Both the prevalence of atrial fibrillation (AF) and oral anticoagulant treatment after intracerebral hemorrhage (ICH) has increased in recent years. Still, a large proportion of these patients are untreated, reflecting the controversy of the decision. There is emerging evidence of the potential benefits of anticoagulants in these patients. In a Swedish population-based study, recurrent ischemic events outnumbered recurrent ICH among ICH survivors and ICH in itself has been identified as an independent predictor of thromboembolic events among patients with AF.

Two recent, Danish observational studies support the reintroduction of oral anticoagulants as being associated with a significant reduction of all-cause mortality and ischemic stroke rates. International guidelines highlight the lack of evidence as to whether and when to resume anticoagulant treatment after ICH. The largest retrospective study examining the optimal time window for initiating treatment included 3 tertiary centers and 234 patients with warfarin-associated ICH. Fifty-nine patients resumed anticoagulant treatment, and the study concluded that resumption should be delayed by 10 to 30 weeks to avoid the early high-risk period for recurrent hemorrhage. In contrast, a systematic review detailing 492 patients suggests that anticoagulation in high-risk patients may be restarted 3 days from the time of intracerebral bleedings, but authors emphasize the limitations inherent in the studies analyzed.

Using the nationwide Swedish Stroke Register, Riksstroke, we studied the relationship between the timing of antithrombotic treatment and the competing risks of severe thrombotic and hemorrhagic events in a cohort of Swedish patients with atrial fibrillation and intracerebral hemorrhage (ICH).

Methods—Patients with atrial fibrillation and a first-ever ICH were identified in the Swedish Stroke Register, Riksstroke, 2005 to 2012. Riksstroke was linked with other national registers to find information on treatment, comorbidity, and outcome. The optimal timing of treatment in patients with low and high thromboembolic risk was described through cumulative incidence functions separately for thrombotic and hemorrhagic events and for the combined end point vascular death or nonfatal stroke.

Results—The study included 2619 ICH survivors with atrial fibrillation with 5759 person-years of follow-up. Anticoagulant treatment was associated with a reduced risk of vascular death and nonfatal stroke in high-risk patients with no significantly increased risk of severe hemorrhage. The benefit seemed to be greatest when treatment was started 7 to 8 weeks after ICH. For high-risk women, the total risk of vascular death or stroke recurrence within 3 years was 17.0% when anticoagulant treatment was initiated 8 weeks after ICH and 28.6% without any antithrombotic treatment (95% confidence interval for difference, 1.4%–21.8%). For high-risk men, the corresponding risks were 14.3% versus 23.6% (95% confidence interval for difference, 0.4%–18.2%).

Conclusions—This nationwide observational study suggests that anticoagulant treatment may be initiated 7 to 8 weeks after ICH in patients with atrial fibrillation to optimize the benefit from treatment and minimize risk. 

Key Words: anticoagulants • atrial fibrillation • cerebral hemorrhage • ischemia • stroke
of antithrombotic treatment and the competing risks of severe thrombotic events, hemorrhagic events, and death from other causes in ICH survivors with AF.

Methods

Study Population
All patients with a first-ever ICH (International Classification of Diseases-Tenth Revision [ICD-10]: I61) recorded in Rikssstroke between July 1, 2005, and December 31, 2012, with a concomitant diagnosis of AF and surviving hospital discharge were included. Patients with traumatic ICH, subdural hematomas, and subarachnoid hemorrhages were not included. The diagnosis of AF was obtained from Rikssstroke or found in the Swedish Inpatient registry (ICD-10: I48) from 1997 to ICH onset.

Data Sources
Patient records were linked from several Swedish nationwide databases so as to describe patient characteristics at the time of ICH, the prescription of antithrombotic drugs after ICH, and any subsequent severe clinical events. Rikssstroke was established in 1994, and since 1998 all hospitals admitting patients with acute stroke in Sweden participate. The register has an estimated coverage of >94% of all patients with acute stroke. The Swedish Dispensed Drug Register carries nationwide information on all dispensed outpatient drug prescriptions collected from all Swedish pharmacies from July 1, 2005. The Swedish Inpatient Register, managed by the National Board of Health and Welfare, has had complete national coverage since 1987, and >99% of all somatic hospital discharges are registered. Diagnostic accuracy, measured by positive predictive value, differs between diagnoses, but is generally 85% to 95%. Information on socioeconomic variables was retrieved from the Longitudinal Integration Database for Health Insurance and Labour Market Studies, managed by Statistics Sweden. Linkage with the Cause of Death Register, managed by the National Board of Health and Welfare, was made to find information on direct and contributory causes of death.

Approval for this study was obtained from the Ethical Review Board, Umeå, Sweden (Dnr 2014-76-32M), as an extension of the EqualStroke project (Dnr 2012-321-31M).

Variable Definitions

Outcome Variables
Two different outcome events were defined. First, thrombotic events were ischemic stroke events (fatal or nonfatal), and all causes of death directly or indirectly caused by a thrombotic event (myocardial infarction or systemic arterial thromboembolism). The second major outcome was hemorrhagic events, defined as either a recurrent ICH (fatal or nonfatal) or any bleeding event directly or indirectly causing death. The 2 outcomes were also combined, similar to the primary end point of the APACHE-AF study (Apxiban Versus Antiplatelet Drugs or No Antithrombotic Drugs After Anticoagulation-Associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation; vascular death or nonfatal stroke). ICD-10 codes listed for thrombotic and hemorrhagic events are available in Table I in the online-only Data Supplement.

Time Variables and Censoring
One of the inherent features of the stroke register is that recurrent events within the first 28 days of onset of a first-ever stroke are not recorded. Therefore, the starting point for outcome follow-up was set at day 28 after index ICH. The starting point for follow-up of antithrombotic treatment was time of first dispensed prescription of antithrombotic treatment after discharge, given that the patient was not on treatment at discharge. Death from any other cause was modeled as the third possible outcome event. Censoring events during follow-up were initiation of dual treatment (anticoagulant-antiplatelet drugs), reaching study-end-date (December 31, 2012) or patients being lost to follow-up because of emigration.

Anticoagulant and Antiplatelet Treatment
Rikssstroke contains information on anticoagulant and antiplatelet treatment at 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. ATC code B01AC was used for antiplatelet drugs. For oral anticoagulant therapy (vitamin K antagonists and direct oral anticoagulants), the following codes were used: B01AA, B01AE, and B01AF. Once having had a dispensed prescription of either of the antithrombotic agents, analyses were performed according to the intention-to-treat principle, unless a patient changed from antiplatelet treatment to anticoagulant treatment or vice versa (prescribed dual therapy). Once prescribed dual therapy, the patient was censored. Information on antithrombotic treatment at the onset of ICH was obtained from Rikssstroke or having had a dispensed prescription 6 months before the index ICH.

Comorbidity
The diagnosis of AF (ICD-10 I48) was based on registry data in Rikssstroke or a diagnosis of AF before the ICH in the Inpatient Register. Hypertension was defined as being on antihypertensive treatment in Rikssstroke or a diagnosis (ICD-10 I10-I15) in the Inpatient Register. An overview of all comorbid factors is present in Table II in the online-only Data Supplement.

Patient Risk Profiles
Two types of risk patients were defined with given sets of clinically important patient characteristics. A low-risk patient was 69 years of age, spent 14 days in hospital after the index ICH, had no previous risk factors other than AF, and had no previous antithrombotic treatment. To evaluate the risk of ischemic stroke in patients with AF, a commonly used risk-stratification score is the CHA2DS2-VASc score (congestive heart failure, hypertension, age [≥75 years; 2 points], diabetes mellitus, stroke/transient ischemic attack [2 points], vascular disease, age [65–74 years], sex [female]). By CHA2DS2-VASc, this patient profile corresponds to 1 point if male and 2 points if female. A high-risk patient was 80 years of age and spent 28 days in hospital. The patient had a previous ischemic stroke, hypertension, and diabetes mellitus and was on previous anticoagulant treatment at the time of ICH (by CHA2DS2-VASc: 6 points if male and 7 points if female). Baseline CHA2DS2-VASc scores were estimated using the same methodology as that of a previous study by Pennlert et al. Additional patient profiles are presented in the online-only Data Supplement.

Statistical Methods
A retrospective power calculation based on the 2619 patients included, of whom 232 (8.9%) received anticoagulants, showed that the study would be able to detect a difference in cumulative incidence of total events of 10% versus 17% between treated and nontreated patients, with 82% power (2-sided test with 5% significance level). Baseline characteristics are summarized in the Table. To explore the relationship of anticoagulant and antiplatelet treatment starting times with the competing risks of thrombotic events, hemorrhagic events and other causes of death, we focused our analyses on the estimation of cumulative incidence functions (CIFs). The CIF is the probability of observing an event before a specified time. CIFs are defined for thrombotic and hemorrhagic events separately and when summed give the CIF of the combined outcome vascular death or nonfatal stroke.

We built a Cox proportional hazard model for each event (Table III in the online-only Data Supplement). This allowed us to adjust for differences in patient characteristics when computing the cause-specific hazards. Each model contained 2 time-varying covariates. For treatments, we used smoothing splines (a nonlinear function whose shape is determined by the data) of start time of anticoagulant or antiplatelet treatment during the treatment periods. To reduce the possibility of overfitting, a linear behavior was used for time periods with few or no data points (after 38 and 69 weeks, respectively). For
age, we used a piecewise linear effect with turning points at the quartiles of the observed ages. Other covariates were selected according to a backward selection algorithm. Because a covariate related to one of the outcomes was not necessarily related to another, we performed model selection for each of the 3 outcomes separately.

The available covariates were baseline characteristics (Table) and a smoothing spline (with a linear behavior after 26 weeks) of time since discharge. Patients with missing values of level of consciousness were treated as a separate category. Other covariates included age (<2% missing). After covariates were selected for each of the 3 models using the same set of patients with information on all covariates (n=2562), the 3 models were refit using the set of patients with information on all covariates selected for at least 1 model (n=2619). The selection algorithm started with the complete model and eliminated the variable that gave the largest decrease in Akaike Information Criterion. Selection ended when the removal of any variable resulted in an Akaike Information Criterion of 2 more than the current Akaike Information Criterion.

For a given set of patient characteristics (ie, the high- and low-risk patients), the cause-specific hazards were combined to compute the thrombotic event, hemorrhagic event, and the combined CIF. Thus, the effect of the treatment starting times could be assessed for each event separately and for the combined events. The main results were stratified by sex and patient risk status. SEs for the CIFs were computed via a parametric bootstrap. Further details are in the online-only Data Supplement. After computing CIFs with and without treatment over a range of start times for a given patient profile, we identified intervals of starting times where the CIFs were significantly different. The optimal time was then chosen as the time of lowest CIF with treatment.

In a confirmatory analysis, empirical CIFs were computed for the total study population and according to treatment status at the estimated optimal time point (8 weeks after stroke). For simple group comparisons (patients on anticoagulant and antiplatelet treatment versus no treatment at 8 weeks), P values were estimated using the χ² test for categorical variables and t-test for age.

Statistical analysis was performed using R. There were 2777 patients in Riksstroke having survived hospital discharge after a first-ever ICH with concomitant AF. We excluded 1 patient because of an obvious recording error. Patients with event times in the 28 days immediately after the time of ICH onset (n=103) and 11 patients who were on both anticoagulant and antiplatelet treatment at discharge (n=11) were removed. The final study population consisted of 2662 patients, 1568 men and 1094 women, with a mean age of 78 years (Figure 1). These 2662 patients were used in the model-building process. One or more baseline characteristics used in the final model of CIFs were missing for 43 patients, and hence the analysis of CIF included 2619 patients. Baseline characteristics of the ICH survivors included in the final model are presented in the Table. Patient characteristics according to treatment status at 8 weeks after ICH are presented in Table IV in the online-only Data Supplement.

The patients constituted 5759 person-years of follow-up from stroke onset to patients were either censored or experienced a new event (median follow-up was 1.7 years). Total follow-up time from treatment initiation was 581 person-years for anticoagulants, and 3,001 person-years for antiplatelets. Of the 232 patients initiating anticoagulant treatment, 59.5% had a dispensed prescription within the first 3 months after onset of ICH. Among the 1136 patients who received antiplatelet therapy, 38.9% claimed a prescription within 3 months.

### Results

The available covariates were baseline characteristics (Table) and a smoothing spline (with a linear behavior after 26 weeks) of time since discharge. Patients with missing values of level of consciousness were treated as a separate category. Other covariates included age (<2% missing). After covariates were selected for each of the 3 models using the same set of patients with information on all covariates (n=2562), the 3 models were refit using the set of patients with information on all covariates selected for at least 1 model (n=2619). The selection algorithm started with the complete model and eliminated the variable that gave the largest decrease in Akaike Information Criterion. Selection ended when the removal of any variable resulted in an Akaike Information Criterion of 2 more than the current Akaike Information Criterion.

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### Outcome

During follow-up, we observed 379 severe thrombotic events of which 302 (79.7%) were ischemic strokes. Of 115 severe hemorrhagic events, 96 (83.5%) were recurrent ICH events.

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**Table. Baseline Characteristics of Patients With Atrial Fibrillation Who Survived a First Intracerebral Hemorrhage in Sweden 2005 to 2012 Included in Analysis (n=2619)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%), Mean (SD) for Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>78.0 (9.1)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1065 (40.7)</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>1309 (50.0)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>900 (34.4)</td>
</tr>
<tr>
<td>University</td>
<td>360 (13.7)</td>
</tr>
<tr>
<td>Missing</td>
<td>50 (1.9)</td>
</tr>
<tr>
<td>Living alone</td>
<td>1266 (48.3)</td>
</tr>
<tr>
<td>ADL dependency before first ICH</td>
<td>301 (11.5)</td>
</tr>
<tr>
<td>Level of consciousness on hospital admission</td>
<td></td>
</tr>
<tr>
<td>Alert</td>
<td>1999 (76.3)</td>
</tr>
<tr>
<td>Drowsy</td>
<td>495 (18.9)</td>
</tr>
<tr>
<td>Unconscious</td>
<td>80 (3.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>45 (1.7)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>605 (23.1)</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>640 (24.4)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>140 (5.3)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>713 (27.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2180 (83.2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>672 (25.7)</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>213 (8.1)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>156 (6.0)</td>
</tr>
<tr>
<td>Dementia</td>
<td>153 (5.8)</td>
</tr>
<tr>
<td>Treatment at ICH onset</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>1239 (47.3)</td>
</tr>
<tr>
<td>AP</td>
<td>1175 (44.9)</td>
</tr>
<tr>
<td>Both AC and AP</td>
<td>205 (7.8)</td>
</tr>
<tr>
<td>Statins</td>
<td>723 (27.6)</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td></td>
</tr>
<tr>
<td>Median (mean) score</td>
<td>4 (4.13)</td>
</tr>
<tr>
<td>Score 0–4</td>
<td>1595 (60.9)</td>
</tr>
<tr>
<td>Score 5–9</td>
<td>1024 (39.1)</td>
</tr>
</tbody>
</table>

AC indicates anticoagulant treatment; ADL, activities of daily living; AP, antiplatelet treatment; CHA2DS2-VASc, congestive heart failure, hypertension, age (≥75 years; 2 points), diabetes mellitus, stroke/transient ischemic attack (2 points), vascular disease, age (65–74 years), sex (female); and ICH, intracerebral hemorrhage.
The 28-day case fatality after ischemic stroke was 17.5% compared with 37.5% after recurrent hemorrhagic stroke ($P<0.001$, $\chi^2$ test). At 3 years, the cumulative incidence of thrombotic events was 14.5%, and the incidence of severe hemorrhagic events was 4.4% (Figure 2).

### Optimal Timing of Treatment

Figures 3A (women) and Figure 3B (men) show the cumulative incidences (CIFs), adjusted for differences in patient characteristics, of thrombotic, hemorrhagic, and the sum of the 2 events (vascular death and stroke) at 3 years after onset of ICH in relation to start time of anticoagulant and antiplatelet treatment. The thick lines represent time periods during which treatment initiation of anticoagulants (black) and antiplatelet therapy (gray) are significantly different from no treatment. The risk reduction of thrombotic events in patients treated with anticoagulants compared with no treatment was statistically significant in the 4- to 16-week interval for both the low- and high-risk patients (Figure 3, top panel, black thick line). Initiation of anticoagulants was not associated with any significantly increased risk of a hemorrhagic event. However, we cannot rule out that the initiation of anticoagulation very early may increase the risk of bleeding, compared with no treatment (Figure 3, mid panel).

In the presented patient profiles (women and men, patients at low risk and at high risk), there was an early U-shaped relationship between timing of initiating anticoagulant treatment and the combined end point of vascular death or stroke (Figure 3, bottom panel). The lowest estimated CIFs of vascular death or nonfatal stroke were found when anticoagulant treatment was started in the 7- to 8-week interval. For high-risk women, the total risk of vascular death or stroke recurrence within 3 years was 17.0% when anticoagulant treatment was initiated 8 weeks after ICH, when compared with 28.6% without any antithrombotic treatment (95% confidence interval [CI] for difference, 1.4%–21.8%). The corresponding risks were 14.3% versus 23.6% (95% CI for difference, 0.4%–18.2%) for high-risk men, 8.2% versus 12.6% (95% CI for difference, −2.1% to 10.8%) for low-risk women, and 7.3% versus 10.7% (95% CI for difference, −2.7% to 9.4%) for low-risk men (Figure 3).

Changing the covariates, instead investigating patients with previous anticoagulant treatment and hypertension and diabetes mellitus, respectively (Figure IV in the online-only Data Supplement) did not change the association of a positive effect of anticoagulants on risk of thrombosis, without an excess risk of hemorrhage. Furthermore, changing the patient profiles had only a minor effect on the optimal treatment initiation time point although the magnitude of the effect of treatment varied (description of the sensitivity analysis is available in the Methods in the online-only Data Supplement).

When compared with no antithrombotic therapy, antiplatelet treatment was not associated with a lowered event risk at
any time of initiating treatment and was associated with an increased risk most of the times (Figure 3).

The unadjusted cumulative incidences of a thrombotic event 3 years after stroke was 6.3% in patients who initiated anticoagulant treatment within 8 weeks after ICH, 18.8% in patients who initiated antiplatelets within 8 weeks, and 13.8% in patients with neither anticoagulants nor antiplatelets within 8 weeks. The corresponding incidences were 6.9%, 3.9%, and 4.4% for hemorrhagic events (Figure V in the online-only Data Supplement). Patients who initiated anticoagulant treatment within 8 weeks after ICH had a reduced rate of thrombotic events (95% CI for difference, −13.9% to −1.0%), with no significantly increased rate of hemorrhagic events (95% CI for difference, −3.7% to 8.7%) as compared with patients without any antithrombotic treatment within 8 weeks.

Discussion

The first main finding in our study is that anticoagulant treatment is associated with a significant reduction in 3-year thrombotic event risk and not associated with a significant increase in hemorrhagic event risk in patients with ICH and AF. This is true for men and women with high and low event risk profiles. In high-risk patients, anticoagulant treatment is also associated with a reduction of the combined event risk of vascular death and nonfatal stroke. The second main observation, of evident clinical significance, is that the optimal time to start anticoagulant treatment in patients with AF who have had an ICH seems to be at around 7 to 8 weeks after the bleeding event. Starting sooner than 7 weeks may possibly involve an increased risk of severe bleeding. Changing patient profile characteristics did not change the optimal treatment initiation.

Figure 3. Cumulative incidence functions (CIFs), adjusted for differences in patient characteristics, at three years after onset of intracerebral hemorrhage (ICH) vs start time of 2 treatments (anticoagulant [AC]=black line; antiplatelet [AP]=gray line) and no treatment (dashed line) for both a low-risk and a high-risk female/male profile (A=female profiles, B=male profiles). The event-specific CIFs (thrombotic and hemorrhagic) sum to the vascular death or stroke CIFs in the bottom row. The thick lines represent time periods during which treatment initiation of AC (black) and AP (gray) are significantly different from no treatment at the 5% level.
time point although the magnitude of the estimated effect of treatment varied.

Awaiting results from randomized controlled trials, observational studies may constitute the best available scientific evidence. The present results are in agreement with those of recent Danish observational studies,12,13 in that an overall benefit of anticoagulant treatment after ICH in patients with AF has been shown. This supports the generalizability of the current findings.

Our nationwide study is, by far, the largest specifically addressing the problem of when to start or reinitiate anticoagulant treatment in patients with AF who have had an ICH. In contrast to previous smaller studies,12,13 the number of patients in the present study has permitted adjustments for available confounders with sufficient statistical power. Rather than using summary scores such as CHA2DS2-VASC and HAS-BLED (bleeding risk score assigning 1 point for the presence of each of the following: hypertension [uncontrolled systolic blood pressure >160 mm Hg], abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, elderly, and concomitant drugs and/or alcohol excess), individual comorbidities were used in the statistical models. Because of a modest and not statistically significant increase in bleeding events in patients with start of anticoagulant treatment early after ICH, the net benefit for all events was not statistically significant before 7 weeks. Even if there are net benefits in subgroups up to 16 weeks, particularly in high-risk patients, the opportunity for early effective secondary prevention should not be missed. It seems therefore that the optimal timing of initiating anticoagulant therapy in patients with AF would be at around 7 to 8 weeks after an ICH.

Similar timing patterns were observed in high-risk and low-risk patients prescribed anticoagulants. In absolute terms, the time-dependent benefits were much larger in high-risk patients. Therefore, the timing of onset of anticoagulant treatment seems to be particularly critical in these patients. In low-risk patients, the difference in risk for recurrent stroke and vascular death after 3 years was not significant in favor of starting anticoagulant therapy at 8 weeks. However, the uncertainty of the estimate was large, why these data could not be used as an argument against starting anticoagulant therapy in patients with low CHA2DS2-VASC scores.

In the present study, the proportion of patients with AF surviving ICH who received anticoagulants was low (8.9%). This seems to reflect the fact that physicians have found the scientific evidence for anticoagulant treatment after an ICH in patients with AF to be lacking or insufficient. No randomized trial has been published, and only recently has support from observational studies been published showing that anticoagulant treatment reduces all-cause mortality and thromboembolic events, even after severe hemorrhagic strokes.27 A recent report on ICH survivors with AF also implies that, paradoxically, the higher the risk of thromboembolic events according to CHA2DS2-VASC score, the lower the probability to receive anticoagulants within the first months after ICH.1 Because patients with higher CHA2DS2-VASC score tend to have an elevated risk of severe bleeding as estimated by the HAS-BLED score,26 this may reflect clinicians’ and patients’ reasonable tendency to minimize risks in the absence of strong evidence.

The between-hospital variation in the use of anticoagulant therapy after ischemic stroke in patients with AF is large in Sweden, ranging from 36% to 100%.14 It therefore seems that hospital traditions and individual doctors’ attitudes are major determinants of the use of anticoagulants in stroke patients with AF. In the present study, we have taken advantage of this random-like heterogeneity in exposure. Yet, the possibility of residual confounding remains. There was a lower risk of death from causes other than thrombotic and hemorrhagic events in patients in whom anticoagulant and antiplatelet treatment was started in the first months after ICH (unpublished data). This may have resulted from a selection where patients with an apparent high risk for nonvascular death were not treated with antithrombotic agents. The increased thrombotic event risk seen for antiplatelet-treated patients could be a real finding, but it could also be a sign of confounding by indication. Although we were able to adjust for several important confounding factors, we cannot fully adjust for the doctor’s view of the patient’s overall health status.

Our study has several limitations. First, in this register-based study, we have not had access to brain imaging data to distinguish between the different subtypes of ICH (lobar and deep ICH involve different risks of recurrent bleeding27). The proportion that had lowered consciousness at onset of ICH (as a proxy for ICH severity) was somewhat lower in patients prescribed anticoagulants than in the other 2 groups (Table IV in the online-only Data Supplement), this difference was adjusted for. Second, validation studies have shown that Riksstroke covers 94% of all hospital admissions for acute stroke24 and that, conversely, there is an overdiagnosis of acute stroke in routine hospital practice and in the Swedish Cause of Death register.28 The national drug register is essentially complete.15 Third, the present study was performed before the large-scale introduction in routine clinical practice of new oral anticoagulants. Therefore, it was not possible to analyze separately the optimal timing of starting new oral anticoagulants after ICH in patients with AF. Fourth, we had no data on functional outcome after the recurrent stroke. Thus, case fatality is the only variable used to describe the severity of the recurrent stroke event, significantly higher after recurrent ICH than after recurrent ischemic strokes. A final limitation is that we had no information on antithrombotic therapy given in hospital and that adherence to anticoagulant or antiplatelet treatment during the follow-up period was not measured. The analyses were by intention-to-treat, whereas the on-treatment effects may have been greater.

A randomized controlled trial on anticoagulants in patients with AF who have had an ICH has recently been initiated.19 It will provide more definite evidence on the size of beneficial and adverse effects than can be obtained from observational studies. It is, however, unlikely that a randomized trial will provide information on the optimal timing over a wide time span in the same way an observational study can.

Conclusions
The optimal timing of starting anticoagulant treatment in patients with AF who have survived an ICH seems to be around 7 to 8 weeks after the hemorrhage. In high-risk patients, anticoagulant treatment started in this interval reduces not only the risk of thrombotic events but also the combined risk of
vascular death and nonfatal stroke. If treatment is started in this interval, there seems to be no excess risk of major bleeding.

Acknowledgments
We thank the members of the Riksstroke Collaboration (http://www.Riksstroke.org).

Sources of Funding
This study was supported by grants from the Swedish Research Council for Health, Working Life and Welfare (grant no. 2011-0657), the Swedish Research Council (2011–2395), by the foundations for medical research administered by Umeå University, by the Foundation for Stroke Research in Northern Sweden and by the County Council of Västerbotten.

Disclosures
Dr Pennlert has served on a scientific advisory board for, and has received lecture fees from, Bayer. Dr Wiklund has served on a scientific advisory board for Boehringer-Ingelheim. The other authors report no conflicts.

References