Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation

Effect of Anticoagulation and Its Timing: The RAF Study

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Background and Purpose—The best time for administering anticoagulation therapy in acute cardioembolic stroke remains unclear. This prospective cohort study of patients with acute stroke and atrial fibrillation, evaluated (1) the risk of recurrent ischemic event and severe bleeding; (2) the risk factors for recurrence and bleeding; and (3) the risks of recurrence and bleeding associated with anticoagulant therapy and its starting time after the acute stroke.

Methods—The primary outcome of this multicenter study was the composite of stroke, transient ischemic attack, symptomatic systemic embolism, symptomatic cerebral bleeding and major extracranial bleeding within 90 days from acute stroke.

Results—Of the 1029 patients enrolled, 123 had 128 events (12.6%): 77 (7.6%) ischemic stroke or transient ischemic attack or systemic embolism, 37 (3.6%) symptomatic cerebral bleeding, and 14 (1.4%) major extracranial bleeding. At 90 days, 50% of the patients were either deceased or disabled (modified Rankin score ≥3), and 10.9% were deceased. High CHA_2DS_2-VASc score, high National Institutes of Health Stroke Scale, large ischemic lesion and type of anticoagulant were predictive factors for primary study outcome. At adjusted Cox regression analysis, initiating anticoagulants 4 to 14 days from stroke onset was associated with a significant reduction in primary study outcome, compared with initiating treatment before 4 or after 14 days: hazard ratio 0.53 (95% confidence interval 0.30–0.93). About 7% of the patients treated with oral anticoagulants alone had an outcome event compared with 16.8% and 12.3% of the patients treated with low molecular weight heparins alone or followed by oral anticoagulants, respectively (P=0.003).

Conclusions—Acute stroke in atrial fibrillation patients is associated with high rates of ischemic recurrence and major bleeding at 90 days. This study has observed that high CHA_2DS_2-VASc score, high National Institutes of Health Stroke Scale, large ischemic lesions, and type of anticoagulant administered each independently led to a greater risk of recurrence and bleedings. Also, data showed that the best time for initiating anticoagulation treatment for secondary stroke prevention is 4 to 14 days from stroke onset. Moreover, patients treated with oral anticoagulants alone had better outcomes compared with patients treated with low molecular weight heparins alone or before oral anticoagulants. **(*Stroke*. 2015;46:2175-2182. DOI: 10.1161/STROKEAHA.115.008891.)**

Key Words: anticoagulant therapy ■ atrial fibrillation ■ hemorrhagic stroke ■ ischemic stroke ■ secondary prevention

In patients with cardioembolic stroke associated with atrial fibrillation (AF), the risk of early stroke recurrence, defined as a new event occurring within 2 weeks, has been reported to range between 0.1% and 1.3% per day.[1,2] Anticoagulant therapy has been proven to be highly effective for the secondary stroke prevention in patients with AF. However, the specific risk/balance for any given patient and which strokes have the most risk and the most benefit remains unclear. To date, randomized clinical trials have failed to produce any evidence supporting the administration of heparin in patients with acute ischemic stroke and AF within 48 hours from stroke onset.[3,4] These randomized trials were done in a much earlier era when overall stroke rates were higher and before the introduction of warfarin alternatives, such as direct oral anticoagulants.

An analysis from the VISTA database found that the early introduction of anticoagulants (2–3 days after stroke), and to a lesser extent antiplatelet agents, were associated with substantially fewer recurrent events over the following weeks without an increased risk of symptomatic intracerebral bleedings.[5]

This international prospective multicenter study in patients with acute stroke and AF evaluated at 90 days from the acute event (1) the risk of recurrent ischemic embolic event and severe bleeding (both intra and extracranial); (2) the risk factors associated with ischemic stroke recurrence, systemic embolism, and symptomatic cerebral bleeding, as well as severe extracerebral hemorrhage; and (3) the risk of recurrence and bleeding associated with anticoagulant therapy and its timing.

Methods

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation (RAF) was a prospective observational study performed between January 2012 and March 2014, which enrolled consecutive patients with acute ischemic stroke and known or newly diagnosed AF without contraindications to anticoagulation. The study was performed in 29 Stroke Units across Europe and Asia. The study was approved by the local Institutional Review Board, if required.

On admission, stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). A cerebral computed tomography examination without contrast or cerebral magnetic resonance was performed on admission in all patients to exclude intracranial hemorrhage. Thrombolysis treatment was given as per standard local protocol, when appropriate. All 29 stroke units provided standard stroke unit care and monitoring. All patients were monitored for blood pressure, temperature, glucose level, heart rate, and blood gases in the first days after stroke. Physicians were free to decide the type of anticoagulant treatment (low molecular weight heparin [LMWH] or oral anticoagulants), as well as the day to initiate it.

AF was classified as paroxysmal (episodes terminating spontaneously within 7 days), persistent (episodes lasting >7 days requiring pharmacological or electric stimulation), or permanent (persisting for >1 year, either because cardioversion failed or was not attempted).

A second brain computed tomography scan or magnetic resonance had to be performed 24 to 72 h from stroke onset in all patients. Hemorrhagic transformation (HT) was defined as any degree of hyperdensity within the area of low attenuation and was classified as either hemorrhagic infarction or parenchymal hematoma.[6,7] HT was considered symptomatic if associated with a decline in neurological status (an increase of 4 points in NIHSS) in the absence of any bleeding evidence on the first computed tomography.[8] The sites and sizes of the qualifying infarcts were determined based on standard templates[9,10]: (1) small, when a lesion was ≤1.5 cm in the anterior or posterior circulation; (2) medium, when a lesion was in a cortical superficial branch of middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery, in a cortical superficial branch of the anterior cerebral artery; (3) large anterior, when a lesion involved the complete territory of MCA, posterior cerebral artery, or anterior cerebral artery, in 2 cortical superficial branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or

in >1 artery territory (eg, MCA associated to anterior cerebral artery territories); (4) large posterior, when a lesion was ≥1.5 cm in the brain stem or cerebellum.[7]

Risk Factors

Data on known stroke risk factors were collected: age, sex, history of hypertension (blood pressure of ≥140/90 mm Hg at least twice before stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (fasting glucose level ≥126 mg/dL preprandial on 2 examinations, glucose level ≥200 mg/dL postprandial, or HbA1c ≥6.5%, or under antidiabetic treatment), current cigarette smoking, past smoking (cessation <5 years ago), hyperlipidemia (total cholesterol ≥200 mg/dL or triglyceride ≥140 mg/dL or already under lipid lowering therapy), history of symptomatic ischemic heart disease (myocardial infarction, history of angina, or existence of multiple lesions on thallium heart isotope scan or evidence of coronary disease on coronary angiography), history of symptomatic peripheral arterial disease (intermittent claudication of presumed atherosclerotic origin; or ankle/arm systolic blood pressure ratio <0.85 in either leg at rest; or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty), alcohol abuse (≥300 g per week), obesity (body mass index ≥30 kg/m^2), or previous stroke/transient ischemic attack (TIA). White matter changes (leukoaraiosis defined on the first computed tomography examination as ill-defined and moderately hypodense areas of ≥5 mm according to published criteria) were investigated.[11] Leukoaraiosis in the deep white matter was dichotomized into absent versus mild, moderate, or severe. Other baseline variables obtained at admission for all patients included fasting serum glucose, fasting serum cholesterol (total, high-density lipoprotein, and low-density lipoprotein), platelet count, International Normalized Ratios, activated thromboplastin times, systolic blood pressure, and diastolic blood pressure.

Data on the use of any antiplatelet, anticoagulants, or thrombolytic agents, before admission, at baseline, and during the follow-up period, were recorded.

The CHA_2DS_2-VASc score (2 points for a history of stroke or age ≥75 years and 1 point each for age 65 to 74 years, a history of hypertension, diabetes, cardiac failure, and vascular disease) before the index event was also calculated.[12]

Evaluation of Outcome

Patients were followed-up prospectively by face-to-face or telephone interviews. Study outcomes were (1) recurrent ischemic cerebrovascular events (stroke or TIA) and symptomatic systemic embolisms; (2) symptomatic cerebral bleedings and major extracerebral bleeding at 90 days.

The primary outcome was the composite of stroke, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding.

Disability and mortality at 90 days were also assessed using the modified Rankin score (mRS). Functional outcome was defined as either nondisabling (mRS 0–2) or disabling (mRS 3–5).

Stroke was defined as the sudden onset of a new focal neurological deficit of vascular origin in a site consistent with the territory of a major cerebral artery and categorized as ischemic or hemorrhagic. HTs found on neuroimaging 24 to 72 hours after onset were not considered outcome events, unless they were classified as being symptomatic. TIA was defined as a transient episode of neurological dysfunction caused by focal brain ischemia without acute infarction. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ confirmed by imaging, surgery, or autopsy. Major extracerebral bleeding was defined as a reduction in the hemoglobin level of at least 2 g per deciliter, requiring blood transfusion of at least 2 U, or symptomatic bleeding in a critical area or organ.[13]

Statistical Analysis

Differences in the characteristics of patients with or without outcome events were tested using χ^2 test. Specifically, univariate tests were applied to compare both clinical characteristics on admission and preexisting risk factors for stroke. An exploratory analysis of all variables was performed with a divisive hierarchical clustering method. Cluster analysis is used to construct smaller groups with similar properties from a large set of heterogeneous data. This form of analysis is an effective way to discover relationships within a large number of variables or observations; the identification of potential predictors for outcome events was subsequently made with a series of multiple logistic regression models. These variables included risk factors, reperfusion therapy, severity of stroke on admission according to NIHSS score, CHA_2DS_2-VASc score, and the dimension of the ischemic lesions. The day of starting anticoagulant treatment was inserted into the models as a continuous or a dichotomized categorical variable either.

Survival function and empirical cumulative hazards function were estimated via Kaplan–Meier estimator for various groups of patients; the differences between survival functions were tested using the Log-rank statistic (or Mantel–Haenszel test) that in the case of large samples has an asymptotic Chi-square distribution.[14]

Patients were censored at the time of an outcome event, death, or if they were lost to follow-up.

The relationship between the survival function and the set of explanatory variables were explored with Cox proportional hazard models. The Cox models provide an estimate of the treatment effect on survival after adjustment for other explanatory variables, including the different lesion size as an ordinal variable. We considered 3 anticoagulant strategies: oral anticoagulant alone, LMWH alone, or followed by oral anticoagulants. In addition, the day of starting anticoagulant therapy was treated as a time-varying covariate for the various outcomes. Also in this case, patients were censored at the time of an outcome event, death, or if they were loss to follow-up.

Furthermore, we estimated additional models to investigate for any possible effect of predictor variables on the specific day an outcome event occurred. These results were reported as a hazard ratio with a 95% confidence interval. A 2-sided P value <0.05 was considered significant.

All statistical analyses were performed using software R, version 3.0.3 (copyright (C) 2013 The R Foundation for Statistical Computing).

Results

Overall, 1037 consecutive patients were included in the study (59 from Asia). Of these, 1029 patients were included in the analysis (8 patients were excluded for incomplete data; Table I in the online-only Data Supplement).

After the acute stroke, 766 patients (74.4%) were treated with anticoagulants and 449 of them received antiplatelets before starting anticoagulants. Concerning the type of anticoagulant therapy, 113 patients (14.7%) received LMWH alone (91 after initial antiplatelet), 284 (37.1%) received vitamin K antagonists (162 after initial antiplatelet), 93 (12.1%) received direct oral anticoagulants (55 dabigatran, 30 rivaroxaban, and 8 apixaban; 62 after initial antiplatelet), and 276 (36.0%) received LMWH followed by vitamin K antagonists (134 after initial antiplatelet). Patients who received LMWH for prophylaxis of venous thromboembolism were not considered to have been treated with anticoagulants.

The mean NIHSS scores on admission were 11.9±7.6 for patients treated with LMWH alone, 6.9±5.9 for those treated with LMWH followed by oral anticoagulants, and 8.3±6.5 for those treated with oral anticoagulants alone.

Of the 263 patients who did not receive anticoagulant treatment, 231 (87.8%) were treated with antiplatelets and 32 did not receive any antithrombotic therapy over the 90-day study period.

The clinical characteristics of the patients treated and not treated with anticoagulants after the acute stroke are listed in Table II in the online-only Data Supplement. Patients not treated with anticoagulants after the acute stroke were on average older and had larger lesions and higher NIHSS on admission compared with patients treated with anticoagulants.

HT on neuroimaging performed 24 to 72 hours after stroke onset was shown in 134 patients (13.0%): 91 (8.8%) had hemorrhagic infarction and 43 (4.2%) had parenchymal hematoma. Of the 230 patients (22.4%) receiving reperfusion therapy (intravenous or intra-arterial reperfusion procedures or the combination of both), 37 (16.1%) had HT (8 symptomatic), which included 23 (10.0%) hemorrhagic infarction and 14 (6.1%) parenchymal hematoma. Overall, 26 out of 37 patients received anticoagulation after the HT.

At 90 days, 1019 patients were available for the final functional outcome analysis (10 patients were lost at follow-up): 510 (50.0%) patients were deceased or disabled (mRS≥3), whereas 111 (10.9%) were deceased.

Risk of Recurrent Ischemic Events or Bleedings

One hundred twenty-three patients had 128 (12.6%) outcome events: 77 (7.6%) had ischemic stroke or TIA or systemic embolism, 37 (3.6%) had symptomatic intracranial bleedings, and 14 (1.4%) had major extracerebral bleeding. The mean times from index stroke to recurrent ischemic stroke, symptomatic intracranial hemorrhage, TIA, and systemic embolism were 34.2±31.4, 22.5±60.8, 43.3±37.9, and 36.7±36.3 days, respectively. The clinical characteristics of the patients with and without outcome events are listed in Table III in the online-only Data Supplement.

Ninety patients of the 766 (11.7%) who received anticoagulants had an outcome event compared with 38 of the 263 (14.4%) who did not receive anticoagulation (P=0.22; Figure I in the online-only Data Supplement): 41 (5.4%) compared with 10 (3.8%) had a hemorrhagic event (P=0.31) and 49 (6.4%) compared with 28 (10.6%) had an ischemic event (P=0.023).

Six patients of the 93 patients (6.4%) treated with direct oral anticoagulants had an outcome event: 2 (2.1%) had symptomatic intracranial bleeding and 4 (4.3%) an ischemic event.

The mean times of starting treatment from the index events were 8.5±12.2 days for patients treated with direct oral anticoagulants, 6.5±10.9 days for patients treated with LMWH, and 12.1±15.8 days for patients treated with vitamin-K antagonist (International Normalized Ratios ≥2).

Risk Factors Associated With the Risk of Recurrent Ischemic Events or Bleedings

The risk of an outcome event (ischemic or hemorrhagic) within 90 days increased with an increase in the CHA_2DS_2-VASc score: patients with score of 2 had no events; score of 3 a rate of 1.7%; score of 4 of 9.8%, score of 5 of 10.2%, score of 6 of 12.3%; score of 7 of 17.0%, and scores of 8 of 20.3%.

From multivariate analysis, high CHA_2DS_2-VASc score, high NIHSS (as continuous or categorical variable), large lesion size, and type of anticoagulant used after the index stroke were predictive factors for the composite primary study outcome event (Table IV in the online-only Data Supplement). Regarding the type of anticoagulant, patients treated with oral anticoagulants alone had a better outcome compared with those treated with LMWH followed by oral anticoagulants or with LMWH alone. This last treatment led to a significantly higher risk of outcome events compared with the other treatments. About 7% of the patients treated with oral anticoagulants alone had an outcome event compared with 16.8% and 12.3% of those treated with LMWHs alone or followed by oral anticoagulants, respectively (P=0.003; Figure 1). Excluding patients with TIA from outcome event, we observed similar results (Figure II in the online-only Data Supplement). Other predictive factors for hemorrhagic events were large lesion and the administration of anticoagulants 14 to 30 days after stroke onset. Moreover, old age and large lesion size were predictive factors for ischemic outcome events (Table IV in the online-only Data Supplement).

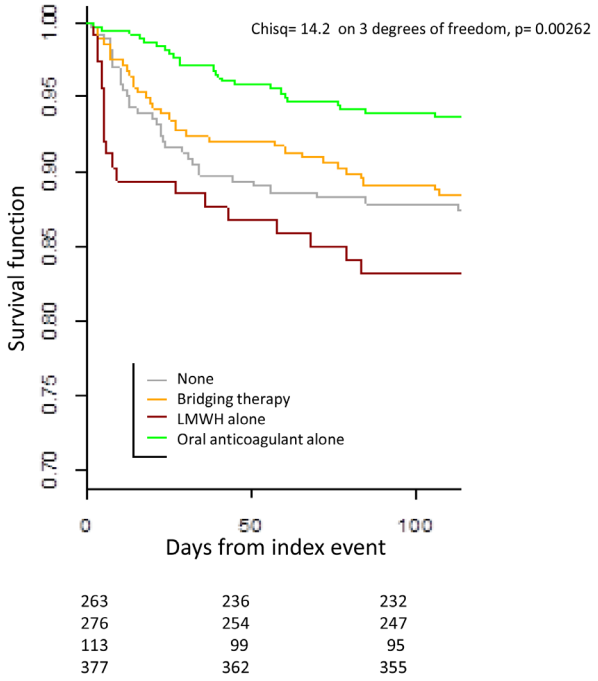
Poststroke Anticoagulation and the Risk of Recurrent Ischemic Events or Bleedings

The unadjusted analysis that evaluated the risk of primary study outcome associated with the day of initiating anticoagulant treatment is reported in Figure IIIA in the online-only Data Supplement. Patients treated with vitamin K antagonists were considered as treated with anticoagulants on the day International Normalized Ratios was ≥2. The lowest risk was observed in patients treated with anticoagulants from day 5 to day 10. Figure IIIB in the online-only Data Supplement reports the unadjusted risk of either an ischemic or hemorrhagic outcome event associated with the day of initiating anticoagulant treatment. The risk of an ischemic event remained stable up to day 15. The lowest risk of a hemorrhagic outcome event was seen from day 5 to day 10.

Based on the results of this unadjusted analysis, we selected the following time-periods for administering anticoagulant therapy to perform an adjusted analysis using the Cox regression model: within 7 days, within 14 days, and between 2 and 14 days. This analysis, adjusted for age, sex, CHA_2DS_2-VASc score, lesion size, reperfusion therapy, and NIHSS on admission, suggested that patients who had been initiated treatment with anticoagulants between 4 and 14 days had a significant reduction in primary study outcome and in ischemic events compared with patients who initiated their treatments before 4 or after 14 days from stroke onset (Figure 2A and 2B). Likewise, anticoagulant treatment initiated between 4 and 14 days also led to a reduction in cerebral bleeding, but this difference was not statistically significant (Figure 2C). Table reports that paring down this treatment period as spread in single day increments reveals that the lowest risk, considering hazard ratios, was between days 12 to 14.

Table also describes the results of the Cox regression analysis for patients treated with anticoagulants within 7 days from their index events compared with those patients treated after 7 days and for patients treated with anticoagulants within 14 days from their index events compared with patients treated after 14 days.

The Cox proportional hazard model corrected for age, sex, CHA_2DS_2-VASc score, and lesion size where the day starting the anticoagulant therapy was treated as a time-varying covariate



Bridging therapy: LMWH (Low Molecular Weight Heparin) followed by oral anticoagulant

Figure 1. Kaplan–Meier survival curves for patients treated with different types of anticoagulation strategies with numbers at risk during various time intervals (outcome event: combination of stroke, transient ischemic attack, symptomatic intracranial hemorrhage, systemic embolism). LMWH indicates low molecular weight heparins.

confirmed that a late start of the anticoagulant therapy determined an increase of the average level of risk for an outcome event (hazard ratio =3.156; 95% confidence interval, 1.924–5.176; $P<0.0001$; Table V in the online-only Data Supplement).

Type of Anticoagulant Administered and the Risk of Recurrent Ischemic Events or Bleedings Associated With the Day of Initiating Anticoagulant Treatment

The different risks of the combined outcome events associated with the day of initiating and type of anticoagulant treatment administered are reported in the Figure 3. A lower risk was seen in patients treated with oral anticoagulant alone, and the graph of Figure 3A indicates the best time for initiating it for secondary stroke prevention seems to be 4 to 14 days from stroke onset. The graphs in the Figures IV and V in the online-only Data Supplement evidence the different risks associated with the day of initiating anticoagulant treatment in patients on different types of anticoagulant for ischemic and hemorrhagic outcome events. Moreover, the graph in the Figure V in the online-only Data Supplement suggests that patients treated with LMWH alone or before warfarin had increased risks of symptomatic intracranial bleeding when treatment was initiated in the first days from index event.

Regarding functional outcome at 90 days from index event, 39.7% (149/375) of patients receiving oral anticoagulants alone were either deceased or disabled (mRS≥3) compared with 72.3% (81/112) and 32.6% (89/273) of those receiving LMWH alone or followed by oral anticoagulants. Among patients not receiving anticoagulant therapy, 73.7% (191/259) were either deceased or disabled.

Lesion Size and the Risk of Recurrent Ischemic Events or Bleedings Associated With the Day of Initiating Anticoagulant Treatment

Large lesion size was associated with higher risks of study outcome events (Figure VI in the online-only Data Supplement).

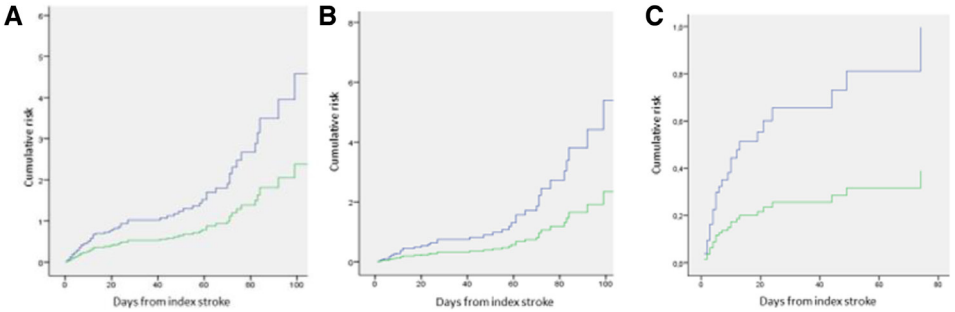


Figure 2. A, All outcome events in patients treated with anticoagulants between days 4 and 14, compared with the other treated patients. Hazard Ratio (HR)=0.53 (0.30–0.93), $P=0.025$. **B**, Ischemic outcome events (stroke, transient ischemic attack, systemic embolism) in patients treated with anticoagulants between days 4 and 14, compared with the other treated patients. HR=0.43 (0.19–0.97), $P=0.043$. **C**, Symptomatic cerebral bleedings in patients treated with anticoagulants between days 4 and 14, compared with the other treated patients. HR=0.39 (0.12–1.19), $P=0.09$. Green, anticoagulation between 4 and 14 days from stroke onset; blue, other treated patients (treatment before 4 or after 14 days).

Table. Hazard Ratios (HR) of Patients Initiating Anticoagulants: Between Days 4 to 13 and 14 Days From Stroke Onset, Within 7 Days From the Acute Event Compared With the Patients Treated After 7 Days, and Within 14 Days From the Acute Stroke Compared With the Patients Treated After 14 Days

Time of Initiating Anticoagulant Treatment	All Outcome Events, HR (95% CI)	Ischemic Outcome Events, HR (95% CI)	Hemorrhagic Outcome Events, HR (95% CI)
Within 7 days	1.35 (0.82–2.22)	1.19 (0.76–1.81)	1.72 (0.75–4.00)
Within 14 days	0.71 (0.47–2.50)	0.61 (0.35–1.06)	1.81 (0.75–4.00)
Between 2 and 14 days	0.67 (0.39–1.14)	0.59 (0.27–1.29)	0.72 (0.29–1.78)
Between 3 and 14 days	0.58 (0.33–1.03)	0.50 (0.23–1.12)	0.51 (0.18–1.47)
Between 4 and 14 days	0.53 (0.30–0.93)	0.43 (0.19–0.97)	0.39 (0.12–1.19)
Between 5 and 14 days	0.47 (0.25–0.87)	0.40 (0.17–0.86)	0.33 (0.10–1.15)
Between 6 and 14 days	0.42 (0.22–0.81)	0.30 (0.11–0.80)	0.37 (0.10–1.37)
Between 7 and 14 days	0.43 (0.23–0.83)	0.25 (0.10–0.65)	0.42 (0.11–1.51)
Between 8 and 14 days	0.42 (0.21–0.87)	0.24 (0.08–0.69)	0.56 (0.15–2.12)
Between 9 and 14 days	0.43 (0.21–0.86)	0.22 (0.07–0.62)	0.48 (0.13–1.78)
Between 10 and 14 days	0.30 (0.13–0.71)	0.18 (0.05–0.63)	0.20 (0.02–1.75)
Between 11 and 14 days	0.29 (0.12–0.71)	0.16 (0.05–0.56)	0.24 (0.03–1.77)
Between 12 and 14 days	0.21 (0.08–0.57)	0.12 (0.03–0.45)	0.27 (0.03–2.17)
Between 13 and 14 days	0.38 (0.13–1.08)	0.21 (0.05–0.85)	0.36 (0.04–3.22)
Day 14	0.38 (0.13–1.11)	0.20 (0.05–0.85)	0.36 (0.04–3.22)

The risks for the combined study outcome events associated with the day of initiating anticoagulant treatment in patients with small or large lesions are reported in Figure 4. Large lesion size was associated with higher risks of study outcome events when anticoagulation was administered within 30 days compared with small lesion size, where the risks associated

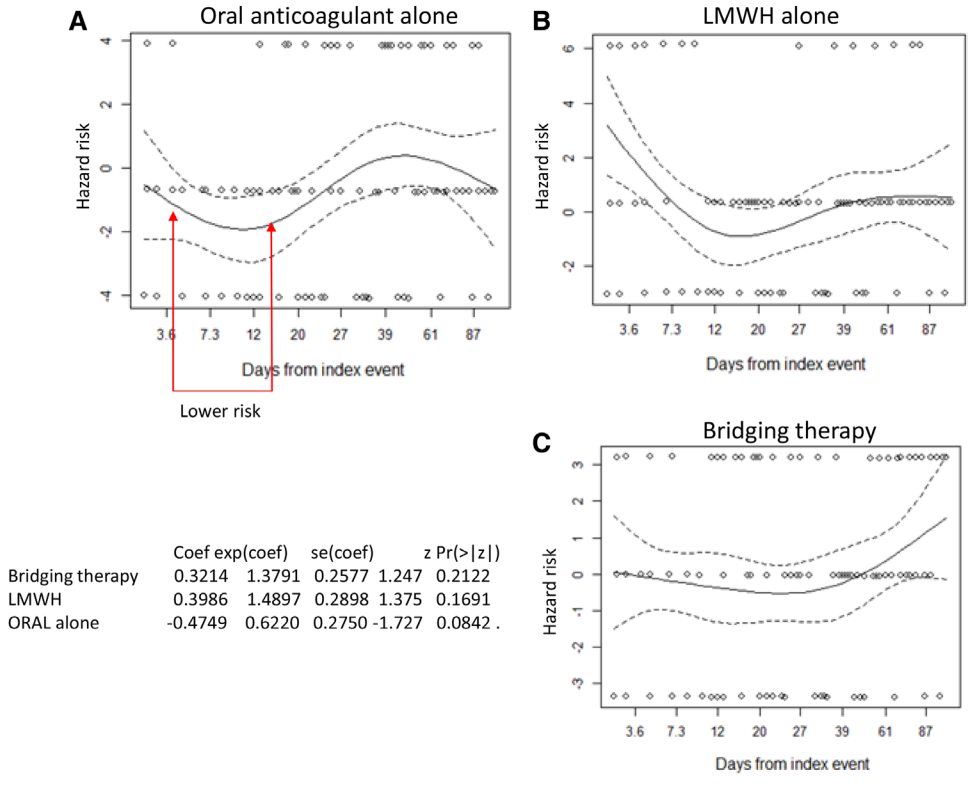


Figure 3. The different risks of the combined outcome events associated with the day of initiating anticoagulant treatment in patients treated with different types of anticoagulant therapy (**A**, oral anticoagulant alone; **B**, low molecular weight heparin alone; **C**, bridging therapy, low molecular weight heparin followed by oral anticoagulants) in a Cox proportional hazard model in which anticoagulant therapy was treated as a time-varying covariate. Hazard risk curves are expressed in terms of standardized residuals from the estimated proportional hazard fitted values.

with the latter remained stable over the study period. The risks for the ischemic study outcome events associated with the day of initiating anticoagulant treatment in patients with small or large lesions are reported in the Figure VII in the online-only Data Supplement.

Discussion

In this study, patients with acute stroke and AF had a 90-day risk of recurrent event equal to 7.6% and a rate of symptomatic cerebral bleeding equal to 3.6%. Our results indicate that initiating anticoagulant treatment between day 4 and day 14 from the acute ischemic stroke is both safe and effective, compared with starting treatment before or after this period.

Usually, the time when to start anticoagulation is based on the size of the lesion, which is considered the main risk factor for HT.[15] In this study, multivariate analysis revealed that large lesions were associated with high rates of symptomatic cerebral bleeding, as well as of stroke recurrence. Indeed, patients with small ischemic lesions could have had underlying etiologies other than cardioembolism, including small vessel disease, which is associated with a lower risk of recurrence.[16] It is plausible that initiating anticoagulation therapy earlier in patients with small lesions and later in patients with large lesions may lead to better safety, but less benefit regarding efficacy. However, In the PRoFESS trial population, in approximately half of the cases with index cardioembolic or small artery disease stroke subtypes, recurrent stroke subtype was the same as the index event.[17] Therefore, it would be reasonable to decide when to start anticoagulation treatment primarily based on the patient CHA_2DS_2-VASc score. Indeed, in our study, a CHA_2DS_2-VASc of 4 was associated with a risk of primary study outcome at 90 days as high as 10%, and this rate increased linearly with an increase in the CHA_2DS_2-VASc score.

In this study, 14.7% of the patients received LMWH alone, 37.8% received vitamin K antagonists, 12.1% received direct oral anticoagulants, and 36.0% received LMWH followed by vitamin K antagonists (bridging therapy). It was found that patients who had received oral anticoagulants alone had a significantly lower risk of bleeding events, compared with patients treated with LMWH followed by oral anticoagulants or LMWH alone; this last regimen was associated with the highest risk of bleeding. This finding may be related to the fact that patients with more severe stroke were more likely to have dysphagia and less likely to have been treated with oral anticoagulants.

Patients who received a direct oral anticoagulant were found to have low risks for both symptomatic intracranial bleeding (2.1%) and ischemic event (4.3%), suggesting the need for further testing these new drugs in the acute phase of ischemic stroke in patients with AF.[18] However, it cannot be excluded that low-risk patients might have been selected for this treatment strategy.

Our study has several limitations. First, the reported associations in our nonrandomized study were undoubtedly influenced by numerous potential confounders, even if adjusted statistical models were used to reduce them. Second, both central adjudication of the outcome events and centralization of vascular imaging for measurement of the ischemic lesions were not performed. Third, a possible bias in the ascertainment of recurrent strokes versus asymptomatic intracranial hemorrhage depending on antithrombotic status could be present given the lack of blinding. Finally, we cannot exclude the possibility that there was a selection bias regarding the starting time of antithrombotic therapy. In fact, most patients either elderly or with severe stroke were not given treatment or received it later compared with more stable patients.

The strengths of our study include its adequate sample size and its prospective design. Our findings reflect real-life experiences and, in view of the complete absence of any randomized data, may provide critical observational information that could assist stroke physicians in better managing acute cerebral ischemia in patients with AF.

In conclusion, this study found that patients with acute stroke and AF have high risks for both ischemic embolic recurrence and severe bleeding at 90 days. Furthermore, this study

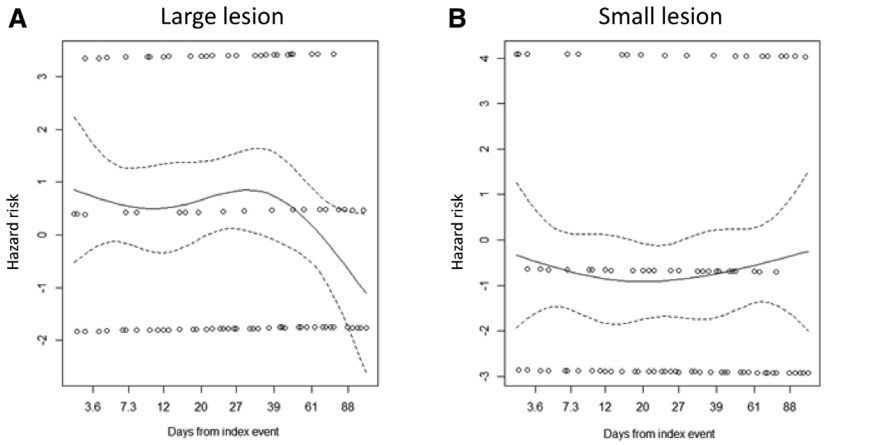


Figure 4. The different risks of the combined outcome events associated with the day of initiating anticoagulant treatment in patients with small or large lesion in a Cox proportional hazard model where anticoagulant therapy was treated as a time-varying covariate. Hazard risk curves are expressed in terms of standardized residuals from the estimated proportional hazard fitted values.

suggests that the best time for initiating anticoagulation treatment as secondary prevention of stroke is 4 to 14 days from the acute event. Moreover, patients treated with oral anticoagulants alone had better outcomes compared with those treated with LMWH alone or before oral anticoagulants. Likewise, patients with large ischemic lesions had higher increased risks of both embolic recurrence and cerebral bleeding, compared with patients with small lesions. A future randomized study assessing for the efficacy of direct oral anticoagulants in the acute phase of stroke in patients with AF is warranted.

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Disclosures

M. Paciaroni received honoraria as a member of the speaker bureau of Sanofi-Aventis, Boehringer Ingelheim, Bayer and Pfizer. G. Agnelli received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer. C. Becattini received honoraria as a member of the speaker bureau of Bristol Meyer Squibb and Bayer. P. Michel received Research Grant by Swiss National Science Foundation and Swiss Heart Foundation; he received speaker fees by Bayer, Boehringer Ingelheim, Covidien, St. Jude Medical; he received honoraria as advisory relationship by Pierre-Fabre, Bayer, Bristol Meyer Squibb, Amgen, and Boehringer Ingelheim. J. Putaala received honoraria for lectures related to atrial fibrillation and anticoagulants for Orion Pharma, Bristol Meyer Squibb, Pfizer, Bayer, and Boehringer Ingelheim. T. Tatlisumak received honoraria as consultant or advisory relationship by Lundbeck and Boehringer Ingelheim. G. Tsivgoulis had research support by European Regional Development Fund, Project St. Anne´s University Hospital, Brno, International Clinical Research Center (FNUSA-ICRC) (No. CZ.1.05/1.1.00/02.0123). D. Toni received honoraria as a member of speaker bureau and as advisory board of Boehringer Ingelheim and Bayer. The other authors report no conflicts.

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SUPPLEMENTAL MATERIAL

Supplemental Table I: Characteristics of the patients

	n=1029
Age (yr, Mean)	77.2±9.5
Male sex	468 (45.5%)
CHA_2DS_2-VASc score before the index event	
0	17 (1.7%)
1	54 (5.2%)
2	91 (8.9%)
3	200 (19.4%)
4	243 (23.6%)
5	206 (20.0%)
6	129 (12.5%)
7	66 (6.4%)
8	20 (1.9%)
9	3 (0.3%)
NIHSS score (Mean)	9.2±7.3
Cholesterol (mg/dL) Mean	180.6±42.7
Hypertension	821 (79.8%)
Hyperlipidemia	332 (32.3%)
Diabetes mellitus	264 (25.7%)
Alcoholism	68 (6.6%)
History of stroke/TIA	266 (7.3%)
Current smoker	75 (18.5%)
Previous use of antiplatelets	466 (45.3%)
Previous use of anticogulants	289 (28.1%)
Previous use of statins	260 (25.3%)
History of congestive heart failure	193 (18.7%)
History of myocardial infarction	166 (16.1%)
History of peripheral artery disease	92 (8.9%)
Pacemaker	85 (8.3%)
Atherosclerosis*	231 (2.4%)
Paroxysmal AF	363 (35.3%)
Permanent AF	474 (46.1%)
Persistent AF	192 (18.6%)
Lesion site and size	
Small lesion	381 (37.0%)
Medium Lesion	369 (35.9%)
Large anterior lesion	220 (21.4%)
Large posterior lesion	59 (5.7%)
Leukoaraiosis	426 (41.4%)
IV thrombolysis/IA procedures	230 (22.3%)
Therapy with anticoagulants after index stroke	766 (74.4%)**
LMWH	113 (11.0%)
Oral anticoagulants (warfarin/DOA)	255 (24.8%)
LMWH followed by oral anticoagulants	276 (26.8%)

* Presence of internal carotid/vertebral artery stenosis ≥50%

** 62 (8%) also received antiplatelets after the initiation of anticoagulation and during their follow-up

IQR = interquartile range

DOA = direct oral anticoagulants

LMWH = low molecular weight heparin

Supplemental Table II. Differences between patients treated and non-treated with anticoagulants after the index stroke

-	Treated with anticoagulants (n=766)	Non-treated (n=263)	p
Age (yr, Median) (IQR)	77 (71-82)	83 (76-88)	0.0001
Male sex	367 (47.9%)	101 (38.4%)	0.01
NIHSS score Median (IQR)	6 (3-12.5)	11 (4-18)	0.0001
Cholesterol (mg/dL) Mean	180.6±43.0	180.2±41.7	0.89
Hypertension	608 (79.4%)	213 (80.1%)	0.17
Hyperlipidemia	254 (33.1%)	78 (29.6%)	0.48
Diabetes mellitus	187 (24.4%)	77 (29.3%)	0.83
Alcoholism	55 (7.2%)	13 (4.9%)	0.25
History of stroke/TIA	190 (24.8%)	76 (28.9%)	0.12
Current smoker	61 (8.0%)	14 (5.3%)	0.79
Previous use of antiplatelets	323 (42.2%)	143 (54.4%)	0.0001
Previous use of anticogulants	253 (33.0%)	36 (13.7%)	0.0001
Previous use of statins	196 (25.6%)	64 (24.3%)	0.86
History of congestive heart failure	142 (18.5%)	51 (19.3%)	0.71
History of myocardial infarction	123 (16.0%)	43 (16.3%)	0.77
History of peripheral artery disease	78 (10.2%)	14 (5.3%)	0.02
Pacemaker	59 (7.7%)	26 (9.8%)	0.29
Atherosclerosis*	172 (17.2%)	59 (22.4%)	0.79
Paroxysmal AF	271 (35.2%)	92 (34.9%)	0.83
Permanent AF	350 (45.9%)	124 (47.1%)	0.72
Persistent AF	145 (18.%)	47 (17.9%)	0.71
Lesion site and size			
Small lesion	317 (41.3%)	63 (23.9%)	0.0001
Medium Lesion	277 (36.2%)	91 (34.6%)	0.65
Large anterior lesion	130 (17.0%)	90 (34.2%)	0.001
Large posterior lesion	43 (5.6%)	16 (6.0%)	0.76
Leukoaraiosis	298 (38.9%)	128 (48.7%)	0.004
IV thrombolysis/IA procedures	188 (24.5%)	42 (16.9%)	0.005

* Presence of internal carotid/vertebral artery stenosis ≥50%

IQR = interquartile range

Supplemental Table III. Differences between patients with and without study outcome events

	Patients with outcome events (n=123)	Patients without outcome events (n=906)	p
Age (yr, Median) (IQR)	81 (74-85)	78 (72-81)	0.04
Male sex	48 (39.0%)	420 (46.3%)	0.14
NIHSS score Median (IQR)	10 (3-17)	7 (2-11)	0.004
Cholesterol (mg/dL) Mean	176.8±45.7	181.0±42.3	0.32
Hypertension	107 (87.0%)	714 (78.8%)	0.05
Hyperlipidemia	39 (31.7%)	293 (32.3%)	0.83
Diabetes mellitus	43 (34.9%)	221 (24.4%)	0.016
Alcoholism	9 (7.3%)	59 (6.5%)	0.70
History of stroke/TIA	30 (24.4%)	236 (26.0%)	0.74
Current smoker	6 (4.9%)	69 (7.6%)	0.26
Previous use of antiplatelets	56 (45.5%)	410 (45.3%)	0.10
Previous use of anticogulants	36 (29.3%)	253 (27.9%)	0.83
Previous use of statins	34 (27.6%)	226 (24.9%)	0.58
History of congestive heart failure	30 (24.4%)	163 (18.%)	0.10
History of myocardial infarction	24 (19.5%)	142 (15.7%)	0.30
History of peripheral artery disease	20 (16.3%)	72 (7.9%)	0.006
Pacemaker	18 (14.6%)	67 (7.3%)	0.01
Atherosclerosis*	31 (25.2%)	200 (22.1%)	0.6
Paroxysmal AF	39 (31.7%)	325 (35.8%)	0.36
Permanent AF	56 (45.5%)	418 (46.1%)	0.92
Persistent AF	28 (22.8%)	163 (18.0%)	0.21
Lesion site and size			
Small lesion	26 (21.1%)	354 (39.1%)	0.0001
Medium Lesion	53 (43.1%)	315 (34.8%)	0.09
Large anterior lesion	39 (31.7%)	181 (19.9%)	0.005
Large posterior lesion	4 (3.2%)	55 (6.0%)	0.30
Leukoaraiosis	61 (49.6%)	365 (40.3%)	0.06
IV thrombolysis/IA procedures	27 (21.9%)	203 (22.4%)	0.9
Therapy with anticoagulants after index stroke	86 (69.9%)	680 (75.0%)	0.22
LMWH	19 (15.4%)	94 (10.3%)	0.01
Oral anticoagulants (warfarin/DOA)	25 (20.3%)	353 (38.9%)	0.0001
LMWH followed by oral anticoagulants	34 (27.6%)	242 (26.7%)	0.26

* Presence of internal carotid/vertebral artery stenosis ≥50%

IQR = interquartile range

DOA = direct oral anticoagulants

LMWH = low molecular weight heparin

Supplemental Table IV. Multivariate proportional hazard-models. Estimated Hazard Ratio (H.R.) for factor variable represent change in hazard with respect to the referring level of the variable.

Variable	Estimated H.R.	Std. Error	Z-value	P-value
Predictive factors for any outcome event				
NIHSS score (continuous variable)				
	0.0351	0.0130	2.654	0.0079
NIHSS (categorical variable. NIHSS 0-2 = reference)				
NHISS (3-7)	1.7350	0.3251	1.695	0.0901
NHISS (7-14)	1.8621	0.3300	1.884	0.0596
NHISS (14-40)	2.1589	0.3193	2.410	0.0159
Lesion size (Large = reference)				
Medium	0.6765	0.2408	-1.623	0.1050
Small	0.3099	0.2809	-4.170	<0.0001
CHA_2DS_2-VASc score				
	1.2660	0.0766	3.080	0.0021
Type of treatment with anticoagulants (bridging therapy [LMWH followed by oral anticoagulants] = reference)				
LMWH*	1.8846	0.3111	1.169	0.2424
No AC**	1.0212	0.2611	0.080	0.9359
Oral AC***	0.4839	0.2794	-2.598	0.0094
Treatment with anticoagulants (dummy variable)				
	0.7789	0.2216	-1.128	0.2590
Predictive factors for ischemic outcome event (stroke – TIA – systemic embolism)				
Age	1.0645	0.0207	3.023	0.0025
Small size (dummy variable)	0.4398	0.3475	-2.364	0.0181
Predictive factors for hemorrhagic outcome events (symptomatic cerebral bleedings combined with serious extra-cerebral hemorrhage)				
Small size (dummy variable)	0.3983	0.4431	-2.078	0.0377
Type of treatment with anticoagulants (bridging therapy [LMWH followed by oral anticoagulants) = reference]				
LMWH*	2.4542	0.3934	2.282	0.0225
Oral AC***	0.7918	0.4590	-2.687	0.0072
Time of initiation of anticoagulants (categorical variable. Within 3 days = reference)				
Days (3-7)	0.6081	0.6448	-0.771	0.4405
Days (8-14)	1.3089	0.5053	0.533	0.5942
Days (15-30)	3.9224	0.4453	3.069	0.0021
Days (31-90)	0.3836	1.0589	-0.905	0.3655

HR = Hazard Ratio
AC = anticoagulants
*Low Molecular Weight heparin alone
** No anticoagulants
*** Oral Anticoagulants alone

Supplemental Table V. Time-dependent proportional Hazard Model. Estimated H.R. for factor variable represent change in hazard with respect to the referring level of the variable. Day of initiation is treated as a time-dependent covariate. NHISS score was discarded from the final model because its high correlation with the other control variables, especially with the lesion size. Low Molecular Weight Heparin (LMWH) therapy is also discarded from the final model because it determines a linear dependence with the other therapies and the day of initiation of anticoagulant therapy. Sex and Age are included in the model as correcting risk variables.

Variable	**Estimated H.R.**	**Standard Error**	**C.I. Lower**	**C.I. Upper**	**P-value**
Age	1.01065	0.01290	0.9854	1.0365	0.4116
Sex (females)	1.05649	0.20677	0.7045	1.5844	0.7904
Day of initiation	3.15568	0.25247	1.9240	5.1760	<0.0001
Oral anticoagulant	0.33159	0.27281	0.1943	0.5660	<0.0001
Bridging therapy	0.69680	0.26180	0.4171	1.1640	0.1676
Large lesion	1.57003	0.22465	1.0108	2.4385	0.0446
Small lesion	0.51148	0.25517	0.3102	0.8434	0.0086
CHA_2DS_2-*VASc*	1.12219	0.06396	0.9900	1.2721	0.0715

HR = Hazard Ratio
CI = Confidence Interval

N= 1029; number of events= 128

Concordance = 0.699 (se = 0.028)
Rsquare = 0.031 (max possible= 0.57)
Likelihood ratio test = 55.14 on 8 df, p=4.153e-09
Wald test = 54.24 on 8 df, p=6.202e-09
Score (log-rank) test = 55.8 on 8 df, p=3.085e-09

Legends

Supplemental Figure I: Kaplan-Meier survival curves in patients treated and not treated with anticoagulants with numbers at risk during various time intervals.

Supplemental Figure II: Kaplan-Meier survival curves for patients treated with different types of anticoagulation strategies with numbers at risk during various time intervals (outcome event: combination of stroke – symptomatic intracranial hemorrhage – Systemic embolism).

Supplemental Figure IIIa. The risk of an outcome event (red line) associated with the day of initiating anticoagulant treatment after the acute stroke (for patients treated with vitamin-K antagonist the day INR≥2 was considered). Logistic regression p=n.s.

Supplemental Figure IIIb. The risk of a study outcome event (ischemic: red line, hemorrhagic: blue line) associated with the day of initiating anticoagulant treatment after the acute stroke (for patients treated with vitamin-K antagonist the day INR≥2 was considered). Logistic regression: Hemorrhagic outcomes p=0.006; Ischemic outcomes p= n.s.

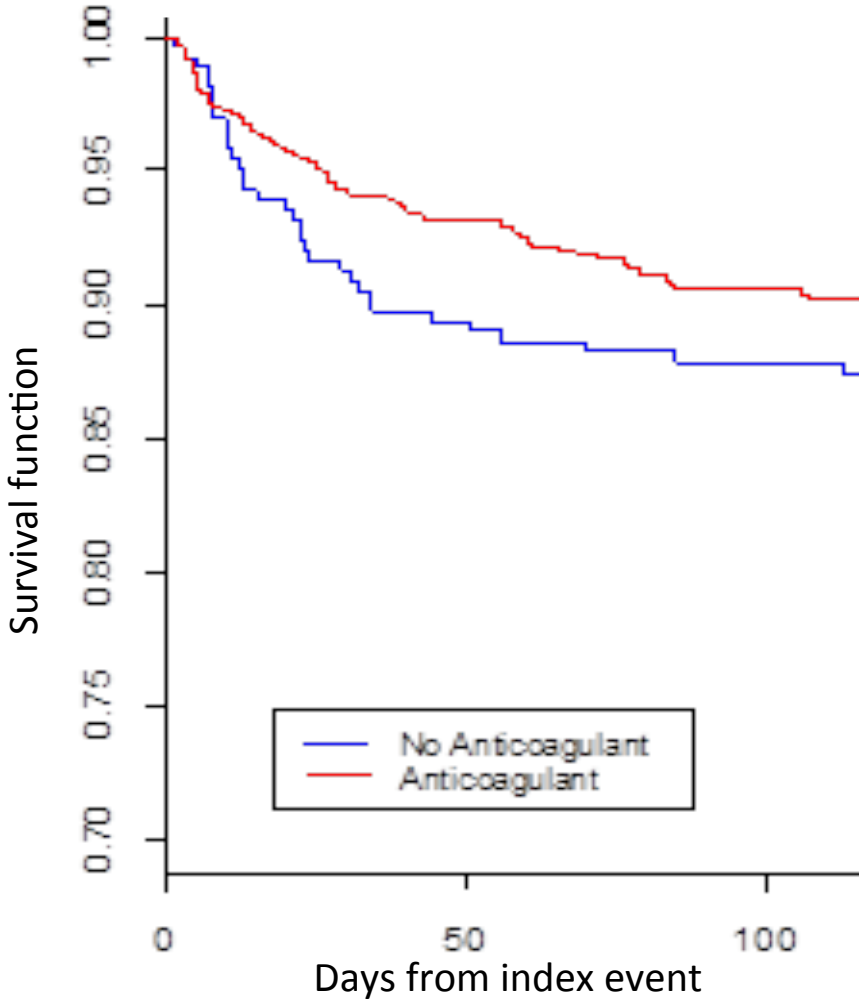
Supplemental Figure IV. The different risks of recurrent ischemic events associated with the day of initiating anticoagulant treatment in patients treated with different types of anticoagulant therapy (a: oral anticoagulant alone; b: Low Molecular Weight Heparin alone; c: bridging therapy, Low Molecular Weight Heparin followed by oral anticoagulant) in a Cox proportional hazard model where anticoagulant therapy was treated as a time-varying covariate. Hazard risk curves are expressed in terms of standardized residuals from the estimated proportional hazard fitted values.

Supplemental Figure V. The different risks of symptomatic intracranial hemorrage associated with the day of initiating anticoagulant treatment in patients treated with different types of anticoagulant therapy (a: oral anticoagulant alone; b: Low Molecular Weight Heparin alone; c: bridging therapy, Low Molecular Weight Heparin followed by oral anticoagulant) in a Cox proportional hazard model in which anticoagulant therapy was treated as a time-varying covariate. Hazard risk curves are expressed in terms of standardized residuals from the estimated proportional hazard fitted values.

Supplemental Figure VI. Kaplan-Meier survival curves for patients with small or large lesions with numbers at risk during various time intervals (outcome event: combination of stroke – TIA - symptomatic intracranial hemorrhage – Systemic embolism).

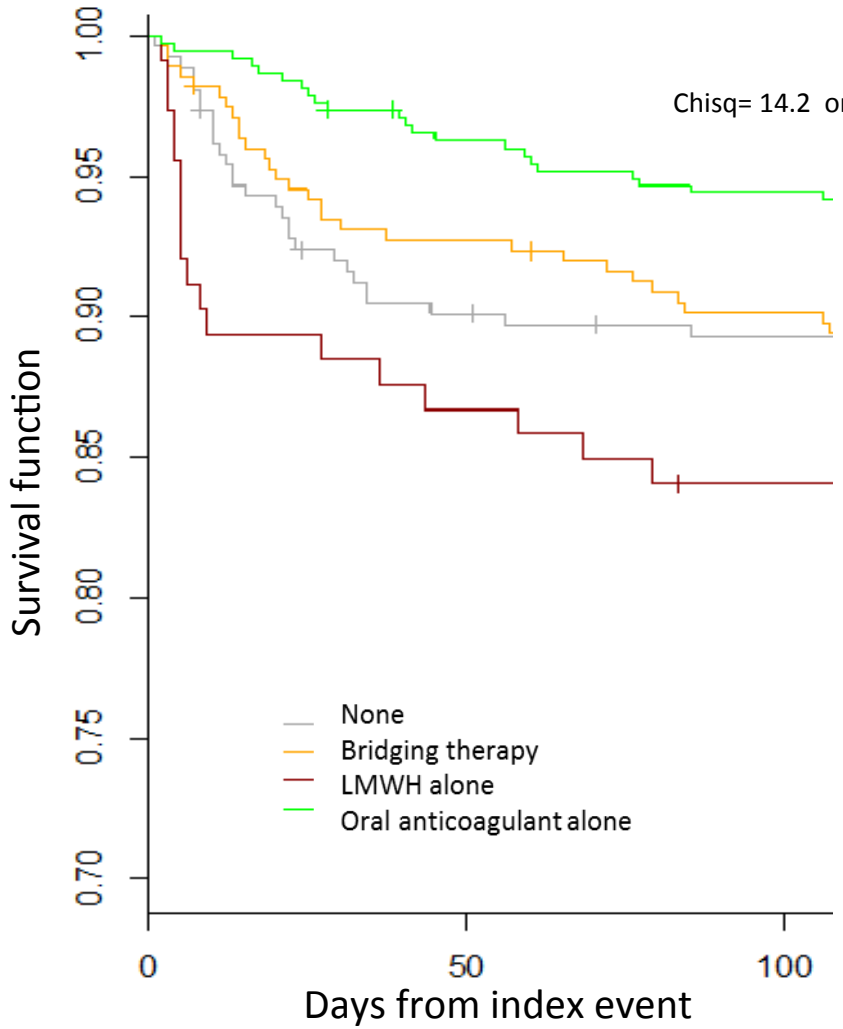
Supplemental Figure VII. The different risks of recurrent ischemic events associated with the day of initiating anticoagulant treatment in patients with small or large lesions in a Cox proportional hazard model where anticoagulant therapy was treated as a time-varying covariate. Hazard risk curves are expressed in terms of standardized residuals from the estimated proportional hazard fitted values.

Supplemental Figure I



263	235	232
766	714	695

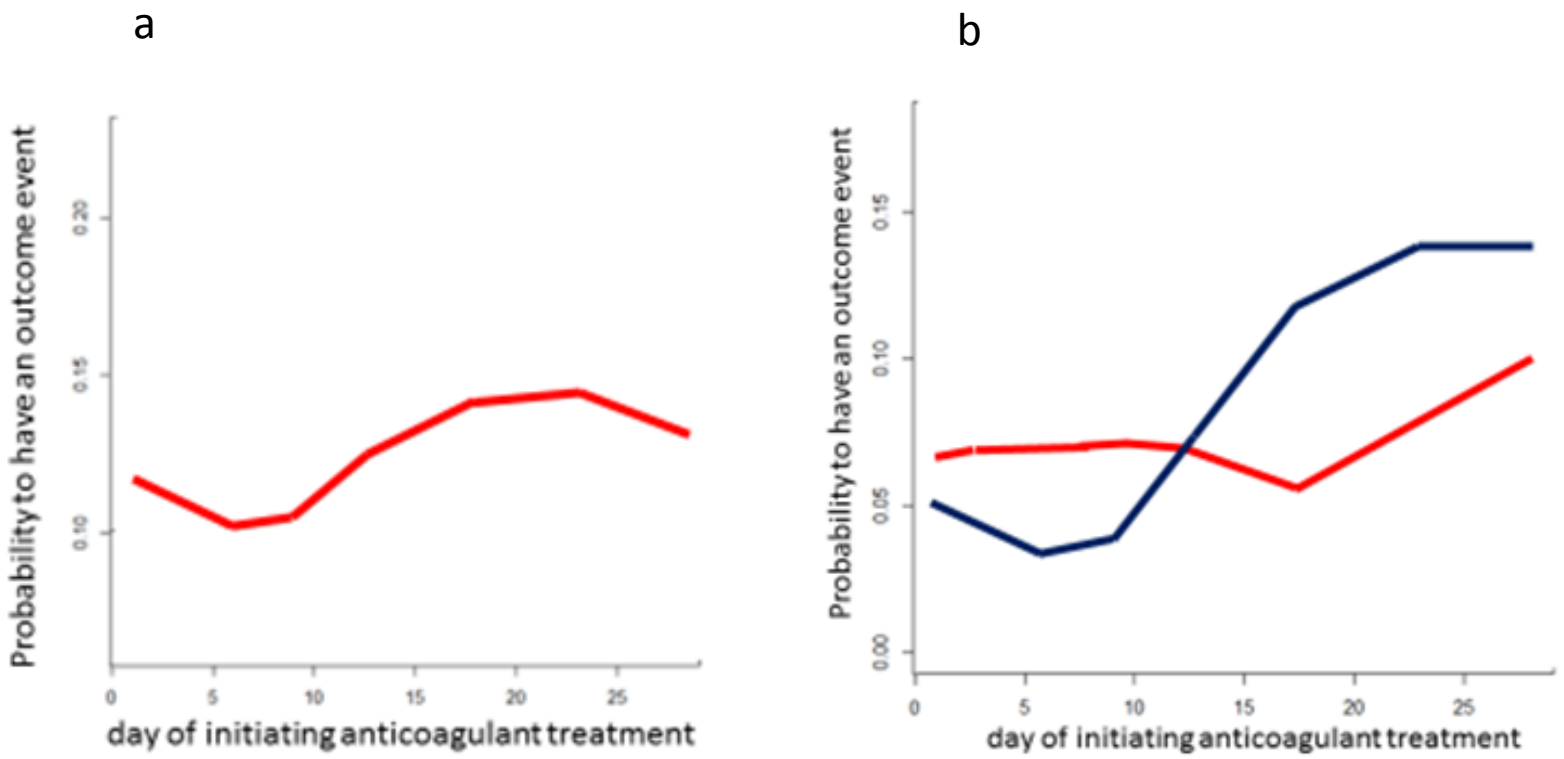
Supplemental Figure II



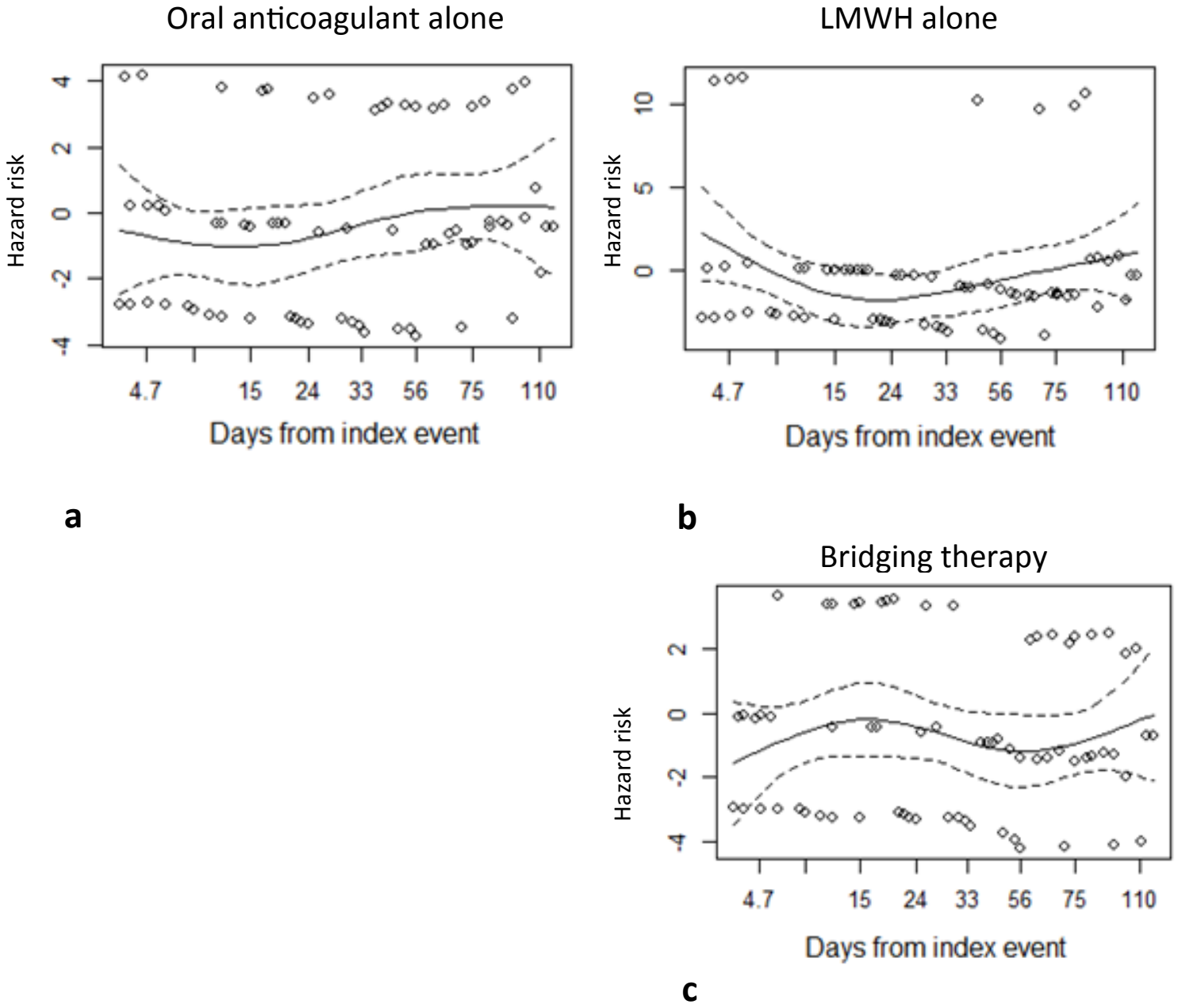
Chisq= 14.2 on 3 degrees of freedom, p= 0.00406

263	236	232
276	255	247
113	99	96
377	362	355

Supplemental Figure III

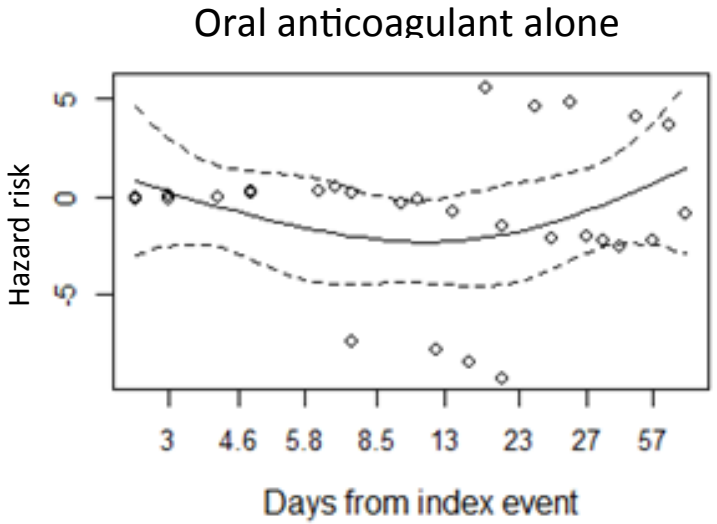


Supplemental Figure IV

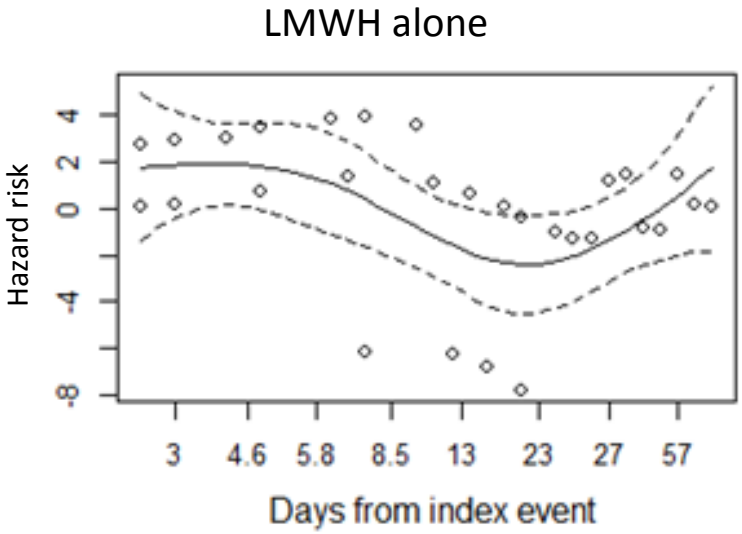


Bridging therapy: LMWH (Low Molecular Weight Heparin) followed by oral anticoagulant

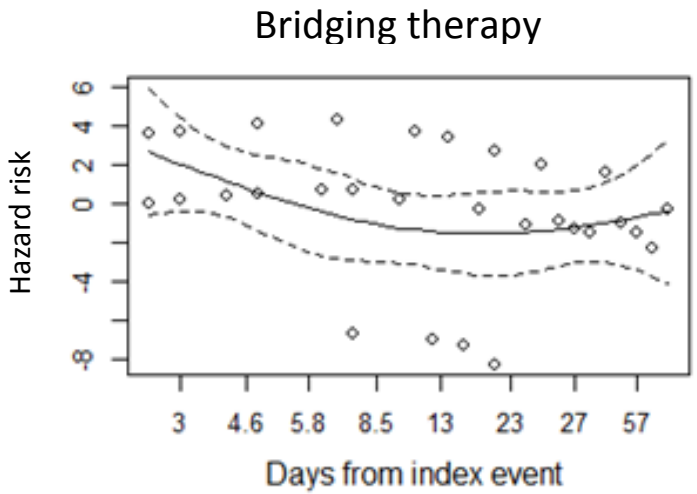
Supplemental Figure V



a



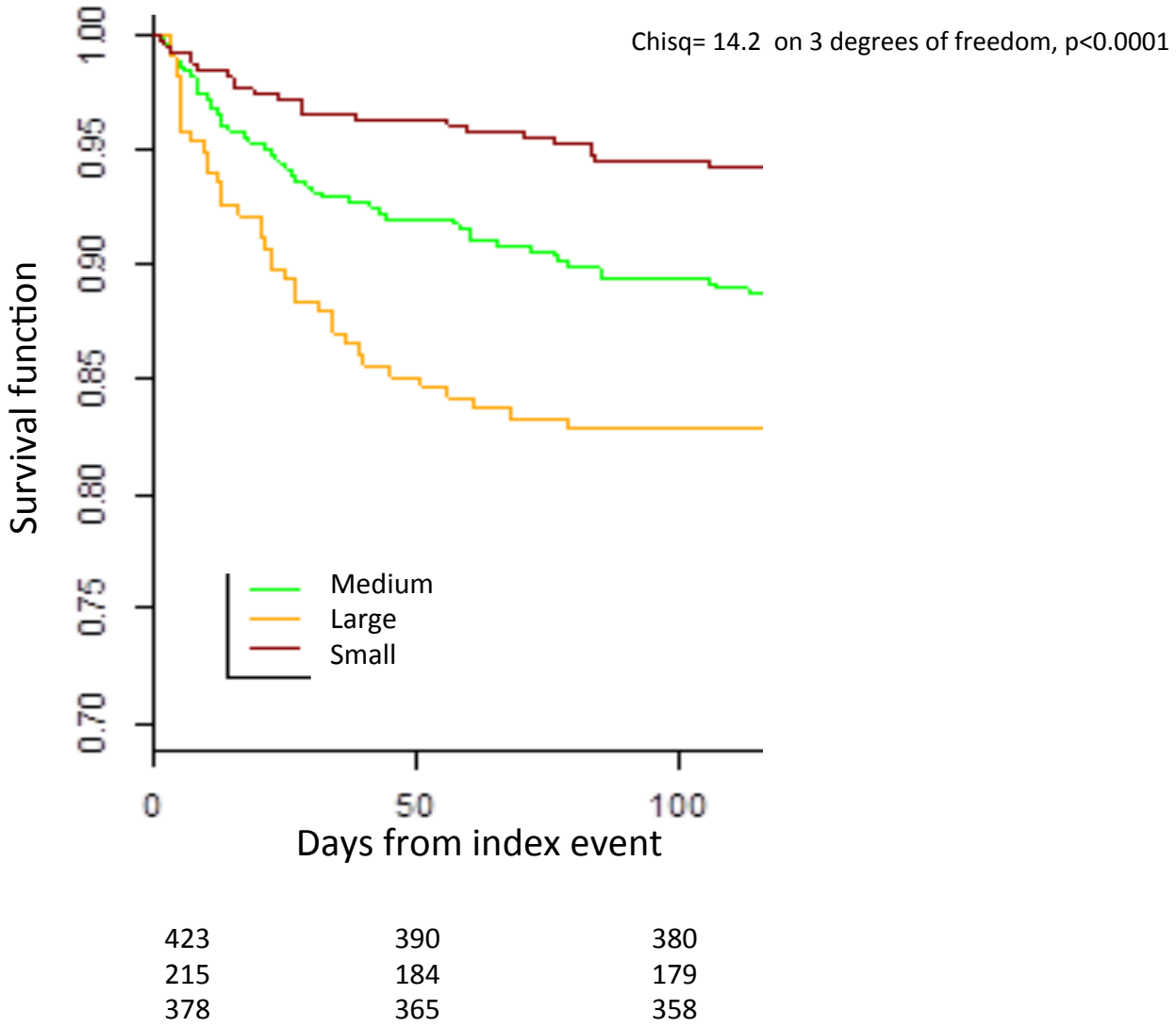
b



c

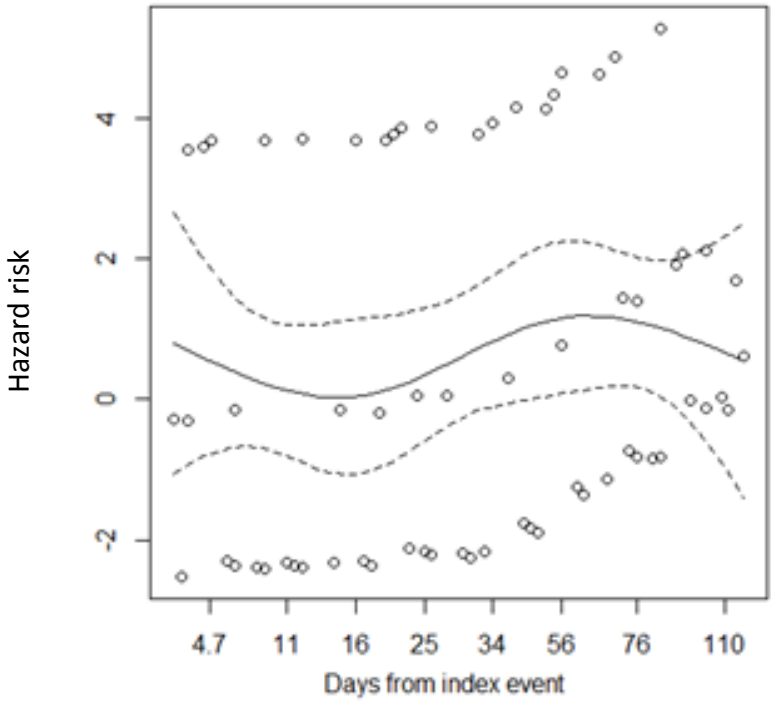
Bridging therapy: LMWH (Low Molecular Weight Heparin) followed by oral anticoagulant

Supplemental Figure VI



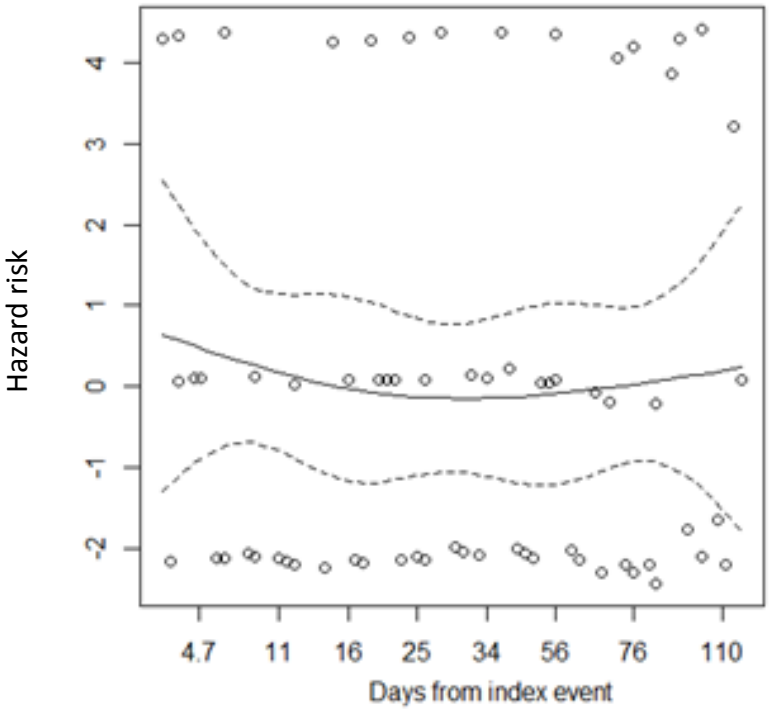
Supplemental Figure VII

Large lesion



a

Small lesion



b

Stroke
Journal of the American Heart Association

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study

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