.001</td>
<td>0.99 (0.99–1.00)</td>
<td>0.016</td>
</tr>
<tr>
<td>Female, sex</td>
<td>0.79 (0.70–0.89)</td>
<td>&lt;0.001</td>
<td>0.84 (0.74–0.96)</td>
<td>0.008</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.31 (1.15–1.49)</td>
<td>&lt;0.001</td>
<td>1.33 (1.15–1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.86 (0.73–1.00)</td>
<td>0.054</td>
<td>0.90 (0.76–1.06)</td>
<td>0.187</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>4.20 (3.50–5.04)</td>
<td>&lt;0.001</td>
<td>4.36 (3.60–5.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication at admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>0.88 (0.78–0.99)</td>
<td>0.035</td>
<td>0.88 (0.77–1.00)</td>
<td>0.049</td>
</tr>
<tr>
<td>APs</td>
<td>0.87 (0.77–0.98)</td>
<td>0.026</td>
<td>0.96 (0.83–1.11)</td>
<td>0.559</td>
</tr>
<tr>
<td>OACs</td>
<td>1.26 (1.00–1.59)</td>
<td>0.052</td>
<td>1.25 (0.97–1.62)</td>
<td>0.090</td>
</tr>
<tr>
<td>Event before index stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.06 (0.89–1.27)</td>
<td>0.493</td>
<td>1.12 (0.92–1.35)</td>
<td>0.266</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.98 (0.81–1.19)</td>
<td>0.840</td>
<td>0.95 (0.77–1.16)</td>
<td>0.589</td>
</tr>
<tr>
<td>ICrH</td>
<td>7.47 (6.08–9.18)</td>
<td>&lt;0.001</td>
<td>7.85 (6.30–9.80)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

APs indicate antiplatelets; CI, confidence interval; ICrH, intracranial hemorrhage; and OACs, oral anticoagulants.
well known that survivors of ICH have an increased risk of new events₂₄,₂₉,₃₀ and that thrombolyis is associated with ICHR in the acute phase.₁₄ In the later phase, however, thrombolyis was associated with decreased risk of hemorrhage. The inclusion criteria for thrombolytic treatment during the study period (age >80 years as an exclusion criterion) resulted in patient selection, which may explain the decreased risk during follow-up. Older age was associated with a decreased risk of ICHR during the first 30 days after stroke, probably because of selection bias when treatment was selected. Age is a known risk factor for primary ICH,₂₃ as we found in the late phase.}

Previous ICH, increasing age, and male sex were associated with increased risk 31 to 365 days after the index stroke, as well as a significant decrease in risk for days 31 to 365. Intravenous thrombolysis, previous ICHR, atrial fibrillation, and male sex were associated with increased risk during the first 30 days, whereas previous ICHR, increasing age, and male sex were associated with increased risk 31 to 365 days after the index stroke. In the Stroke Prevention by Aggressive Reduction of Cholesterol Levels study (SPARCL, 80 mg of atorvastatin) and the Heart Protection study (HPS, 40 mg of simvastatin), lipid-lowering therapy was associated with slightly increased risk of ICH.³₁,³₂ In this study, no such association with lipid-lowering therapy (statins) was found. However, we did not have data on statin-type or dose and could therefore not perform more specific analyses. Simvastatin of 20 to 40 mg daily was the standard lipid-lowering therapy during the study period.

Antiplatelet and OAC treatments are known to be associated with increased risk of ICRH. Interestingly, we did not find an increased risk associated with antiplatelet or OAC treatment at discharge after multivariable adjustment. Also, the cumulative incidence of ICRH decreased despite an increased use of antiplatelets and OACs. This may be due to increased use of antihypertensive treatments during the study period or to less severe strokes. In patients with OAC treatment, time above the therapeutic range was associated with an increased risk of ICH.³₃ Sweden has a high quality of anticoagulant treatment with a time in therapeutic range ≈76%,³₄ indicating a low risk.

In the early phase after IS, large lesions and cardioembolic stroke are suggested as risk factors of ICRH.³₅ Furthermore, microbleeds may increase the risk of both lacunar infarction and ICH.³₆ However, because MRI was not routinely performed and because the assumed stroke cause or stroke type was not included as variables in the registry, we could not include these aspects in our analyses.

### Strengths and Limitations

With data on 196,675 patients with IS, of which 3186 had an ICRH within the first year after IS, this epidemiological study is the largest to investigate the risk of ICRH and ICH after IS. The large number of patients in the 2 patient registries that were included in this study enabled precise estimates even in subsets of patients. In combination with our 12-year inclusion period, the analysis of trends over time was possible. Because the study population was fairly unselected, the external validity of the results should be high.

A study of baseline data in Rikssstroke for 1995 to 2008 showed that the proportion of stroke patients included in the registry increased from 75% to 80% to 85% and that there was an increase in patients included from older age groups.³⁷ Less selection bias may affect data trends over time. We lack data on the severity of the index stroke and location of the ICH (lobar or nonlobar). We have no data on changes in treatment and compliance after hospital discharge. We also lack information on actual blood-pressure levels, blood lipid values, or kidney function, which may affect the analysis of predictors.

### Conclusions

The incidence of ICRH within 1 year after IS was 1.97% per year at risk. The corresponding risk in a reference population matched for age and sex was 0.13%. In this study population, there was a trend over time showing a significant increase in hemorrhage risk within 30 days of stroke, as well as a significant decrease in risk for days 31 to 365. Intravenous thrombolysis, previous ICRH, atrial fibrillation, and male sex were associated with increased risk during the first 30 days, whereas previous ICRH, increasing age, and male sex were associated with increased risk 31 to 365 days after the index stroke. In the late phase, however, thrombolyis was associated with decreased risk of hemorrhage. The inclusion criteria for thrombolytic treatment during the study period (age >80 years as an exclusion criterion) resulted in patient selection, which may explain the decreased risk during follow-up.

### Table 5. Univariable and Multivariable Cox-Regression Analyses of Predictors of ICRH Within 31 to 365 d of Ischemic Stroke (Index Stroke, 2004–2009)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Multivariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.01 (1.01–1.02)</td>
<td>&lt;0.001</td>
<td>1.01 (1.01–1.02)</td>
<td>0.002</td>
</tr>
<tr>
<td>Female, sex</td>
<td>0.79 (0.67–0.93)</td>
<td>0.004</td>
<td>0.75 (0.63–0.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.35 (1.14–1.61)</td>
<td>0.001</td>
<td>1.09 (0.88–1.35)</td>
<td>0.434</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.12 (0.92–1.36)</td>
<td>0.256</td>
<td>1.09 (0.89–1.34)</td>
<td>0.426</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0.46 (0.24–0.85)</td>
<td>0.014</td>
<td>0.48 (0.25–0.92)</td>
<td>0.028</td>
</tr>
<tr>
<td>Medication at discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>0.77 (0.65–0.91)</td>
<td>0.002</td>
<td>0.86 (0.72–1.03)</td>
<td>0.104</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>0.96 (0.81–1.15)</td>
<td>0.670</td>
<td>0.88 (0.73–1.07)</td>
<td>0.194</td>
</tr>
<tr>
<td>APs</td>
<td>0.72 (0.59–0.87)</td>
<td>0.001</td>
<td>0.83 (0.62–1.12)</td>
<td>0.219</td>
</tr>
<tr>
<td>OACs</td>
<td>1.39 (1.12–1.71)</td>
<td>0.002</td>
<td>1.21 (0.86–1.71)</td>
<td>0.267</td>
</tr>
<tr>
<td>Event before index stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.95 (0.74–1.23)</td>
<td>0.715</td>
<td>0.93 (0.71–1.21)</td>
<td>0.563</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.25 (0.99–1.59)</td>
<td>0.062</td>
<td>1.19 (0.93–1.52)</td>
<td>0.176</td>
</tr>
<tr>
<td>ICRH</td>
<td>3.12 (2.11–4.63)</td>
<td>&lt;0.001</td>
<td>3.00 (1.98–4.52)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

APs indicate antiplatelets; CI, confidence interval; ICRH, intracranial hemorrhage; and OACs, oral anticoagulants.
stroke. Importantly, frequent use of antithrombotic treatments and statins did not affect the 1-year incidence of ICH.

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Disclosures
None.

References


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SUPPLEMENTAL MATERIAL

Supplemental figure 1. Cumulative incidence of ICrH 1 year after ischemic stroke during four consecutive time intervals and ICrH incidence for a reference group matched for age and sex.