Optimal Timing of Anticoagulant Treatment After Intracerebral Hemorrhage in Patients With Atrial Fibrillation

Johanna Pennlert, MD; Rosanna Overholser, PhD; Kjell Asplund, MD, PhD; Bo Carlberg, MD, PhD; Bart Van Rompaye, PhD; Per-Gunnar Wiklund, MD, PhD; Marie Eriksson, PhD

Background and Purpose—This study aims to provide observational data on 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. (Stroke. 2017;48:314-320. DOI: 10.1161/STROKEAHA.116.014643.)

Key Words: anticoagulants ■ atrial fibrillation ■ cerebral hemorrhage ■ ischemia ■ stroke

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 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 Riksstroke
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 subarachno-
idal hemorrhages were not included. The diagnosis of AF was
obtained from Riksstroke or found in the Swedish Inpatient registry
(ICD-10: I14) from 1997 to ICH onset.

Data Sources
Patient records were linked from several Swedish nationwide data-
bases so as to describe patient characteristics at the time of ICH, the
prescription of antithrombotic drugs after ICH, and any subsequent
severe clinical events. Riksstroke 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
contains nationwide information on all dispensed outpatient drug pre-
scriptions 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 diag-
noses, 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, simi-
lar to the primary end point of the APACHE-AF study (Apixaban
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 avail-
able 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 anti-
thrombotic treatment was time of first dispensed prescription of anti-
thrombotic 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 was initiation of dual treatment (anticoagulants-antiplatelet drugs),
reaching study-end date (December 31, 2012) or patients being lost
to follow-up because of emigration.

Anticoagulant and Antiplatelet Treatment
Riksstroke contains information on anticoagulant and antiplatelet
treatment at hospital discharge. The first registered dispensed pre-
scription, 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 ther-
apy (vitamin K antagonists and direct oral anticoagulants), the fol-
lowing 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 antplatelet 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 Riksstroke or having
had a dispensed prescription 6 months before the index ICH.

Comorbidty
The diagnosis of AF (ICD-10 I14) was based on registry data in
Riksstroke or a diagnosis of AF before the ICH in the Inpatient
Register. Hypertension was defined as being on antihyperten-
sive treatment in Riksstroke 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 treat-
ment. 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], dia-
betes 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 hos-
pital. 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
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 <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.  

### Results

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, 58.9% claimed a prescription within 3 months.

### 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.
The 28-day case fatality after ischemic stroke was 17.5% compared with 37.5% after recurrent hemorrhagic stroke ($P<0.001$, chi-square 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.
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 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 not could 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 events.8,9,25 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 stroke28 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 definitive 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.

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Disclosures
Dr Pennlert has served on a scientific advisory board for Boehringer-Ingelheim. The other authors report no conflicts.

References


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## SUPPLEMENTARY MATERIAL

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Supplementary Methods.

**Table I.** List of ICD-codes used to define outcome variables.

**Severe hemorrhagic outcome events**

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<td>Recurrent intracerebral hemorrhage</td>
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Data below derived from the Swedish Cause of Death register:

**Intracranial**

- Subarachnoidal hemorrhage: I60
- Subdural hemorrhage: I62
- Epidural hemorrhage: G95.1

**GI-tract**

- Oesophageal hemorrhage: I850, I983
- Gastro-oesophageal laceration-hemorrhage syndrome: K22.6
- Ulcer with hemorrhage/Duodenal hemorrhage: K25-28 only subcodes 0-2, 4-6
- Unspecified GI-hemorrhage: K922
- Haemorrhoidal bleeding: I841, I858, I844
- Hemorrhage of anus and rectum: K625
- Haematemesis: K920
- Melena: K921
- Haemoperitoneum: K66.1
- Acute hemorrhagic gastritis: K29.0

**Joint**

- Haemarthrosis: M250

**UG tract**

- Hemorrhage of prostate: N421
- Other uterine/vaginal bleeding: N93.8-9
- Postmenopausal bleeding: N95.0
- Haematuria: R31, N02
- Haematometra: N85.7
Nose/throat/respiratory tract

Hemorrhage from throat/airways, unspecified  
R048, R049

Hemorrhage from throat  
R04.1

Hemoptysis  
R04.2

Epistaxis  
R04.0

Eye

Conjunctival hemorrhage  
H11.3

Choroidal hemorrhage  
H31.3

Retinal hemorrhage  
H35.6

Vitreous hemorrhage  
H43.1

Other bleedings

Hemopericardium  
I31.2

Anemia following major bleeding  
D629

Hemorrhage, not elsewhere classified  
R58.9

Otorrhagia  
H92.2

Hematoma of broad ligament  
N83.7

Postoperative hemorrhage  
T810

Severe thrombotic events

Ischemic stroke  
I63, from Riksstroke (fatal or non-fatal)

Data below from the Swedish Cause of Death register:

Other fatal thromboembolic events  
I21, I22, I23, I74
Table II. List of ICD-10 codes and registers used to assess comorbidity at baseline. IPR – The Swedish Inpatient register, RS – Riksstroke – the Swedish Stroke Register, SDDR – the Swedish Dispensed Drug Register.

<table>
<thead>
<tr>
<th>Baseline covariates</th>
<th>ICD-10 code(s) and register origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>I48 RS or IPR</td>
</tr>
<tr>
<td>Stroke severity</td>
<td>RS - 3 levels</td>
</tr>
<tr>
<td>Ischemic Stroke/TIA</td>
<td>I63, G45 or RS</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>I63, IPR</td>
</tr>
<tr>
<td>History of VTE</td>
<td>I26, I80 (except 180.0) O87.1, O22.3, O22.5, I81, I82, IPR</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>I20 (except I20.1), I21 I22 I23 I24 I25.2, IPR</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>I65, I70-73 (except 171.1, 171.2, I73.0, I73.1, I73.8, I73.8A, I73.8B, I73.8C, I73.8D, I73.8W and I73.9A), IPR</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>I05-08, I09.1, I34-39, Z95.2, Z95.3, Z95.4, I342, I050, Q232, procedure codes FG, FJE, FJF, FK, FM, IPR</td>
</tr>
<tr>
<td>Hypertension</td>
<td>I10-15 IPR or RS</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>E10-14, IPR or RS</td>
</tr>
<tr>
<td>Dementia</td>
<td>F00-F03, IPR</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>E78, IPR or treated with statins &lt; 6 months prior to ICH, found in the SDDR</td>
</tr>
<tr>
<td>Smoking</td>
<td>RS</td>
</tr>
<tr>
<td>ADL dependency</td>
<td>RS</td>
</tr>
<tr>
<td>Living alone</td>
<td>RS</td>
</tr>
</tbody>
</table>
Supplementary Statistical methods

Cause-specific hazards

We first built a Cox PH model of the following form for each of the three causes separately, each time treating the other events as censorings:

- a piecewise linear function of age, with turning points at the quartiles,
- a smoothing spline of AC start time, with an indicator of treatment as a time varying covariate, in three steps: 1 month, 3 months or 6 months after onset of ICH, to reduce the possibility of overfitting, the shape was constrained to be linear after 272 days after the treatment start time for AC (90th percentile),
- a smoothing spline of AP start time, with an indicator of treatment as a time varying covariate, in three steps: 1 month, 3 months or 6 months after onset of ICH, to reduce the possibility of overfitting, the shape was constrained to be linear after 482 days after the treatment start time for AP (90th percentile),
- a smoothing spline of time since hospital discharge, with linear behavior after 186 days after hospital discharge,
- a dummy coding of each of the 16 categorical variables listed under "Patient Characteristics."

Our model selection procedure started from the complete model, and used backwards selection as follows:

1. First, we removed covariates which lead to a decrease in AIC, while protecting the treatment smoothing splines as the covariates of interest, the smoothing spline for the second time-scale, and the commonly accepted risk factors of age, sex and consciousness at admission.
2. Secondly, we assessed the need for the second time-scale, time since hospital discharge.
3. Next, we reduced the complexity of the treatment effects: removing the steps (1, 3 or 6 months after onset of ICH) in the indicator of treatment for AP and AC if the reduced model had a lower AIC.
4. We further reduced the covariate effects using AIC, this time also allowing sex and consciousness to be excluded, but still protecting age, and a single smoothing spline for each treatment during the treatment period.
5. Finally, we reassessed the need for a second-time scale.

Smoothing parameters for each smoothing spline were chosen by AIC. Models were selected on the subset of patients with complete covariate information and re-fit using data from all patients with covariate information on the chosen covariates.

The cause-specific hazard ratios for the covariates without splines from these three models are shown in table III. The smoothing splines of start time of AP and AC treatments and the second time scale are shown in figures I and II, along with pointwise 95% confidence intervals. The effect of age, which was modeled as a piecewise linear function, is shown in figure III.

<table>
<thead>
<tr>
<th></th>
<th>Thrombotic events</th>
<th>Hemorrhagic events</th>
<th>Other Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% LCL</td>
<td>95% UCL</td>
</tr>
<tr>
<td>Sex: Female</td>
<td>1.31</td>
<td>1.06</td>
<td>1.61</td>
</tr>
<tr>
<td>Age (per 1 yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 73 yrs</td>
<td>1.05</td>
<td>1.01</td>
<td>1.09</td>
</tr>
<tr>
<td>&gt; 80 yrs</td>
<td>0.98</td>
<td>0.90</td>
<td>1.06</td>
</tr>
<tr>
<td>&gt; 85 yrs</td>
<td>0.97</td>
<td>0.87</td>
<td>1.09</td>
</tr>
</tbody>
</table>

Table III: Cause-specific hazard ratios with 95% confidence intervals for severe thrombotic events, hemorrhagic events and other deaths. Separate Cox proportional hazard models were built for three events with a piecewise linear function of age and a smoothing spline of start time for each of the two treatments. See figures I, II and III for a visual representation of smoothing splines of treatment start times, time since discharge and of the age effects. The table lists variables that entered into at least one of the three models: blanks in the table mean that the variable in the corresponding row did not come into the model of the corresponding column. The following variables were not significant in any model: education, living alone, venous thromboembolism, valvular disease, ischemic heart disease, statin treatment before stroke, or hospital. Data are not given on variables eliminated in the backward selection processes.
This calculation required specification of a covariate CIF each Since the baseline instantaneous hazard at risk of event hazard function for cause but event type from where of the form We followed a Cox proportional hazards Furthermore, the all given a covariate trajectory is: characteristics and time

\[ \lambda_i(u|x^*(u)) = \lambda_{0i}(u) \exp(x^*(u)\beta_i), \]

where \( \lambda_{0i}(u) \), the baseline hazard, is assumed to be independent of the covariate trajectories, and \( \exp(x^*(u)\beta_i) \) describes the effect of the covariate trajectory on the hazard at time \( u \).

The model parameter \( \beta_i \) for a given cause \( i \) was estimated by fitting a Cox PH model for \( \lambda_i(u|x^*(u)) \) on the data from \( n = 2662 \) subjects, with covariates from the model building procedure described earlier and with all events but event type \( i \) censored. Let \( \hat{\beta}_i \) denote this estimate. We used a Breslow type estimator for the cumulative hazard function for cause \( i \), \( A(t|x^*(t)) \),

\[ A_i(t|x^*(t)) = \sum_{k=1}^{n} \int_{0}^{t} \frac{\exp(x^*(u)\beta_i)dN_{i,k}(u)}{\sum_{l}^{K} Y_{i,l}(u)\exp(x^*(u)\beta_i)} \]

where \( N_{i,k}(u) \) is an indicator for event \( i \) at time \( u \) for the \( k \)th subject and \( Y_{i,l}(u) \) is an indicator for subject \( k \) being at risk of event \( i \) at time \( u \). Given \( A_i(t|x^*(t)) \) for each cause, the overall survival function was estimated as:

\[ S(t|x^*(t)) = \exp(-\sum A_i(t|x^*(t))). \]

Since the baseline instantaneous hazard \( \lambda_{i0}(u) \) is not specified in a Cox PH model, we chose to approximate each \( \lambda_i(u|x^*(u)) \) with a piecewise constant function and thus arrived at the estimate

\[ \text{CIF}_i(t|x^*(t)) = \sum_{l=1}^{M} S(u_l|x^*(u_l)) \left[ A_i(u_l|x^*(u_l)) - A_i(u_{l-1}|x^*(u_{l-1})) \right] / (u_t - u_{l-1}), \]

where \( u_0, u_1, \ldots, u_M \) is a partition of \( (0, t) \).

This calculation required specification of a covariate trajectory: we considered male and female versions of the "high risk" and "low risk" profiles described in the manuscript. In order to explore the effect of varying treatment
type and start time, we computed the cause-specific and all-cause CIFs for a range of start-times (28 to 365 days after onset of ICH, in increments of 10) and for each treatment type (AP, AC, or neither).

Confidence intervals for the cumulative incidence functions

We used a parametric bootstrap to obtain confidence intervals for the difference in CIFs for patients with and without treatment (AC or AP). A bootstrap sample dataset was created from the original set of patient characteristics as described below.

For each patient in the dataset:
1. an event time was generated from the estimated all-cause survival function using the inverse probability transform,
2. the type of event was decided using a multinomial experiment with probabilities of each event type equal to the proportions of cause-specific hazards at the event time from step 1,
3. a censoring time was generated from the Kaplan Meier estimate of survival from the observed censor times,
4. the minimum of the times in 1 and 3 was selected and the associated event type chosen.

Once a bootstrap sample dataset was created, the three Cox PH models for thrombotic events, hemorrhagic events and deaths from other causes were refit, using the bootstrapped outcomes but the same covariates as selected for the original dataset. Next, the cause-specific CIFs were estimated as for the original dataset.

The sampling distributions of the cause-specific CIFs were estimated from the above bootstrap scheme and examined via QQ-plots. Since these distributions appeared to be normal, we computed 95% confidence intervals for the estimate of the differences in CIF with and without treatment (AC or AP) at a given start time as:

\[
\text{estimate } \pm 1.96 \times \text{standard deviation (bootstrap estimates)}. 
\]

Treatment start times where a significance difference was found, i.e. regions where the CI of the difference did not include 0) are indicated by thick lines in plots of cause-specific and all-cause CIFs for the male and female versions of our high and low risk patient profiles (manuscript figure 3).

Sensitivity analysis of minimizing AC start time

We define the optimal time to start AC treatment for a given patient profile as the AC treatment start time that minimizes the sum of the CIFs of thrombotic and hemorrhagic events at 3 years after ICH: this time can be seen for our profiles of high and low risk patients by locating the time on the horizontal axis that corresponds to the minimum value of the CIF of vascular death or stroke 3 years after onset of ICH on the AC treatment curve (manuscript Figure 3). To see how this optimal time changed across patient profiles, we computed the relevant CIF curve for a series of patient profiles, starting from a profile with no risk factors, and adding the covariates shown in supplement table III one at a time until all risk factors were included. Risk factors were added in order of the magnitude of the associated cause-specific hazard ratio; four different ages were considered, one in each quartile of the observed ages, and two hospital discharge times. The resulting optimal start times were all found to be within the range of 7-8 weeks after onset of ICH. Because our model will suggest similar optimal times for profiles with risk factors that correspond to similar sums of log cause specific hazard ratios for a given event type in supplement table III (for example, the optimal start time of a profile with a single risk factor of baseline AC will be similar to a profile with a single risk factor of baseline AP), we expect this finding to be relatively robust. Supplemental Figure IV demonstrates the CIFs for two additional patient profiles.

Software

We used the statistical software R, version 3.2.1, for all calculations. The package "survival" was used to fit Cox PH models with time-varying covariates and smoothing splines. The calculations for the CIFs were programmed using the formulas mentioned before, which relied on the results of Cox PH models.
Additional figures of cause-specific instantaneous hazard functions

Figure I: Cause-specific log hazard ratios with 95% confidence intervals (CIs) as a function of start time of treatment (AC or AP).

Interpretation of figure I

Top left: the instantaneous hazard of a thrombotic event is significantly lower compared to no treatment when AC treatment was started within 12 weeks of the onset of ICH, holding all other covariates in the model constant; no difference was observed after 12 weeks. Bottom left: the instantaneous hazard of a thrombotic event was significantly higher for all patients who started AP in the year following ICH, compared to patients who did not start a treatment. Top center: no significant difference in instantaneous hazard of a hemorrhagic event was observed between patients who received AC or no treatment in the first year after ICH. Bottom center: the instantaneous hazard of a hemorrhagic event was observed to be significantly higher for patients who received AP in the first year after ICH compared with patients who received no treatment. Top right: no significant difference was found in instantaneous hazard of death from another cause in patients who received AC or no treatment. Bottom right: patients who received AP around 22 weeks after ICH had a significantly lower instantaneous hazard of death from another cause compared to those patients who received no treatment; no difference was detected when AP treatment was started at other times during the first year after ICH.
Figure I: Log hazard ratios with 95% confidence intervals (CIs) for time since hospital discharge.

**Interpretation of Figure I**

While the instantaneous hazards of hemorrhagic or thrombotic events appear to be primarily driven by time since onset of ICH, part of the hazard of death from other causes is driven by the time since hospital discharge. The hazard generally decreases as time since discharge increases.

Figure III: Cause-specific log hazard ratios for age.

**Interpretation of Figure III**

Age was included in the models as a piece-wise linear function with turning points at the observed quartiles. All three risks increase with age for younger subjects; the risk of death from other causes increases for all age groups. The observed ages ranged from 42 to 98.
Supplementary results

Table IV: Baseline characteristics of patients included in analysis (n=2619) and treatment status at 8 weeks (trtm – treatment, AC – anticoagulant, AP – antiplatelet, SD – standard deviation, ADL – activities of daily living, IS – ischemic stroke, VTE – venous thromboembolism). P-values for group comparisons between AC- and AP-treated vs non-treated patients at 8 weeks (X²-tests for categorical variables, t-test for age).

<table>
<thead>
<tr>
<th></th>
<th>No trtm at 8 weeks (n=2033)</th>
<th>AC at 8 weeks (n=97)</th>
<th>p-value</th>
<th>AP at 8 weeks (n=489)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>77.86(9.18)</td>
<td>76.62(9.01)</td>
<td>0.194</td>
<td>78.9(8.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>Female Sex</td>
<td>817(40.2)</td>
<td>39(40.2)</td>
<td>0.997</td>
<td>209(42.7)</td>
<td>0.302</td>
</tr>
<tr>
<td>Level of Education</td>
<td></td>
<td></td>
<td>0.837</td>
<td></td>
<td>0.348</td>
</tr>
<tr>
<td>Primary</td>
<td>1012(49.8)</td>
<td>45(46.4)</td>
<td></td>
<td>252(51.5)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>692(34.0)</td>
<td>35(36.1)</td>
<td></td>
<td>173(35.4)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>288(14.2)</td>
<td>14(14.4)</td>
<td></td>
<td>58(11.9)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>41(2.0)</td>
<td>3(3.1)</td>
<td></td>
<td>6(1.2)</td>
<td></td>
</tr>
<tr>
<td>Living Alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>972(47.8)</td>
<td>47(48.5)</td>
<td>0.902</td>
<td>247(50.5)</td>
<td>0.283</td>
</tr>
<tr>
<td>Missing</td>
<td>4(0.2)</td>
<td>0(0)</td>
<td></td>
<td>4(0.8)</td>
<td></td>
</tr>
<tr>
<td>ADL dependency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>238(11.7)</td>
<td>5(5.2)</td>
<td>0.047</td>
<td>58(11.9)</td>
<td>0.924</td>
</tr>
<tr>
<td>Level of consciousness*</td>
<td></td>
<td></td>
<td>0.057</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Alert</td>
<td>1514(74.5)</td>
<td>81(83.5)</td>
<td></td>
<td>404(82.6)</td>
<td></td>
</tr>
<tr>
<td>Drowsy</td>
<td>412(20.3)</td>
<td>14(14.4)</td>
<td></td>
<td>69(14.1)</td>
<td></td>
</tr>
<tr>
<td>Unconscious</td>
<td>68(3.3)</td>
<td>1(1.0)</td>
<td></td>
<td>11(2.2)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>39(1.9)</td>
<td>1(1.0)</td>
<td></td>
<td>5(1)</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>465(22.9)</td>
<td>36(37.1)</td>
<td>0.001</td>
<td>104(21.3)</td>
<td>0.446</td>
</tr>
<tr>
<td>Previous IS</td>
<td>466(22.9)</td>
<td>30(30.9)</td>
<td>0.068</td>
<td>144(29.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>VTE</td>
<td>109(5.4)</td>
<td>10(10.3)</td>
<td>0.038</td>
<td>21(4.3)</td>
<td>0.338</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>535(26.3)</td>
<td>29(29.9)</td>
<td>0.435</td>
<td>149(30.5)</td>
<td>0.064</td>
</tr>
<tr>
<td>Condition</td>
<td>Group 1</td>
<td>Group 2</td>
<td>p-value</td>
<td>Group 3</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1676(82.4)</td>
<td>85(87.6)</td>
<td>0.187</td>
<td>419(85.7)</td>
<td>0.086</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>489(24.1)</td>
<td>30(30.9)</td>
<td>0.123</td>
<td>153(31.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>155(7.6)</td>
<td>19(19.6)</td>
<td>0.000</td>
<td>39(8.0)</td>
<td>0.794</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>117(5.8)</td>
<td>7(7.2)</td>
<td>0.548</td>
<td>32(6.5)</td>
<td>0.506</td>
</tr>
<tr>
<td>Dementia</td>
<td>12(6.0)</td>
<td>0(0)</td>
<td>0.013</td>
<td>31(6.3)</td>
<td>0.778</td>
</tr>
<tr>
<td>AC at baseline</td>
<td>916(45.1)</td>
<td>77(79.4)</td>
<td>0.000</td>
<td>246(50.3)</td>
<td>0.037</td>
</tr>
<tr>
<td>AP at baseline</td>
<td>884(43.5)</td>
<td>20(20.6)</td>
<td>0.000</td>
<td>271(55.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>Both AC and AP at baseline</td>
<td>147(7.2)</td>
<td>8(8.2)</td>
<td>0.706</td>
<td>50(10.2)</td>
<td>0.027</td>
</tr>
<tr>
<td>Statins</td>
<td>527(25.9)</td>
<td>34(35.1)</td>
<td>0.046</td>
<td>162(33.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*For level of consciousness, the variables were grouped into alert, drowsy/unconscious when comparing AC treated patients to non-treated.*
**Figure IV**: Cumulative incidence functions (CIFs), adjusted for differences in patient characteristics, at three years after onset of ICH vs. start time of two treatments (AC=black line, AP=grey line) and no treatment (dashed line) for a 78-year old with hypertension and previous AC and a 78-year old with diabetes and previous AC, female/male patient 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 (grey) are significantly different from no treatment at the 5% level.
Figure V: Empirical cumulative incidence functions (CIF) in patients with AC, AP or no antithrombotic treatment 8 weeks after ICH.
Supplementary references