Brief Report

Warfarin-Associated Intracerebral Hemorrhage After Ischemic Stroke

Signild Åsberg, MD, PhD; Marie Eriksson, PhD; Karin M. Henriksson, MD, PhD; Andreas Terént, MD, PhD

Background and Purpose—The aim was to investigate the risk of intracerebral hemorrhage (ICH) in patients with ischemic stroke taking warfarin and whether this risk changed over time.

Methods—Between 2001 and 2008, the Swedish Stroke Register registered 12790 patients with ischemic stroke discharged on warfarin. The patients were studied in two 4-year periods (inclusion 2001–2004: follow-up until 2005 and inclusion 2005–2008: follow-up until 2009) for which rates of subsequent ICH were calculated. Adjusted hazard ratios, comparing the second period with the first period, were estimated in Cox regression models.

Results—Of 6039 patients, 58 patients (1.0%) in the first period and 69 of 6751 patients (1.0%) in the second period had subsequent ICH. Annual rates of ICH ranged from 0.37% in the first period to 0.39% in the second period (adjusted hazard ratio, 1.04; 95% confidence interval, 0.73–1.48).

Conclusions—In this nationwide study, the risk of warfarin-associated ICH among ischemic stroke patients was low and did not change during the 2000s. (Stroke. 2014;45:00-00.)

Key Words: anticoagulants stroke

The incidence of intracerebral hemorrhage (ICH) after ischemic stroke is higher than in the general population, but data from observational studies are sparse. Although time between stroke and randomization varies (14 days-years), subgroup analyses of new oral anticoagulant (NOAC) trials offer modern insight into the incidence of ICH. NOAC is an alternative to warfarin, but in the Swedish guidelines for prevention of cardioembolic stroke, warfarin and NOAC have the same recommendation as first-line drugs; therefore, it is important to recognize both the advantages and disadvantages of warfarin in clinical practice, especially for future comparison with NOAC. The aim was to investigate the risk of ICH in patients with ischemic stroke taking warfarin and whether this risk changed during the 2000s.

Materials and Methods

Data Sources and Subjects

This register-based observational study used routinely collected data from 2 national registers linked through the patients’ unique personal identification numbers; detailed presentation of the registers is available in Tables I and II in the online-only Data Supplement. Briefly, the Swedish Stroke Register identified the index-ischemic stroke and recurrent stroke (after 28 days) and was linked with the Cause of Death Register, which provided information on the date of death.

The study comprised patients with first-ever ischemic stroke, who were discharged on warfarin, and survived the index-ischemic stroke by 28 days. The main outcome of interest was ICH, but all recurrent strokes and all-cause death were considered. Because ICHs are rare events, the patients were studied in 2 groups: period 1 from January 2001 to December 2004 and period 2 from January 2005 to December 2008. These patients were followed for a minimum of 1 year after the index-ischemic stroke, until death, or end of observation in December 2005 or December 2009. As death certificate has compulsory registration, even for Swedish residents living abroad, it was assumed that there was no missing data on death date. All analyses, performed in agreement with privacy legislation in Sweden, were approved by the Ethical Committee of Uppsala University Hospital, Sweden, Reg. No. 2009/355.

Statistical Methods

The incidence rates per 100 person-years for subsequent ICH, ischemic stroke, and all-cause death were calculated. Univariable and multivariable Cox proportional hazard regression models were used to calculate hazard ratio and 95% confidence interval for subsequent events for the second period versus the first period of the 2000s. The multivariable models included age, sex, atrial fibrillation (AF), hypertension, diabetes mellitus, and antiplatelet (ie, in addition to warfarin), with missing values included as a separate category. There were no significant interactions between the covariates when 2-way interaction terms were included in the model. In a sensitivity analysis, the hazard ratio for subsequent ICH after ischemic stroke was estimated for each year in the study period, with 2001 as the reference year.

Separate logistic regression models, adjusted for age and sex, estimated the mean increase per year of AF among patients on warfarin. IBM SPSS Statistics version 21.0 was used for all analyses, and the level for significance was 0.05.
During the two 4-year periods, all ischemic stroke survivors discharged on warfarin (n=12,790) were included in the study, irrespective of whether they had AF or not (Figure I in the online-only Data Supplement). In the second period, a higher proportion of patients had AF, hypertension, and warfarin as single therapy (Table 1). The proportion of patients with AF increased from 63.9% (n=3,857) in the first period to 72.1% (n=4,870) in the second period, with a mean increase of 9.3% per year (P<0.001). Mean time of follow-up was 2.6 years, with a minimum follow-up time of 1 year.

During 31,800 person-years, there were 1,237 recurrent strokes, of which 127 were ICH. Annual rates of ICH ranged from 0.37% in the first period to 0.39% in the second period (adjusted hazard ratio, 1.04; 95% confidence interval, 0.91–1.16), with no alteration in the adjusted model.

### Discussion

In this nationwide register-based study, the stroke recurrence rate was low. AF increased as an indication for warfarin, but the risk of warfarin-associated recurrent stroke, neither as ICH nor as ischemic event, did not change between 2001 and 2008. In observational studies, the cumulative risk of stroke recurrence during the first year varies between 4.8% and 11.1%. These variations can be explained by methodological differences, such as the exclusion of early stroke recurrence (<28 days) in this study. The incidence of warfarin-associated ICH (≈0.4% in both periods) in our study reflected real life, but was lower than data presented for warfarin in trials of NOAC.5,6 In subgroups of patients with previous stroke, the annual rate of ICH in patients allocated...
warfarin is 0.8% in safety analyzes of dabigatran, 1.0% in analyzes of apixaban, and 0.5% in analyzes of rivaroxaban. AF, particularly in patients with previous stroke, is a major risk factor for stroke recurrence. Even though AF, as an indication for warfarin, increased during the study period, the rate of recurrent ischemic stroke did not.

As the proportion of registered patients (>85%) and valid variables (>95%) in the Swedish Stroke Register is high, we consider the results can be generalized to the Swedish population and other countries with an equally organized healthcare system. Despite potential limitations related to the register-based design, this study provides new information concerning ICH and stroke recurrence among ischemic stroke patients on warfarin.

Acknowledgments
The authors thank the members of the Riksstroke Collaboration (http://www.Riks-Stroke.org).

Disclosures
Dr Terént has received a research grant from AstraZeneca R&D. Dr Henriksson is a paid employee of AstraZeneca R&D. The other authors report no conflicts.

References
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Data Supplement (unedited) at:
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ONLINE SUPPLEMENTAL DATA

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**Supplemental Table I.** Presentation of The Swedish Stroke Register (Riksstroke) and The Swedish Cause of Death Register

<table>
<thead>
<tr>
<th></th>
<th>The Swedish Stroke Register (Riksstroke)</th>
<th>The Cause of Death Register†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Held by</td>
<td>The Steering Committee of Riksstroke</td>
<td>The National Board of Health and Welfare</td>
</tr>
<tr>
<td>Initiated</td>
<td>1994</td>
<td>1961</td>
</tr>
<tr>
<td>Aim</td>
<td>1) To support high and consistent quality of care for stroke patients throughout Sweden &lt;br&gt;2) To provide a database for research on stroke management and outcomes in routine clinical settings.</td>
<td>1) To describe causes of death &lt;br&gt;2) To study demographic trends in mortality</td>
</tr>
<tr>
<td>Inclusion</td>
<td>All strokes (except subarachnoid hemorrhages) that led to in-patient treatment in Sweden</td>
<td>All deaths among Swedish residents, whether the deceased was a Swedish citizen or not, and whether the death occurred in Sweden or abroad.</td>
</tr>
<tr>
<td>Estimated coverage</td>
<td>90-96% on first-ever stroke, &gt;85% including recurrent stroke</td>
<td>100% of all-cause death, 98-99% on causes of death</td>
</tr>
<tr>
<td>Extracted data for the study</td>
<td>See Variables in Supplemental table II</td>
<td>Date of all-cause death</td>
</tr>
<tr>
<td>Variables not covered by the registry</td>
<td>e.g. PK&amp;INR, diagnosis of heart failure or valve disease, recurrent stroke within 28 days</td>
<td>-------</td>
</tr>
<tr>
<td>Sponsors</td>
<td>The National Board of Health and Welfare and The Swedish Society and the Federation of Swedish County Councils</td>
<td>Government agency under the Ministry of Health and Social Affairs.</td>
</tr>
</tbody>
</table>

* http://riksstroke.org/?content=start&lang=eng&text=  
† http://www.socialstyrelsen.se/register/dodsorsaksregistret
Supplemental Table II. List of variables and missing values in a study of 12,790 patients with first ischemic stroke and discharged on warfarin during 2001 until 2008

<table>
<thead>
<tr>
<th>Variable in Riksstroke</th>
<th>Definition</th>
<th>Missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; period</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>I63-64&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>I61&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>Excluding subarachnoid hemorrhage and transient ischemic attack</td>
<td>1.5&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>CT-scan</td>
<td>During hospital stay</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Index ischemic stroke</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Subsequent ICH</td>
<td></td>
</tr>
<tr>
<td>Comorbid diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>I48&lt;sup&gt;‡&lt;/sup&gt; Previously diagnosed or recently identified</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Treatment for hypertension at onset of stroke</td>
<td>2.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>E10-14&lt;sup&gt;‡&lt;/sup&gt; Previously diagnosed or recently identified</td>
<td>0.5</td>
</tr>
<tr>
<td>Admission medication</td>
<td>Antithrombotics on admission</td>
<td>0.2</td>
</tr>
<tr>
<td>Discharge medication</td>
<td>Antithrombotics at discharge</td>
<td>1.2&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>*</sup> By International Classification of Diseases; 10<sup>th</sup> revision, registered after 28 days from any previous stroke

<sup>†</sup> Out of 8,173 patients with or without recurrent stroke

<sup‡</sup> Out of 8,066 patients with or without recurrent stroke

<sup>§</sup> Out of 48,896 patients with or without warfarin

<sup>**</sup> Out of 54,509 patients with or without warfarin
**Supplemental Figure 1.** Flow chart of inclusion in the study of 12,790 patients with first ischemic stroke and discharged on warfarin registered in the Swedish Stroke Register between 2001 and 2008

ICH=intracerebral hemorrhage, RS=recurrent stroke, IS=ischemic stroke, AF=atrial fibrillation, AP=antiplatelets, AT=antithrombotic therapy. Blue color indicates patients in the Stroke Register, red color indicates excluded patients, green color indicates patients included in the study.