Antithrombotic Treatment Following Intracerebral Hemorrhage in Patients With and Without Atrial Fibrillation

Johanna Pennlert, MD; Kjell Asplund, MD, PhD; Bo Carlberg, MD, PhD; Per-Gunnar Wiklund, MD, PhD; Aase Wisten, MD, PhD; Signild Åsberg, MD, PhD; Marie Eriksson, PhD

Background and Purpose—Patients who survive intracerebral hemorrhage (ICH) often have compelling indications for anticoagulant and antiplatelet medication. This nationwide observational study aimed to determine the extent and predictors of antithrombotic treatment after ICH in Sweden.

Methods—Patients with a first-ever ICH in the Swedish Stroke Register (Riksstroke) 2005 to 2012 who survived hospital discharge were included. Riksstroke data were individually linked with other national registers to determine comorbid conditions and dispensed prescriptions of antithrombotic agents.

Results—Among the 2777 patients with atrial fibrillation (AF), the proportion with a dispensed prescription of antithrombotic agents was 8.5% (anticoagulants) and 36.6% (antiplatelet agents) within 6 months and 11.1% (anticoagulants) and 43.6% (antiplatelet agents) within 1 year. Among the 11 268 patients without AF, the corresponding figures were 1.6% (anticoagulants) and 13.8% (antiplatelet agents) within 6 months and 2.0% (anticoagulants) and 17.5% (antiplatelet agents) within 1 year. In patients with AF, predictors of anticoagulant treatment were less severe ICH, younger age, previous anticoagulation, valvular disease, and previous ischemic stroke. High CHA2DS2-VASc (congestive heart failure, hypertension, age, diabetes mellitus, stroke [doubled], vascular disease, age, and sex category [female]) scores did not correlate with anticoagulant treatment. There was a positive correlation between high CHA2DS2-VASc and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol) scores ($r=0.590, P<0.001$).

Conclusions—In majority of patients who receive antithrombotic agents, treatment is initiated within 6 months of ICH. Still, many patients with compelling indications for antithrombotic treatment are not prescribed antithrombotic agents. Factors other than high risk of embolic stroke by CHA2DS2-VASc in ICH survivors with concurrent AF are used to guide the anticoagulant treatment decision in Swedish clinical practice. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.009087.)

Key Words: anticoagulation ■ antiplatelet agent ■ atrial fibrillation ■ intracerebral hemorrhage
reported in the literature. Previous studies have shown that anticoagulants are more likely to be restarted in those with lower ICH severity and in patients with valve prostheses in situ.

One of the largest studies regarding antiplatelet drugs after ICH included 120 patients with subsequent antiplatelet exposure and found that median time to prescription was 14.8 months. Diabetes mellitus, ischemic heart disease, and nitrate use at baseline have been reported as predictors for AP use after ICH. A recent multiple cohort study showed great variation in clinical practice and a lack of consistent associations with restarting antithrombotic treatment.

The main objective of this study was to investigate the timing of, predictors of, and the extent to which antithrombotic therapy is prescribed to ICH survivors in Sweden. We examined both resumptions of previous antithrombotic treatment as well as new dispensed prescriptions in patients with and without AF.

Methods

**Study Population**

A total of 20,768 patients with a first-registered ICH (International Code of Disease (ICD)-10 I61) were identified in the Swedish Stroke Register (Riksstroke) from July 1, 2005, through December 31, 2012. Among these, 861 patients had a previous diagnosis of ICH identified in the Swedish Inpatient Register (IPR) after 1997 and were excluded. Of the remaining 19,907 patients, 14,092 patients were discharged alive from the hospital before the study end date. A total of 47 patients were lost to follow-up because they were lacking a Swedish civil registration number (n=34) or because of obvious registration date errors (n=13). The remaining 14,045 patients were then followed for prescription of antithrombotic therapy (anticoagulants and antiplatelet drugs) until date of death, emigration, or study end date (December 31, 2012), whichever occurred first.

**Data Sources**

Riksstroke was established in 1994 to monitor, support, and improve the quality of Swedish stroke care. The register is estimated to cover 94% of all stroke patients treated in Swedish hospitals, and all hospitals admitting acute stroke patients participate (72 hospitals in 2012). Riksstroke data were linked with data from the Swedish Dispensed Drug Register to find the date of the first dispensed prescription of anticoagulant and antiplatelet treatment after hospital discharge. Cross matching of data was made through patients’ unique personal identification numbers. Riksstroke data were also linked with the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA by its Swedish acronym) at Statistics Sweden to add information on education. Risk factors and comorbidities were retrieved from Riksstroke and from the IPR. IPR data from 1997 onward were used. All analyses were approved by the Regional Ethical Review Board at Umeå University, Umeå, Sweden (2012-321-31M, 2014-76-32M).

**Variable Definitions**

**Anticoagulant and Antiplatelet Treatment**

The Anatomic Therapeutic Chemical (ATC) classification system was used for classifying therapeutic drugs. The definition of anticoagulant treatment after ICH (warfarin or novel oral anticoagulants, ATC-codes B01AA, B01AE, B01AF) or antiplatelet therapy (ATC-code B01AC) was having had a dispensed prescription of the medication from a Swedish pharmacy after hospital discharge. The first registered dispensed prescription, if any, from each of the groups of antithrombotic agents was derived from the Swedish Dispensed Drug Register. Baseline data on antithrombotic treatment at the time of ICH were retrieved from Riksstroke, which carries information on current medication at the time of stroke.

**Comorbidity**

Hypertension was defined as a history of hypertension according to the IPR or ongoing antihypertensive treatment at the time of acute stroke according to Riksstroke. Previous diagnoses of AF and diabetes mellitus were identified using the IPR and baseline information registered in Riksstroke. Information on valvular disease (ICD-10: I05-09, I33-39) was retrieved from the IPR, as well as that of previous venous thromboembolism (deep venous thrombosis and pulmonary embolism), thyroid disease, pulmonary disease, renal disease, history of gastrointestinal bleeding, myocardial infarction, ischemic heart disease, and previous ischemic stroke. Alcohol index is a set of diagnostic codes used by the Swedish Board of Health and Welfare for annual reporting on alcohol-related mortality, and the ICD-10 codes inherent in the index were also found through linkage with the IPR. Detailed information on the included ICD-10 codes is listed in Table 1 in the online-only Data Supplement.

**Risk Stratification Scores**

The CHA$_2$DS$_2$-VASc scoring system awards 2 points each for previous stroke/TIA and age ≥75 years and 1 point each for age 65 to 74 years, congestive heart failure, hypertension, diabetes mellitus, vascular disease (peripheral arterial disease, coronary heart disease, and aortic plaque), and female sex. A higher score implies an increased risk of thromboembolic events, and the maximum score is 9. In this study, congestive heart failure garnered points only when a patient had been hospitalized because of a primary diagnosis of heart failure (ICD-10 code I50).

When assessing HAS-BLED, clinical indicators include age, hypertension, renal impairment, liver disease, stroke history, previous bleeding, concomitant medication, alcohol use, and labile INR (poorly controlled anticoagulant treatment). The maximum score, indicating high risk of major bleeding, is 9. In this study, a modified HAS-BLED score similar to that of Friberg et al was derived because data on INR levels during anticoagulant therapy were not available. In the concomitant medication variable, we were only able to include antiplatelet drugs, if any, at baseline. For all ICD-10 codes attributed to each entity in calculating the above scores, see Table 1 in the online-only Data Supplement.

**Statistical Methods**

To compare baseline characteristics between patients with and without AF, χ²-tests for categorical variables and t-tests for continuous variables were used. Patients with dispensed prescriptions of both anticoagulants and antiplatelet agents were analyzed in both treatment groups. The time to the first dispensed prescription of antiplatelet drugs and anticoagulants, respectively, were described by Kaplan–Meier survival curves. Patients were censored at time of death, time of emigration, or at study end date (December 31, 2012). Hazard ratios with 95% confidence intervals were then estimated using simple Cox proportional-hazard regression for unadjusted analysis. We examined the graph of the log-minus-log of the survival function to detect major deviations from the proportional hazard assumption. All variables with P≤0.10 found in the simple regression model were then included in multivariable Cox regression models. Age was included as a categorical factor (18–64, 65–74, 75–84, and ≥85 years). An additional multivariable analysis instead included age and age$^2$ as continuous covariates. Because there were no substantial differences between the 2 analyses, only the outcome from the analysis including age groups is presented. Because CHA$_2$DS$_2$-VASc and HAS-BLED includes information on other covariates (eg, age and hypertension), they were
only analyzed in the univariate model. Logistic regression, including year of ICH as a continuous covariate, were used to assess secular trends in concomitant AF, treatment at time of ICH, and 1 year after discharge. Patients with and without AF were analyzed separately, except for the analyses of resumption of therapy where AF instead was included as a covariate. SPSS version 22.0 (IBM SPSS Statistics) was used for all analyses, and the level of significance was 0.05.

Results

The study included 14,045 patients discharged from hospital alive after a first ICH and comprised 37,870 person-years of follow-up for anticoagulant treatment and 29,898 years of follow-up for antiplatelet drugs. Mean age at ICH was 71.5 years, and 43.6% were females. At time of the ICH, 39.0% of the patients were on any antithrombolic treatment; 1454 patients (10.4%) were on anticoagulants, 4018 patients (28.6%) were on antiplatelet drugs, and 132 patients (0.9%) were on both drugs. We observed an increasing proportion of anticoagulant treatment at the time of the ICH: 8.1% in 2006 compared with 14.6% in 2012 (P<0.001 assuming a linear trend). No such trend was seen for antiplatelet treatment. Possible indications for antithrombotic therapy at baseline were predominantly AF (n=2777), previous ischemic stroke (n=2185), ischemic heart disease (n=2278), and history of venous thromboembolism (n=574). There was a trend toward a larger proportion of ICH survivors with concurrent AF: 17.7% in 2006 compared with 22.0% in 2012 (P<0.001, assuming a linear trend). Patients with AF were older and carried a larger burden of conventional cardiovascular risk factors (apart from smoking) compared with patients without AF. Table II in the online-only Data Supplement presents baseline characteristics of the ICH survivors.

The median follow-up time (ie, time to censoring or treatment) for anticoagulant and antiplatelet treatment was 837 and 521 days (mean 985 and 778 days), respectively. After hospital discharge, 679 patients had a dispensed prescription of anticoagulants anytime during follow-up, and 3883 patients received antiplatelet agents. Of these, 274 had dispensed prescriptions of both anticoagulants and antiplatelet drugs during follow-up.

Patients With Atrial Fibrillation

One year after hospital discharge, 1055 patients (43.6%) had a dispensed prescription of an antiplatelet agent and 258 (11.1%) were dispensed anticoagulant treatment in the AF population (Figure 1). In the multivariable analysis, independent factors associated with dispensed prescriptions of anticoagulants after discharge were younger age, previous ischemic stroke, anticoagulants at onset, and valvular disease. Factors associated with dispensing of antiplatelet agents were previous ischemic stroke, hypertension, and both anticoagulant and antiplatelet treatment at ICH onset. Patients with dementia were less likely to get anticoagulant treatment. Less severe stroke at onset was associated with increased likelihood of receiving anticoagulant and antiplatelet treatment after discharge (Table). Previous gastrointestinal bleeding, smoking, thyroid disease, pulmonary disease, excess alcohol use, and history of venous thromboembolism did not show any association with receiving either antiplatelet or anticoagulant treatment after discharge (data not shown).

In patients with AF, there was a secular trend of increasing anticoagulant use one year after discharge (8.3% in 2006 versus 17.2% in 2011, P<0.001 assuming a linear trend). One year after ICH, the proportion of AF patients on anticoagulant treatment varied between 8% and 14% in the 6 healthcare regions of Sweden.

High CHA2DS2-VASc scores did not seem to correlate with early (6 months) prescription of anticoagulants (Figure 2). There was a positive Spearman correlation between high CHA2DS2-VASc and HAS-BLED scores (r=0.590, P<0.001).

The distribution of CHA2DS2-VASc scores in the AF population is presented in Table III in the online-only Data Supplement. A total of 4.2% (117/2777) of the patients scored below 2 points, and the median value was 4 points.

Patients Without Atrial Fibrillation

Out of the 11,268 patients without AF, 302 patients were on anticoagulant treatment at time of ICH. One year after ICH, 1786 patients without concurring AF (17.5%) had antiplatelet therapy and 206 (2%) were on anticoagulants (Figure 1). In the multivariable analysis, subsequent anticoagulant treatment was predicted by anticoagulants at onset, history of venous thromboembolism, and valvular disease (Table IV in the online-only Data Supplement).

When assessing antiplatelet drugs, patients who had severe ICH were less prone to receiving antiplatelet drugs after discharge, whereas diabetes mellitus, hypertension, previous ischemic stroke, ischemic heart disease, and previous antiplatelet and statin treatment were characteristics associated

![Figure 1](http://stroke.ahajournals.org/)

Figure 1. Kaplan–Meier curves of time to dispensed prescriptions of anticoagulant (AC) and antiplatelet (AP) treatment after hospital discharge in intracerebral hemorrhage (ICH) survivors. Survivors with atrial fibrillation (A) and without atrial fibrillation (B).
with subsequent antiplatelet treatment in the multivariable analysis (Table IV in the online-only Data Supplement).

Resumption of Antithrombotic Treatment

Out of the 1454 patients on anticoagulants at time of ICH (see Table V in the online-only Data Supplement, for baseline characteristics of patients with prior-to-ICH anticoagulant treatment), 299 resumed treatment over the study period: 10.4% within 3 months and 21.2% within 1 year (Figure 3). Median time to resumption of anticoagulants was 101 days among those who resumed treatment. In total, 1760 of the 4018 patients on antiplatelet agents resumed treatment: 24.7% within 3 months and 39.9% within 1 year (Figure 3).

Independent predictors for resuming anticoagulant treatment were younger age ($P<0.001$), lower stroke severity, and valvular disease (hazard ratios [95% confidence interval], 3.10 [2.36–4.02]). Previous ischemic stroke did not show any association with restarting anticoagulants. Patients with concurrent AF were less likely to restart anticoagulation than those without AF (hazard ratios [95% confidence interval], 0.72 [0.55–0.95]).

Independent predictors for resumption of antiplatelet agents were ischemic heart disease, previous ischemic

### Table. Univariate and Multivariable Cox’s Regression Analyses* of Dispensed Anticoagulant (AC) or Antiplatelet (AP) Prescriptions in Patients With Atrial Fibrillation at ICH Onset (N=2777)

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulants</th>
<th></th>
<th>Antiplatelet Agents</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Univariate HR (95% CI)</td>
<td>P Value</td>
<td>Multivariable HR (95% CI)*</td>
<td>Univariate HR (95% CI)</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>18–64 y (ref.)</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>65–74</td>
<td>0.622 (0.602–1.122)</td>
<td>0.724 (0.527–0.994)</td>
<td>1.331 (1.065–1.665)</td>
<td>1.187 (0.944–1.491)</td>
</tr>
<tr>
<td>75–84</td>
<td>0.484 (0.356–0.660)</td>
<td>0.448 (0.326–0.617)</td>
<td>1.349 (1.093–1.666)</td>
<td>1.226 (0.987–1.523)</td>
</tr>
<tr>
<td>≥85</td>
<td>0.208 (0.134–0.321)</td>
<td>0.209 (0.133–0.329)</td>
<td>1.144 (0.913–1.433)</td>
<td>1.090 (0.862–1.380)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.805 (0.643–1.008)</td>
<td>0.059</td>
<td>1.107 (0.878–1.396)</td>
<td>0.910 (0.812–1.020)</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school (ref.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>1.416 (1.119–1.792)</td>
<td>1.122 (0.881–1.429)</td>
<td>1.209 (1.071–1.364)</td>
<td>1.155 (1.020–1.307)</td>
</tr>
<tr>
<td>University</td>
<td>1.468 (1.079–1.997)</td>
<td>1.209 (0.886–1.651)</td>
<td>0.987 (0.830–1.173)</td>
<td>0.964 (0.809–1.148)</td>
</tr>
<tr>
<td>Fully conscious at hospital admission</td>
<td>1.878 (1.363–2.568)</td>
<td>&lt;0.001</td>
<td>1.915 (1.385–2.647)</td>
<td>1.225 (1.063–1.412)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.058 (0.824–1.358)</td>
<td>0.657</td>
<td>1.048 (0.919–1.194)</td>
<td>0.485</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>1.315 (1.036–1.668)</td>
<td>0.024</td>
<td>1.406 (1.099–1.798)</td>
<td>0.001</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1.337 (0.842–2.125)</td>
<td>0.219</td>
<td>0.971 (0.743–1.270)</td>
<td>0.832</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.691 (0.990–2.889)</td>
<td>0.054</td>
<td>1.527 (0.889–2.621)</td>
<td>0.734</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.041 (0.822–1.318)</td>
<td>0.739</td>
<td>1.242 (1.102–1.400)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.255 (0.922–1.707)</td>
<td>0.149</td>
<td>1.372 (1.168–1.610)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.067 (0.833–1.368)</td>
<td>0.606</td>
<td>1.145 (0.909–1.301)</td>
<td>0.036</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>2.741 (2.033–3.695)</td>
<td>&lt;0.001</td>
<td>2.450 (1.810–3.316)</td>
<td>0.068</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.220 (0.082–0.589)</td>
<td>0.003</td>
<td>0.302 (0.112–0.814)</td>
<td>0.014</td>
</tr>
<tr>
<td>AC at stroke onset</td>
<td>2.415 (1.941–3.007)</td>
<td>&lt;0.001</td>
<td>1.896 (1.466–2.452)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AP at stroke onset</td>
<td>0.591 (0.462–0.755)</td>
<td>&lt;0.001</td>
<td>0.956 (0.720–1.269)</td>
<td>0.012</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>1.551 (1.249–1.925)</td>
<td>&lt;0.001</td>
<td>1.073 (0.854–1.348)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td></td>
<td>0.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0–2</td>
<td>1.196 (0.886–1.597)</td>
<td>0.668</td>
<td>0.557–0.802</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3–4 (ref.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>0.629 (0.414–0.956)</td>
<td>0.187</td>
<td>1.198 (1.014–1.416)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Score 0–1</td>
<td>1.456 (0.945–2.243)</td>
<td>0.664</td>
<td>0.485–0.911</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2–4 (ref.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>0.963 (0.767–1.210)</td>
<td>1.274</td>
<td>1.136–1.428</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHADS2-VASc indicates congestive heart failure, hypertension, age, diabetes mellitus, stroke [doubled], vascular disease, age, and sex category (female); HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol; and ICH, intracerebral hemorrhage.

*Multivariable models include all variables with $P<0.10$ in the univariate analyses except for CHA2DS2-VASc and HAS-BLED.
stroke, statin treatment, and lower stroke severity. AF was also an independent predictor of restarting antiplatelet agents (hazard ratios [95% confidence interval]: 1.32 [1.18–1.48]). We did not observe an increase in early resumption of either anticoagulants or antiplatelet drugs over time when assessing only those previously on antithrombotic treatment as we did for patients with AF and subsequent anticoagulant treatment.

Discussion

Our study demonstrates that among patients who receive antithrombotic treatment after ICH, a majority is prescribed the agents within 6 months. Still, many patients with compelling indications for antithrombotic treatment are not prescribed antithrombotic agents. CHA2DS2-VASc does not seem to be a marker for subsequent anticoagulant treatment in patients with AF, suggesting limited use of the score in current clinical practice regarding these patients. There is also a strong positive correlation between a high CHA2DS2-VASc and a high HAS-BLED score in ICH survivors with concurrent AF. Of the variables shared by both scores, previous ischemic stroke and younger age were associated with anticoagulant therapy.

Resumption of anticoagulant treatment is more common in patients with other indications for anticoagulation than AF. Our results indicate that, among non-AF patients, there may be even more compelling reasons for anticoagulation, such as valvular disease and mechanical valve prostheses. Younger age (most likely with fewer contraindications) also contributes.

There has been an increase of anticoagulant prescription to ICH survivors with AF over the study period, suggesting that there might be ongoing changes in clinical practice, regardless of the weak evidence guiding this decision. The lack of consensus with regard to restarting anticoagulant treatment is also reflected in varying clinical practice in different Swedish healthcare regions.

The use of antithrombotic treatment before ICH in this study is in line with recent reports.6,7 Also in line with previous studies, we report an increasing proportion of patients with concomitant AF.5 In AF survivors, previous anticoagulant treatment also predicts subsequent antiplatelet therapy, and this implies that many doctors shift their patients from anticoagulant to antiplatelet therapy after discharge. In the light of recent recommendations to avoid aspirin to prevent ischemic stroke in patients with AF,10 this practice seems obsolete.

Antiplatelet prescription is common after ICH. We saw a similar proportion of ICH survivors who were subsequently prescribed antiplatelet agents, as reported in a study from Scotland.1

Compared with previous studies, this study includes a large number of patients as a result of the nationwide coverage of Riksstroke. All hospitals that admit acute stroke patients participate in the registry with an estimated coverage of 94% of all stroke events in the country.21 Linkage with other administrative registers enables Riksstroke to access more complete information on the occurrence of comorbid conditions, drug use, and socioeconomic status. This study’s dependency on linked register data can also be considered a limitation because possible sources of recording errors and bias cannot be excluded. Another limitation is that assessing individual CHA2DS2-VASc and HAS-BLED scores by using register data is likely to give lower scores than is actually the case. The extent of underdiagnosis is largely unknown and is likely to change over time.27 Another limitation is that we might be overestimating the time to treatment in those who already had antithrombotic drugs at home and possibly were instructed at discharge to continue taking them at home. We also lacked information on medication during the hospital stay.

The question of whether and when to prescribe antithrombotic agents to ICH survivors is one of the major contemporary dilemmas for stroke physicians. The increasing proportion of both prior-to-ICH anticoagulant treatment and AF among ICH survivors further adds to the importance of this question.

Acknowledgments

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Disclosures
None.

References
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Antithrombotic treatment following intracerebral hemorrhage in patients with and without atrial fibrillation

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Supplemental Tables

Supplemental Table I
List of ICD-codes used to assess comorbidity and for calculation of risk stratification scores.

<table>
<thead>
<tr>
<th>Condition</th>
<th>ICD-10 code(s)</th>
</tr>
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<tbody>
<tr>
<td>Ischemic stroke</td>
<td>I63</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>I48 or reported in Riksstroke (RS)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>I10-15 or reported in RS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>E10-14 or reported in RS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>I50</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>I26, I80 (except 180.0) O87.1, O22.3</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>I26</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>I20-25</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>I21 I25.2</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>I05-09 I33-39</td>
</tr>
<tr>
<td>Dementia</td>
<td>F00-F03</td>
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<tr>
<td>Alcohol Index</td>
<td>E244 F10 G312 G621 G721 I426 K292 K70</td>
</tr>
<tr>
<td></td>
<td>K860 O354 P043 Q860 T51 Y90-91 Z502</td>
</tr>
<tr>
<td></td>
<td>Z714</td>
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<tr>
<td>Mechanical heart valve prosthesis</td>
<td>Z95.2</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>I850, I983, K22.6, K25-28 only subcodes 0-2, 4-6, K922, I841, I858, I844, K625, K920, K921, K661, K290</td>
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<tr>
<td>Chronic pulmonary disease</td>
<td>J40-70</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>E00-07</td>
</tr>
<tr>
<td>Heart failure</td>
<td>I50</td>
</tr>
<tr>
<td>Platelet or coagulation defect</td>
<td>D65-69</td>
</tr>
<tr>
<td>Liver disease</td>
<td>K70-77 Z94.4, procedure codes: JJC, JJB</td>
</tr>
<tr>
<td>Renal disease</td>
<td>N17-19, Z94.0, Y841, Z992, procedure codes: KAS, KAC</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>I342 I050 I052 Q232</td>
</tr>
</tbody>
</table>

**CHA_{2}DS_{2}-VASc**

1.50, primary diagnosis for hospitalization

<table>
<thead>
<tr>
<th>Condition</th>
<th>ICD-10 code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>I10-15 or reported in RS</td>
</tr>
<tr>
<td>Age&gt;=75</td>
<td>E10-14 or reported in RS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>I63, G45 or reported in RS</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>I20 (except I20.1) I21 I22 I23 I24 I25.2, I74, I65, I70-73, (except I71.1, I71.2, I73.0, I73.1, I73.8, I73.8A, I73.8B, I73.8C, I73.8D, I73.8W and I73.9A)</td>
</tr>
</tbody>
</table>

Age 65-74
Female sex
Vascular disease
Modified HAS-BLED

Hypertension I10-15 or reported in RS
Age >= 65
Previous ischemic stroke I63
Bleeding All patients awarded 1 point
Liver disease K70-77 Z94.4, procedure codes: JJC, JJB
Renal disease N17-19, Z94.0, Y841, Z992,
procedure codes: KAS, KAC
Drugs/Alcohol Alcohol index (see above) or antiplatelets at time of intracerebral hemorrhage
Labile INR Data missing

Supplemental Table II
Baseline Characteristics and risk factors at onset of Intracerebral Hemorrhage (ICH). Patients with and without Atrial Fibrillation (AF) at onset are presented separately. $\chi^2$-tests for categorical variables, unpaired t-test for age. AC = Anticoagulants, AP = Antiplatelet therapy.

<table>
<thead>
<tr>
<th></th>
<th>Total n(%)</th>
<th>No AF</th>
<th>AF n(%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean(range)</td>
<td>71.5(18-103)</td>
<td>69.9(18-103)</td>
<td>78.2(42-100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-64</td>
<td>3978(28.3)</td>
<td>3738(33.2)</td>
<td>240(8.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65-74</td>
<td>3402(24.2)</td>
<td>2787(24.7)</td>
<td>615(22.1)</td>
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</tr>
<tr>
<td>75-84</td>
<td>4286(30.5)</td>
<td>3111(27.6)</td>
<td>1175(42.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;=85</td>
<td>2379(16.9)</td>
<td>1632(14.5)</td>
<td>747(26.9)</td>
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</tr>
<tr>
<td>Female sex</td>
<td>6121(43.6)</td>
<td>4970(44.1)</td>
<td>1151(41.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Primary school</td>
<td>6190(44.1)</td>
<td>4817(42.7)</td>
<td>1373(49.4)</td>
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</tr>
<tr>
<td>Secondary school</td>
<td>5111(36.4)</td>
<td>4148(36.8)</td>
<td>963(34.7)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>2422(17.2)</td>
<td>2038(18.1)</td>
<td>384(13.8)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>322(2.3)</td>
<td>265(2.4)</td>
<td>57(2.1)</td>
<td></td>
</tr>
<tr>
<td>Fully conscious at hospital admission</td>
<td></td>
<td>8418(74.4)</td>
<td>2096(75.5)</td>
<td>0.307</td>
</tr>
<tr>
<td>Yes</td>
<td>10514(74.9)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3315(23.6)</td>
<td>2682(23.8)</td>
<td>634(22.8)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>216(1.5)</td>
<td>169(1.5)</td>
<td>47(1.7)</td>
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<tr>
<td>Medical history</td>
<td>2318(16.5)</td>
<td>1673(14.8)</td>
<td>645(23.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetes mellitus</td>
<td>2185(15.6)</td>
<td>1486(13.2)</td>
<td>699(25.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Previous ischemic stroke</td>
<td>574(4.1)</td>
<td>438(3.9)</td>
<td>136(4.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>336(2.4)</td>
<td>250(2.2)</td>
<td>86(3.1)</td>
<td>0.007</td>
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<tr>
<td>Pulmonary embolism</td>
<td>2278(16.2)</td>
<td>1470(13.0)</td>
<td>808(29.1)</td>
<td>&lt;0.001</td>
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<tr>
<td>Ischemic heart disease</td>
<td>10020(71.3)</td>
<td>7708(68.4)</td>
<td>2312(83.3)</td>
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<tr>
<td>Hypertension</td>
<td>1133(8.1)</td>
<td>428(3.8)</td>
<td>705(25.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Heart failure</td>
<td>379(2.7)</td>
<td>171(1.5)</td>
<td>208(7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>754(5.4)</td>
<td>582(5.2)</td>
<td>172(6.2)</td>
<td>0.031</td>
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<tr>
<td>Smoking</td>
<td>Frequency (%)</td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1623 (11.6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10845 (77.2)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1577 (11.2)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol index</td>
<td>611 (4.4)</td>
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<tr>
<td>TIA</td>
<td>1073 (7.6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1352 (9.6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure, primary diagnosis for hospitalization</td>
<td>433 (3.1)</td>
<td>&lt;0.001</td>
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<td>Thyroid disease</td>
<td>750 (5.3)</td>
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<td>Chronic pulmonary disease</td>
<td>1017 (7.2)</td>
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<td>Renal disease</td>
<td>496 (3.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>Liver disease</td>
<td>184 (1.3)</td>
<td>0.943</td>
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<td>Mechanical heart valve prosthesis</td>
<td>113 (0.8)</td>
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<tr>
<td>AC at stroke onset</td>
<td>1454 (10.4)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>AP at stroke onset</td>
<td>4018 (28.6)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Statin treatment</td>
<td>3306 (21.6)</td>
<td>&lt;0.001</td>
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</table>

*Fully conscious corresponds to alert, RLS 1, on the Reaction Level Scale (RLS).

---

**Supplemental Table III**

CHA$_3$DS$_2$-VASc- and HAS-BLED-score distribution in patients at ICH with concurrent atrial fibrillation. N = 2777.

<table>
<thead>
<tr>
<th>CHA$_3$DS$_2$-VASc Score</th>
<th>Frequency (%)</th>
<th>HAS-BLED-Score</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>20 (0.7)</td>
<td>0</td>
<td>29 (1.0)</td>
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<tr>
<td>1</td>
<td>97 (3.5)</td>
<td>1</td>
<td>32 (11.7)</td>
</tr>
<tr>
<td>2</td>
<td>313 (11.3)</td>
<td>2</td>
<td>1145 (41.2)</td>
</tr>
<tr>
<td>3</td>
<td>560 (20.2)</td>
<td>3</td>
<td>325 (11.7)</td>
</tr>
<tr>
<td>4</td>
<td>677 (24.4)</td>
<td>4</td>
<td>940 (33.8)</td>
</tr>
<tr>
<td>5</td>
<td>507 (18.3)</td>
<td>5</td>
<td>300 (10.8)</td>
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<tr>
<td>6</td>
<td>376 (13.5)</td>
<td>6</td>
<td>38 (1.4)</td>
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<tr>
<td>7</td>
<td>170 (6.1)</td>
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</tr>
<tr>
<td>8</td>
<td>49 (1.8)</td>
<td>8</td>
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</tr>
<tr>
<td>9</td>
<td>8 (0.3)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2777 (100)</td>
<td>2777 (100)</td>
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</tr>
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</table>
**Supplemental Table IV**
Univariate and multivariable * Cox’s proportional regression for dispensed anticoagulant or antiplatelet prescriptions in patients without atrial fibrillation at ICH † onset (N=11268). Hazard ratios (HR) and 95% confidence intervals (CI).

<table>
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<tr>
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<th>Anticoagulants</th>
<th>Antiplatelet agents</th>
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<td>Univariate analysis (HR(95%CI))</td>
<td>p-value</td>
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<td><strong>Age groups</strong></td>
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<tr>
<td>18–64 years (Ref.)</td>
<td>0.025</td>
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</tr>
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<td>65–74</td>
<td>1.263 (0.976-1.635)</td>
<td>0.260 (0.966-1.644)</td>
</tr>
<tr>
<td>75–84</td>
<td>0.976 (0.740-1.288)</td>
<td>0.868 (0.653-1.154)</td>
</tr>
<tr>
<td>≥85</td>
<td>0.666 (0.429-1.033)</td>
<td>0.644 (0.409-1.014)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>0.901 (0.726-1.119)</td>
<td>0.345</td>
</tr>
<tr>
<td><strong>Level of Education</strong></td>
<td>0.871</td>
<td>0.000</td>
</tr>
<tr>
<td>Primary school (Ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>1.008 (0.795-1.278)</td>
<td>0.821 (0.754-0.894)</td>
</tr>
<tr>
<td>University</td>
<td>0.988 (0.733-1.330)</td>
<td>0.725 (0.649-0.811)</td>
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<tr>
<td>Fully conscious at hospital admission</td>
<td>1.282 (0.973-1.688)</td>
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<td><strong>Medical history</strong></td>
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<td>Diabetes mellitus</td>
<td>1.092 (0.815-1.464)</td>
<td>0.554</td>
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<tr>
<td>Ischemic Stroke</td>
<td>1.536 (1.155-2.043)</td>
<td>0.003</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>8.253 (6.342-10.741)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.599 (1.208-2.118)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.942 (0.752-1.180)</td>
<td>0.603</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.837 (1.142-2.955)</td>
<td>0.012</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>10.994 (7.737-15.481)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.315 (0.118-0.845)</td>
<td>0.022</td>
</tr>
<tr>
<td>AC at onset</td>
<td>19.146 (15.045-24.366)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AP at onset</td>
<td>0.997 (0.780-1.275)</td>
<td>0.982</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>1.608 (1.261-2.050)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Multivariable models include all variables with p<0.10 in the univariate analyses except CHA2DS2-VASc and HAS-BLED.
† ICH – Intracerebral hemorrhage
### Supplemental Table V
Baseline Characteristics of ICH-patients who survived discharge with prior-to-ICH anticoagulant treatment (AC). (ICH = intracerebral hemorrhage)

<table>
<thead>
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<th>Total N(%)</th>
<th>Atrial fibrillation</th>
<th>No atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior-to-ICH AC</td>
<td>1454 (100)</td>
<td>1152</td>
<td>302</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>75.9</td>
<td>76.9</td>
<td>72.2</td>
</tr>
<tr>
<td>Female sex</td>
<td>553 (38.0)</td>
<td>421 (36.5)</td>
<td>132 (43.7)</td>
</tr>
<tr>
<td>Fully conscious at ICH</td>
<td>1152 (79.2)</td>
<td>912 (79.2)</td>
<td>240 (79.5)</td>
</tr>
<tr>
<td>Restarting anticoagulation</td>
<td>299 (20.6)</td>
<td>207 (18.0)</td>
<td>92 (30.5)</td>
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<tr>
<td>Previous ischemic stroke</td>
<td>350 (24.1)</td>
<td>388 (33.7)</td>
<td>80 (26.5)</td>
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<td>Hypertension</td>
<td>1229 (84.5)</td>
<td>1015 (88.1)</td>
<td>214 (70.9)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>132 (9.1)</td>
<td>52 (4.5)</td>
<td>80 (26.5)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>387 (26.6)</td>
<td>350 (30.4)</td>
<td>37 (12.3)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>447 (30.7)</td>
<td>363 (31.5)</td>
<td>84 (27.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>250 (17.2)</td>
<td>208 (18.1)</td>
<td>42 (13.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>323 (22.2)</td>
<td>263 (22.8)</td>
<td>60 (19.9)</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>98 (6.7)</td>
<td>53 (4.6)</td>
<td>45 (14.9)</td>
</tr>
<tr>
<td>prosthesis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mitral stenosis</td>
<td>11 (0.8)</td>
<td>7 (0.6)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>889 (61.1)</td>
<td>463 (40.2)</td>
<td>102 (33.8)</td>
</tr>
<tr>
<td>Platelet or coagulation defect</td>
<td>299 (20.6)</td>
<td>228 (19.8)</td>
<td>71 (23.5)</td>
</tr>
</tbody>
</table>
Abstract

Antithrombotic Treatment Following Intracerebral Hemorrhage in Patients With and Without Atrial Fibrillation

Johanna Pennlert, MD; Kjell Asplund, MD, PhD; Bo Carlberg, MD, PhD, et al.

Department of Public Health and Clinical Medicine and Department of Medicine, Umeå University, Sweden.

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