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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Received January 23, 2015; final revision received May 19, 2015; accepted June 2, 2015.

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Guest Editor for this article was Bruce Ovbiagele, MD.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.008891/-/DC1.

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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).

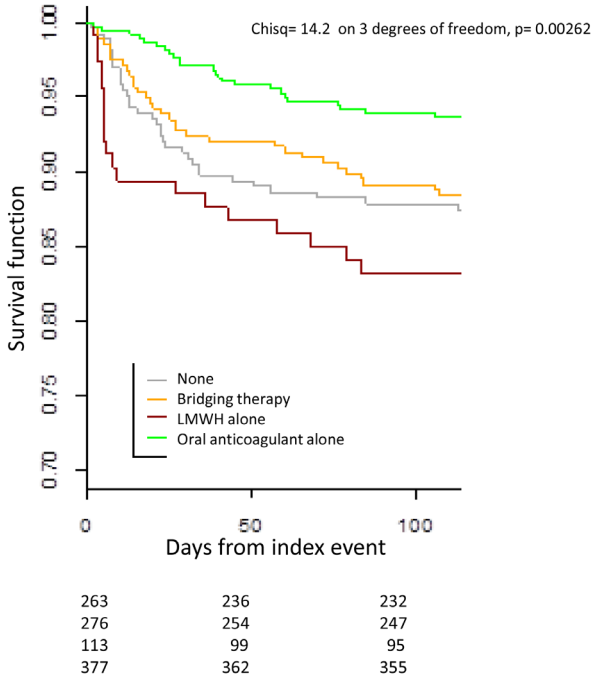
Poststroke Anticoagulation and the Risk of Recurrent Ischemic Events or Bleedings

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).

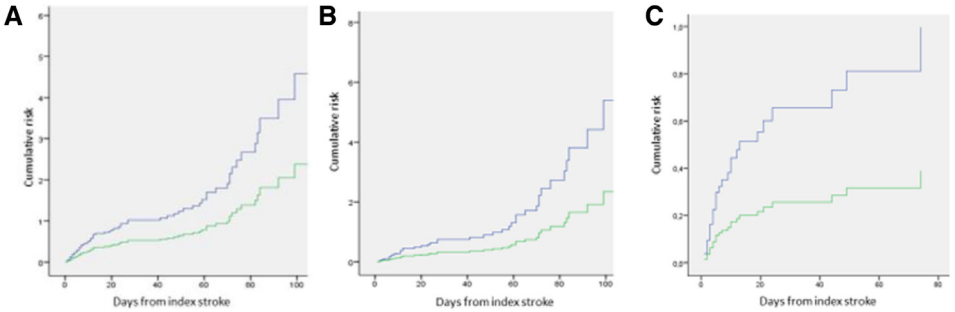
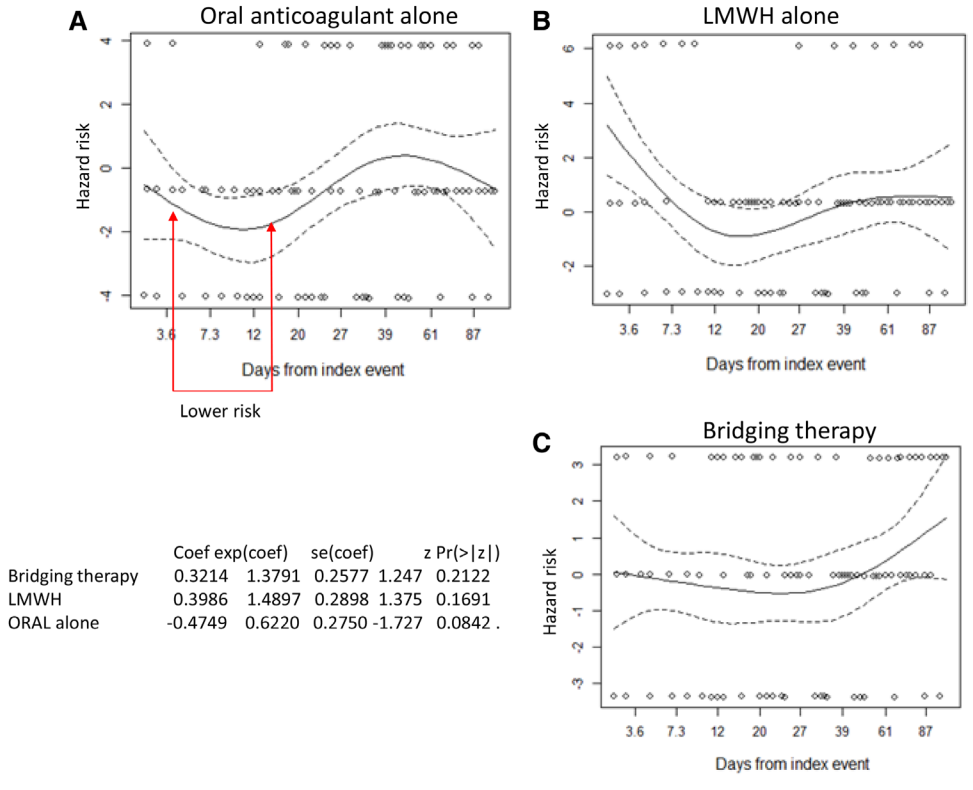


Figure 2. A, All outcome events in patients treated with anticoagulants between days 4 and 14, compared with the other treated patients. Hazard Ratio (HR)=0.53 (0.30–0.93), $P=0.025$. **B**, Ischemic outcome events (stroke, transient ischemic attack, systemic embolism) in patients treated with anticoagulants 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



	Coef	exp(coef)	se(coef)	z	Pr(>|z|)
Bridging therapy	0.3214	1.3791	0.2577	1.247	0.2122
LMWH	0.3986	1.4897	0.2898	1.375	0.1691
ORAL alone	-0.4749	0.6220	0.2750	-1.727	0.0842 .

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

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

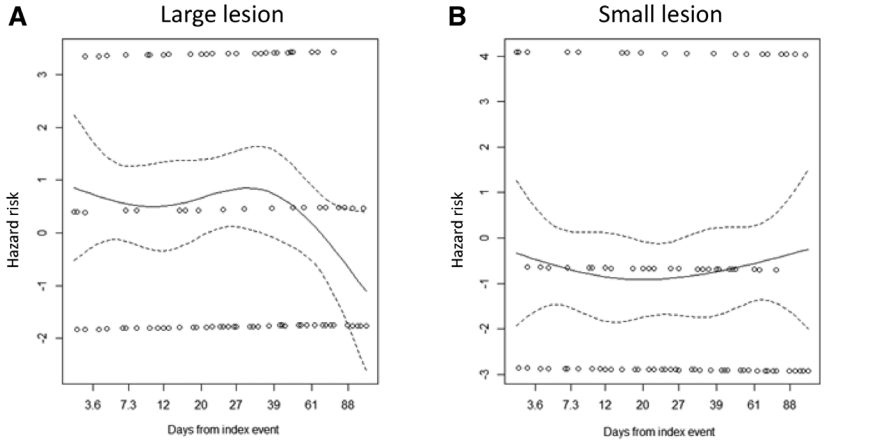


Figure 4. The different risks of the combined outcome events associated with the day of initiating anticoagulant treatment in patients with small or large lesion in a Cox proportional hazard model where anticoagulant therapy was treated as a time-varying covariate. Hazard risk curves are expressed in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

Acknowledgment

We thank Thomas Charles Kilcline for his important editorial assistance.

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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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

Maurizio Paciaroni, Giancarlo Agnelli, Nicola Falocci, Valeria Caso, Cecilia Becattini, Simona Marcheselli, Christina Rueckert, Alessandro Pezzini, Loris Poli, Alessandro Padovani, Laszló Csiba, Lilla Szabó, Sung-Il Sohn, Tiziana Tassinari, Azmil H. Abdul-Rahim, Patrik Michel, Maria Cordier, Peter Vanacker, Suzette Remillard, Andrea Alberti, Michele Venti, Umberto Scoditti, Licia Denti, Giovanni Orlandi, Alberto Chiti, Gino Gialdini, Paolo Bovi, Monica Carletti, Alberto Rigatelli, Jukka Putaala, Turgut Tatlisumak, Luca Masotti, Gianni Lorenzini, Rossana Tassi, Francesca Guideri, Giuseppe Martini, Georgios Tsivgoulis, Kostantinos Vadikolias, Chrissoula Liantinioti, Francesco Corea, Massimo Del Sette, Walter Ageno, Maria Luisa De Lodovici, Giorgio Bono, Antonio Baldi, Sebastiano D'Anna, Simona Sacco, Antonio Carolei, Cindy Tiseo, Monica Acciarresi, Cataldo D'Amore, Davide Imberti, Dorjan Zabzuni, Boris Doronin, Vera Volodina, Domenico Consoli, Franco Galati, Alessio Pieroni, Danilo Toni, Serena Monaco, Mario Maimone Baronello, Kristian Barlinn, Lars-Peder Pallesen, Jessica Kepplinger, Ulf Bodechtel, Johannes Gerber, Dirk Deleu, Gayane Melikyan, Faisal Ibrahim, Naveed Akhtar, Maria Giulia Mosconi, Valentina Bubba, Ilenia Silvestri and Kennedy R. Lees

Stroke. 2015;46:2175-2182; originally published online June 30, 2015;
doi: 10.1161/STROKEAHA.115.008891
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

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.

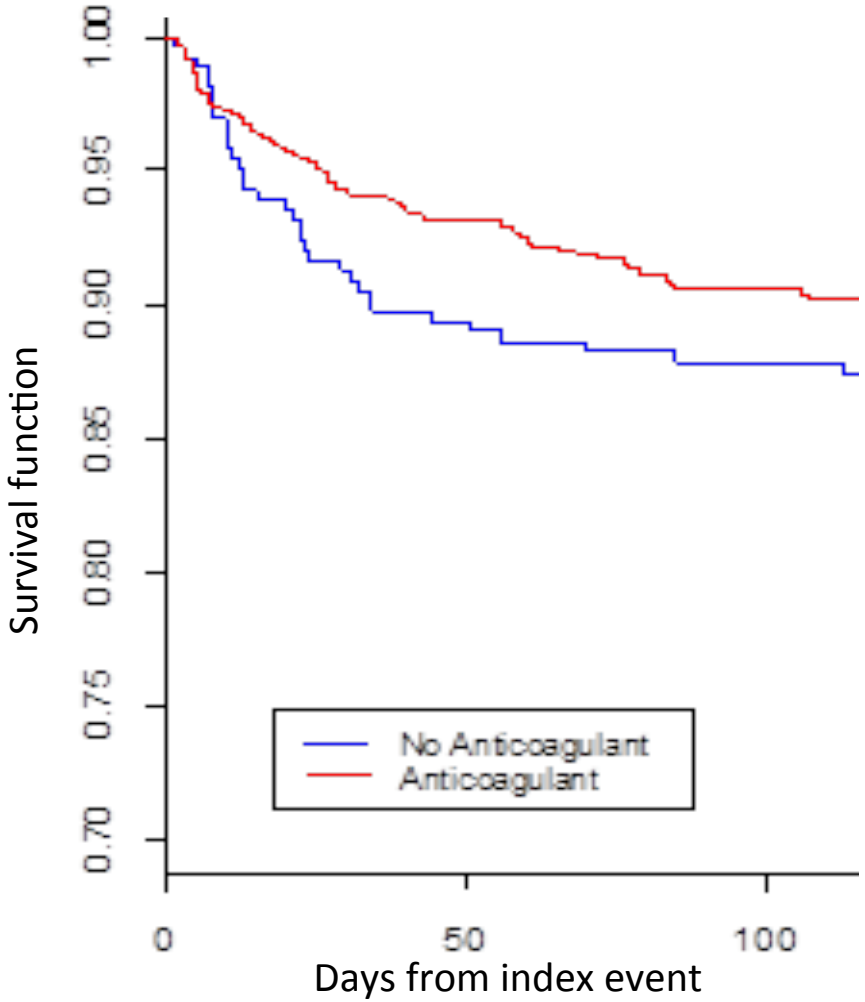
Supplemental Figure IV. The different risks of recurrent ischemic events associated with the day of initiating anticoagulant treatment in patients treated with different types of anticoagulant therapy (a: oral anticoagulant alone; b: Low Molecular Weight Heparin alone; c: bridging therapy, Low Molecular 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).

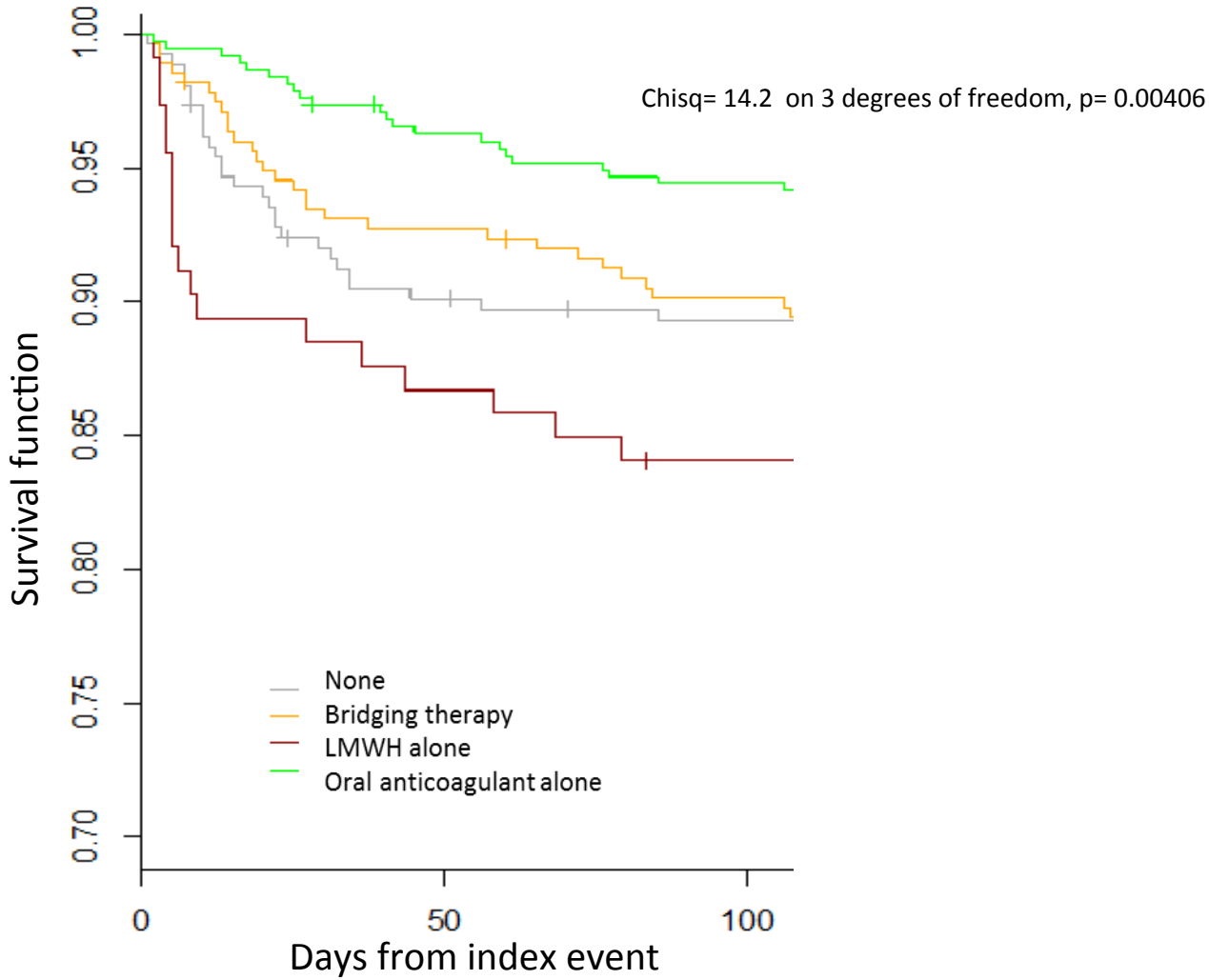
Supplemental Figure VII. The different risks of recurrent ischemic events associated with the day of initiating anticoagulant treatment in patients with small or large lesions in a Cox proportional hazard model where anticoagulant therapy was treated as a time-varying covariate. Hazard risk curves are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

Supplemental Figure I



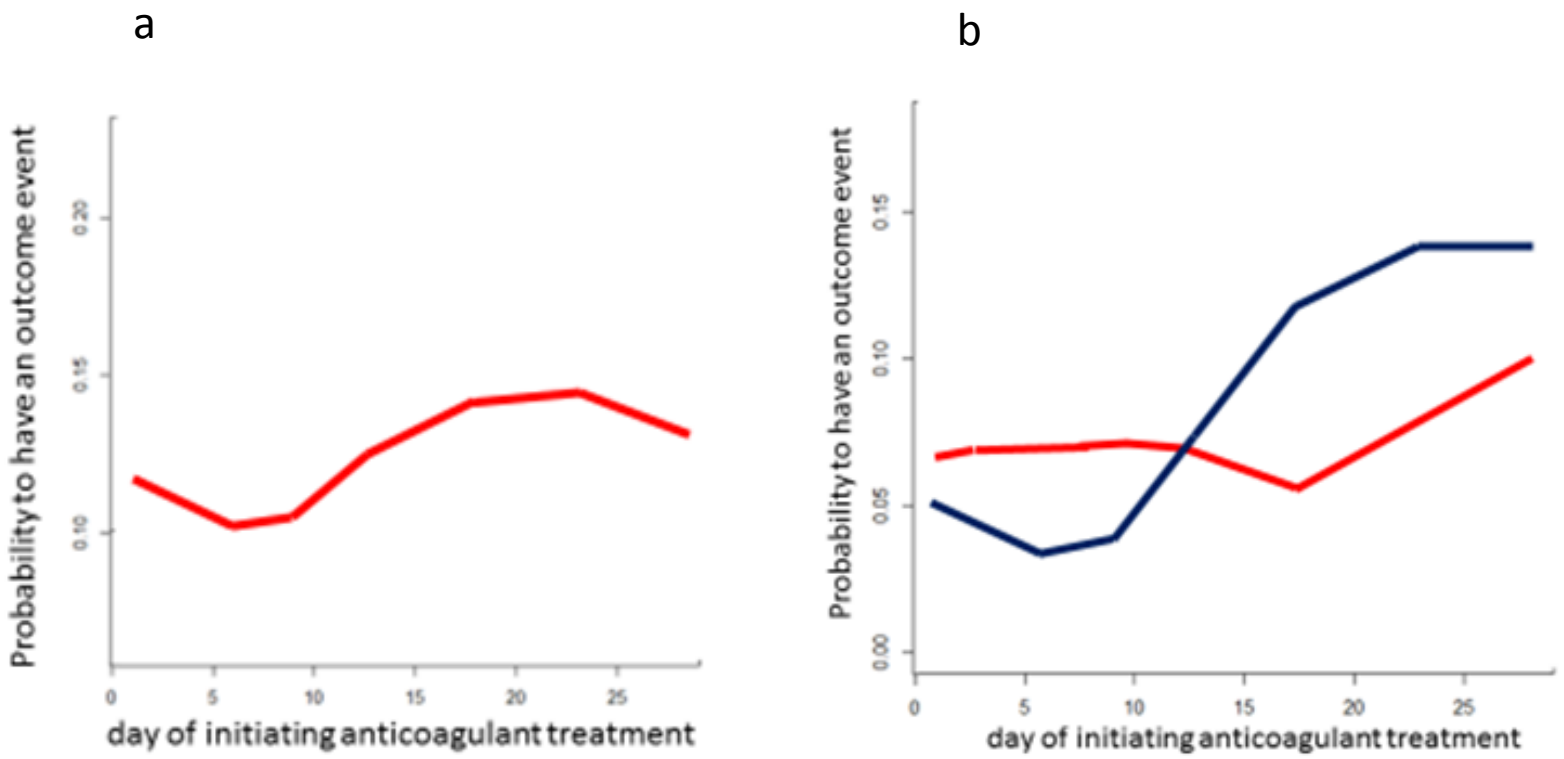
263	235	232
766	714	695

Supplemental Figure II

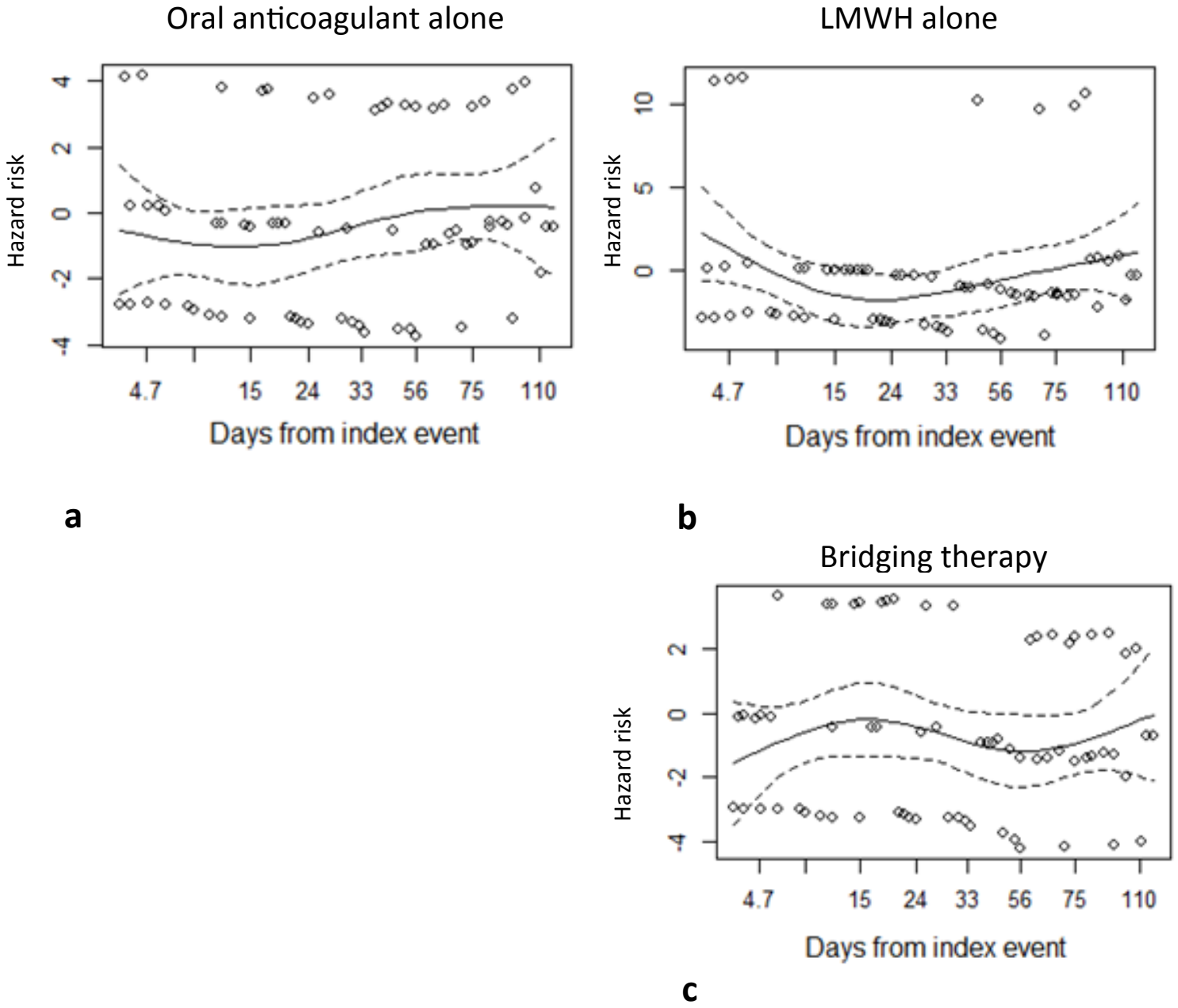


263	236	232
276	255	247
113	99	96
377	362	355

Supplemental Figure III

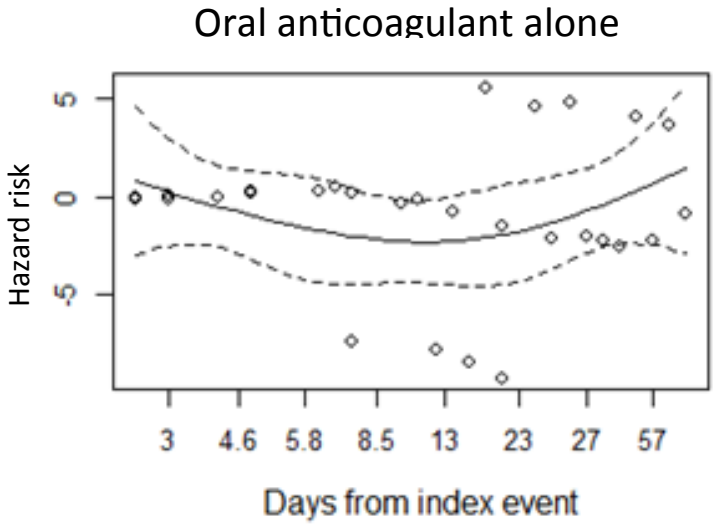


Supplemental Figure IV

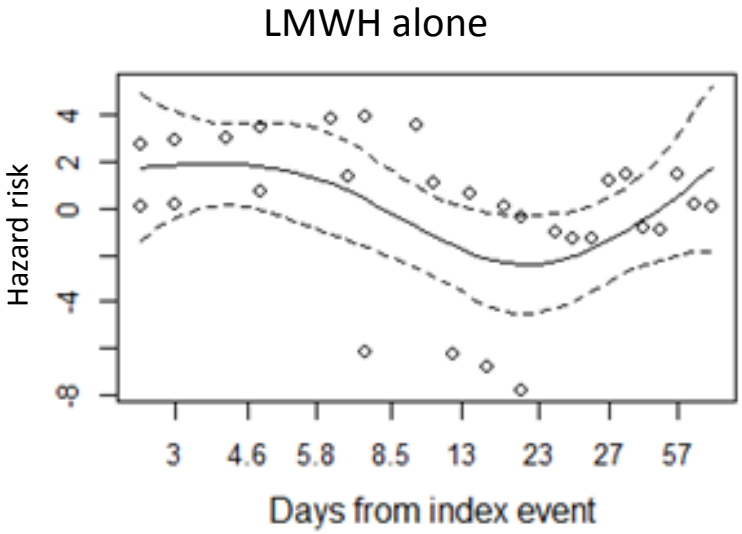


Bridging therapy: LMWH (Low Molecular Weight Heparin) followed by oral anticoagulant

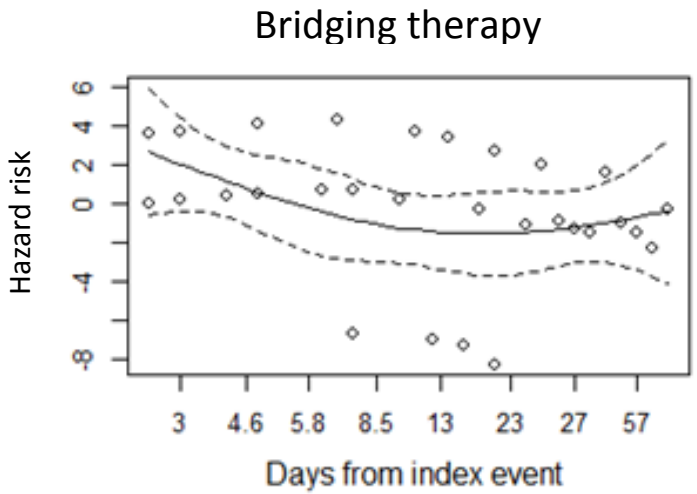
Supplemental Figure V



a



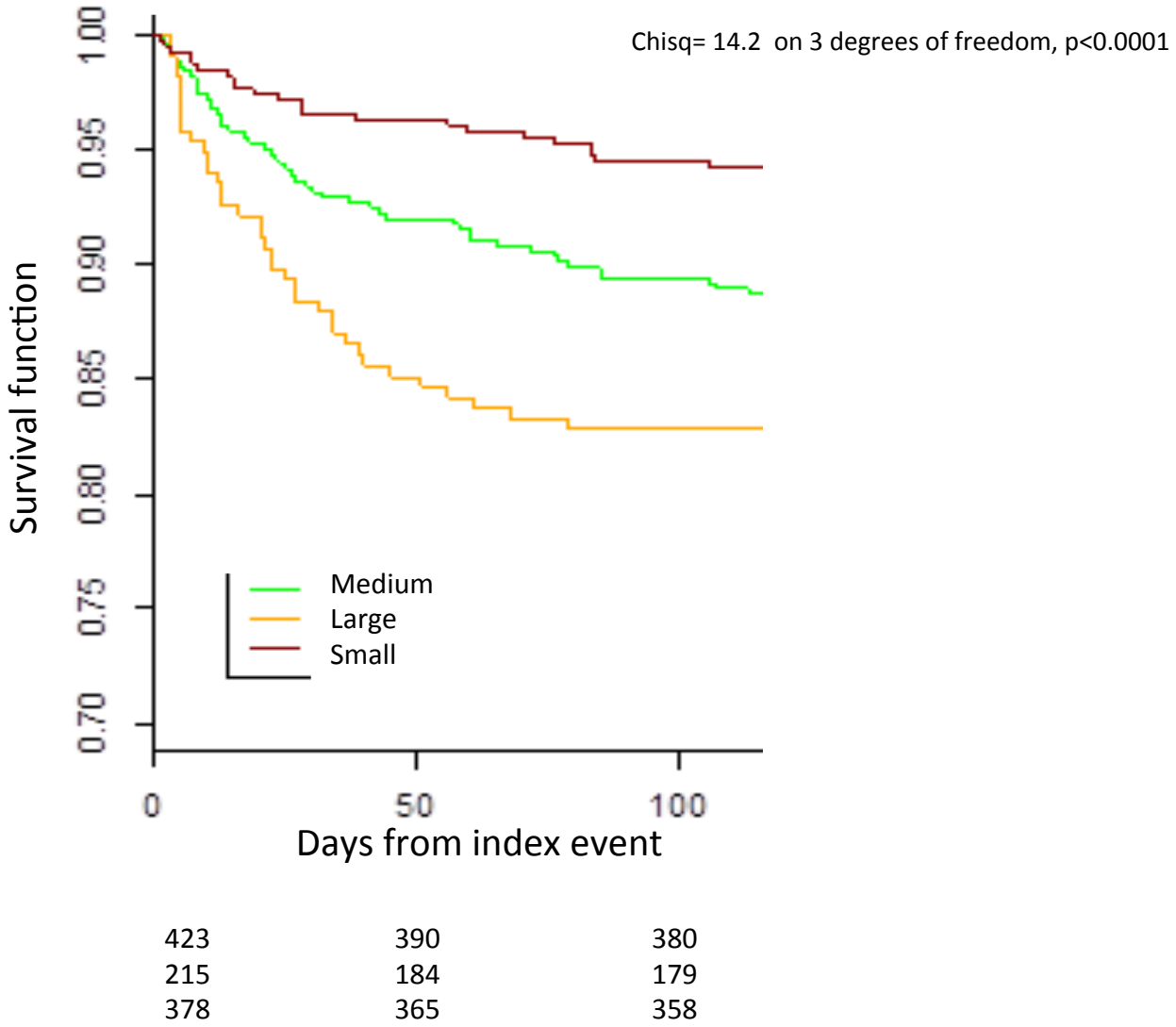
b



c

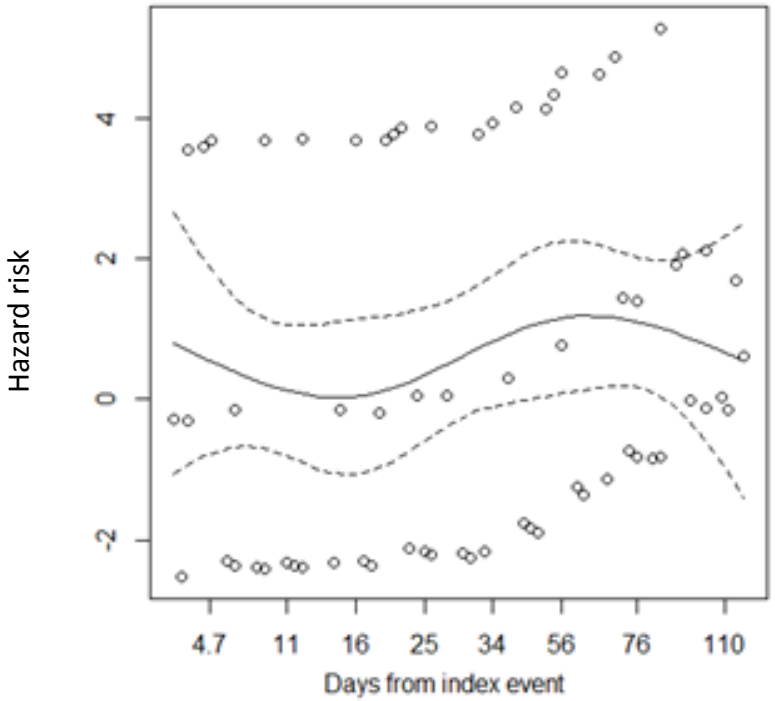
Bridging therapy: LMWH (Low Molecular Weight Heparin) followed by oral anticoagulant

Supplemental Figure VI



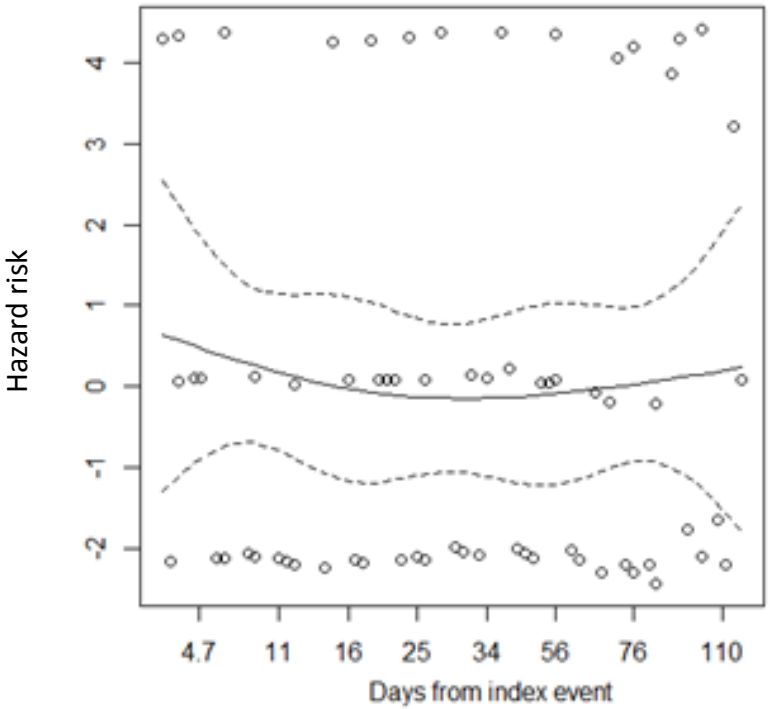
Supplemental Figure VII

Large lesion



a

Small lesion



b

Full Article

心房細動を伴う急性虚血性脳卒中患者における早期再発と脳出血
―抗凝固薬とその投与タイミングの影響：RAF 試験

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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背景および目的：急性心原性脳塞栓症に対する抗凝固療法の最適な実施時期は，いまだ不明である。心房細動を伴う急性脳卒中患者を対象とした前向きコホート研究を実施し，(1) 虚血イベントの再発および重度出血のリスク，(2) 再発および出血の危険因子，(3) 急性脳卒中発症後の抗凝固療法およびその開始時期に関連する再発および出血リスク，を評価した。
方法：今回の多施設共同研究では，主要転帰として，急性脳卒中の発症から 90 日以内における脳卒中，一過性脳虚血発作（TIA），症候性全身性塞栓症，症候性脳出血および頭蓋外大出血からなる複合イベントを検討した。
結果：登録者 1029 例中 123 例において 128 件のイベント（12.6%）が発生した［虚血性脳卒中または TIA または全身性塞栓症 77 件（7.6%），症候性脳出血 37 件（3.6%），頭蓋外大出血 14 件（1.4%）］。急性脳卒中の発症後 90 日目の時点で，患者の 50%が死亡または身体障害［modified Rankin score（mRS）≧ 3］に至っており，10.9%が死亡していた。主要転帰の予測因子は，高い CHA_2DS_2-VASc スコア，高い NIHSS，大きい虚血病変，抗凝固薬の種類であった。調整済みの Cox 回帰分析では，脳卒中発症後 4 ～ 14 日目時点の抗凝固薬の開始が，それ以前またはその後の治療開始に比べ，主要転帰の有意な減少につながった［ハザード比 0.53（95%信頼区間 0.30 ～ 0.93）］。転帰イベントが認められたのは，経口抗凝固薬のみで治療した患者では約 7%であったが，低分子量ヘパリンのみ，またはその後に経口抗凝固薬を投与した患者では，それぞれ 16.8%および 12.3%であった（$P = 0.003$）。
結論：心房細動患者における急性脳卒中では，発症後 90 日目の時点で，虚血イベントの再発および大出血が高率に認められる。本研究では，高い CHA_2DS_2-VASc スコア，高い NIHSS，大きい虚血病変，投与した抗凝固薬の種類がそれぞれ独立して再発および出血の高リスクに関連した。また，データから，二次脳卒中予防のための抗凝固薬を開始する最適なタイミングは，脳卒中の発症後 4 ～ 14 日目の時点であることが示された。さらに，経口抗凝固薬のみを投与した患者は，低分子量ヘパリンのみまたは経口抗凝固薬の前に低分子量ヘパリンを投与した患者に比べ，転帰が良好であった。
Stroke 2015; 46: 2175-2182. DOI: 10.1161/STROKEAHA.115.008891.

心房細動（AF）から心原性脳塞栓症を発症した患者において，脳卒中の早期再発リスク（2 週間以内に発生した新規イベントとして定義）は 1 日あたり 0.1 ～ 1.3%と報告されている[1,2]。抗凝固療法は，心房細動患者の二次脳卒中予防にきわめて有効であることが証明されている。しかし，各患者に特有のリスク／バランスや，最もリスクが高い脳卒中はどれか，また，どの脳卒中が治療の恩恵を受けやすいかは，依然として不明である。現在のところ，無作為化臨床試験において，心房細動に伴う急性虚血性脳卒中患者に対する脳卒中発症後 48 時間以内のヘパリン投与を支持するエビデンスは提示されていない[3,4]。しかし，これらの無作為化試験が実施されたのはかなり前の時代であり，当時は全ての脳卒中率が高く，直接作用型経口抗凝固薬などのワルファリン代替薬はいまだ導入されていなかった。

VISTA データベースの解析では，抗凝固薬の早期導入（脳卒中発症後 2 ～ 3 日目）と，これより効果は低いが抗血小板薬の導入により，その後数週間の再発イベントを大きく抑制でき，症候性脳内出血のリスクも上昇しないことが示されている[5]。

今回の心房細動を伴う急性脳卒中患者を対象とした多国間の前向き多施設共同研究では，急性イベントから 90 日目の時点において以下の項目を評価した。すなわち，(1) 虚血性塞栓イベントの再発および重度出血（頭蓋内および頭蓋外）のリスク，(2) 虚血性脳卒中の再発，全身性塞栓症，症候性脳出血，重度の脳外出血に関連する危険因子，(3) 抗凝固療法およびそのタイミングに関連する再発および出血のリスクである。

方　法

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation（RAF）試験は，2012 年 1 月～ 2014 年 3 月に実施された前向き観察研究であり，抗凝固薬の禁忌がなく，心房細動の診断を受けていたか，新規診断を受けた急性虚血性脳卒中の連続した患者を対象とした。本研究はヨーロッパおよびアジアの stroke unit 29 施設で実施された。必要に応じ，各施設の治験審査委員会の承認を得た。

入院時，患者の脳卒中重症度を NIHSS で評価した。入院時にすべての患者で脳の単純 CT 検査または脳 MRI を実施し，頭蓋内出血を除外した。適切であれば，各施設の標準プロトコルに従って血栓溶解薬を投与した。29 施設の stroke unit すべてにおいて，標準の脳卒中治療およびモニタリングが行われた。脳卒中の発症後 2 ～ 3 日中にすべての患者で血圧，体温，血糖値，心拍数，血液ガスをモニターした。抗凝固薬の種類［低分子量ヘパリン（LMWH）または経口抗凝固薬］およびその開始日は，医師が自由に決定した。

心房細動は，発作性（7 日以内に自然に治まる），持続性（7 日超，持続し，薬物治療または電気刺激を必要とする），慢性（電気的除細動の無効または未実施により，1 年超，持続している）に分類した。

2 回目の脳 CT または MRI は，すべての患者で脳卒中発症後 24 ～ 72 時間の時点で実施することとした。出血性変化（hemorrhagic transformation）は，低吸収域内にある何らかの高濃度所見と定義し，出血性梗塞または脳

実質血腫のいずれかに分類した[6,7]。出血性変化は，神経学的状態の低下（NIHSS で 4 ポイントの増加）が認められ，初回 CT で出血のエビデンスがなければ，症候性と判断した[8]。本研究に適格な梗塞の部位および大きさは，標準テンプレートを基準に以下のように決定した[9,10]。すなわち，（1）前方または後方循環系にある 1.5 cm 以下の病変は「小病変」，（2）中大脳動脈（MCA）皮質枝（浅枝），MCA 深枝，内側境界領域，後大脳動脈皮質枝（浅枝），前大脳動脈皮質枝（浅枝）にある病変は「中病変」，（3）MCA または後大脳動脈または前大脳動脈の全領域，MCA 皮質枝（浅枝）2 本，MCA の深枝につながる MCA 皮質枝（浅枝），または 2 つ以上の動脈領域（前大脳動脈領域につながる MCA など）にある病変は「前方大病変」，（4）脳幹または小脳にある 1.5 cm 以上の病変は「後方大病変」とした[7]。

危険因子

脳卒中の危険因子として知られている以下の項目についてデータを収集した。すなわち，年齢，性別，高血圧の既往（脳卒中発症前に測定した血圧が少なくとも 2 回 140/90 mm Hg 以上，またはすでに降圧薬による治療を受けている），糖尿病の既往（食前に測定した 2 回の空腹時血糖値が 126 mg/dL 以上，食後血糖値 200 mg/dL 以上，HbA1c 6.5％以上または抗糖尿病治療を受けている），現在の喫煙状況，過去の喫煙歴（禁煙 5 年未満），高脂血症（総コレステロール 200 mg/dL 以上，中性脂肪 140 mg/dL 以上，またはすでに脂質低下治療を受けている），症候性虚血性心疾患の既往（心筋梗塞，狭心症の既往，タリウムによる心臓 RI 検査で多発病変が存在する，または冠動脈造影検査で冠動脈疾患のエビデンスを認める），症候性末梢動脈疾患の既往（アテローム性動脈硬化が原因と推定される間欠跛行，左右いずれかの安静時の足首／上腕収縮期血圧比が 0.85 未満，または下肢切断，再建または血管形成手術による間欠跛行の既往），アルコールの乱用（週に 300 g 以上），肥満（BMI 30 kg/m^2 以上），脳卒中／一過性脳虚血発作（TIA）の既往のデータである。白質の変化［最初の CT 検査における白質希薄化（leukoaraiosis）について，既報の基準により，境界不明瞭かつやや低濃度の 5 mm 以上の領域と定義］を検討した[11]。深部白質の希薄化（leukoaraiosis）について「なし」，「軽度」「中等度」「重度」のいずれかに分類した。そのほか入院時に全患者で収集したベースラインの変数は，空腹時血清血糖，空腹時血清コレステロール（総，高比重リポ蛋白，低比重リポ蛋白），血小板数，国際標準化比，活性化トロンボプラスチン時間，収縮期血圧，拡張期血圧であった。

入院前，ベースライン時，追跡調査期間中の抗血小板薬，抗凝固薬，血栓溶解薬の使用について，データを記録した。

指標イベント発症前の CHA_2DS_2-VASc スコア（脳卒中の既往または年齢 75 歳以上は 2 点，年齢 65 ～ 74 歳，高血圧，糖尿病，心不全，血管疾患の既往は各 1 点）も算出した[12]。

転帰の評価

患者の追跡調査は前向きに，対面または電話での聞き取りにより実施した。研究の転帰は，発症後 90 日目の時点における（1）虚血性脳血管イベント（脳卒中または TIA）の再発および症候性全身性塞栓症，（2）症候性脳出血および脳外大出血，とした。

主要転帰は脳卒中，TIA，症候性全身性塞栓症，症候性脳出血および脳外大出血の複合イベントとした。

90 日目時点の身体障害および死亡も modified Rankin score（mRS）により評価した。機能的転帰は，身体障害なし（mRS 0 ～ 2）または身体障害あり（mRS 3 ～ 5）として定義した。

脳卒中は，新しい局所の神経学的障害が突然発症し，その原因が主要脳動脈領域と一致する部位の血管にある場合と定義し，虚血性か出血性かに分類した。発症後 24 ～ 72 時間の神経画像検査で検出された出血性変化は，症候性であると分類されない限り，転帰イベントとはみなさなかった。TIA は，急性梗塞を除く局所脳虚血を原因とした神経学的障害の一過性エピソードと定義した。全身性塞栓症は，画像検査，手術または剖検で確認された四肢または器官の急性血管閉塞と定義した。脳外大出血は，1 dL あたり 2 g 以上のヘモグロビン値低下，2 単位以上の輸血を必要とする出血，または重要な領域または器官の症候性出血と定義した[13]。

統計解析

転帰イベントが認められた患者と認められなかった患者における特徴の差は，χ^2 検定で解析した。特に，入院時の臨床的特徴と既存の脳卒中危険因子の比較には，単変量検定を使用した。全変数の探索的解析は分割階層クラスタリング法により実施した。クラスター解析は，大きな不均質データセットから，同様の性質を持つ小グループを形成するために使用する。この解析形態は，多数の変数や観察結果の中の関連性を発見するのに有効な方法であり，本研究ではその後に一連の多重ロジスティック回帰モデルで転帰イベントの予測因子を特定した。これらの変数には危険因子，再灌流療法，入院時の NIHSS スコアによる脳卒中重症度，CHA_2DS_2-VASc ス

コア，虚血病変の大きさを含めた。連続または二値カテゴリ変数として，抗凝固療法の開始日をモデルに取り入れた。

Kaplan–Meier 推定量により，さまざまな患者群の生存時間関数および経験的な累積ハザード関数を推定した。生存関数の差は，症例数が多い場合に漸近的 χ^2 分布となるログランク統計量（または Mantel–Haenszel 検定）により解析した[14]。

患者は転帰イベント，死亡，または追跡調査が不能となった時点で打ち切りとした。

生存時間関数と一連の探索的変数との関連性は，Cox 比例ハザードモデルで検討した。Cox モデルでは，順序変数としてのさまざまな病変の大きさなど，他の探索的変数を調整後，生存に対する治療の効果を推定した。本研究では 3 つの抗凝固療法，すなわち経口抗凝固薬のみ，LMWH のみ，または LMWH 投与後に経口抗凝固薬を投与する治療法について検討した。また，抗凝固療法の開始日を，さまざまな転帰の時変共変量として扱った。この場合も，転帰イベント，死亡，または追跡調査が不能となった時点で打ち切りとした。

さらに，転帰イベントが発生した特定の日に対する予測変数の影響を検討するため，追加で別のモデルも推定した。これらの結果は，ハザード比および 95％信頼区間として報告した。両側 P 値＜ 0.05 を有意と判断した。

統計解析はすべて，ソフトウェア R，バージョン 3.0.3［copyright（C）2013 The R Foundation for Statistical Computing］で実施した。

結　果

本研究では全体で 1037 例の連続した患者を検討した（アジアから 59 例）。このうち 1029 例が解析対象となった［データが不完全なため 8 例を除外。オンラインのデータ補遺（Data Supplement）の表 I］。

急性脳卒中の発症後，766 例（74.4％）に抗凝固薬が投与され，そのうち 449 例は抗凝固薬の開始前に抗血小板薬の投与を受けていた。抗凝固療法の種類に関しては，LMWH のみが 113 例（14.7％，91 例は最初に抗血小板薬を投与），ビタミン K 拮抗薬が 284 例（37.1％，162 例は最初に抗血小板薬を投与），直接作用型経口抗凝固薬が 93 例（12.1％，ダビガトラン 55 例，リバーロキサバン 30 例，アピキサバン 8 例。62 例は最初に抗血小板薬を投与），LMWH に続いてビタミン K 拮抗薬が 276 例（36.0％，134 例は最初に抗血小板薬を投与）であった。静脈血栓塞栓症の予防を目的に LMWH を投与された患者は，抗凝固薬の投与患者とみなさなかった。

入院時の平均 NIHSS スコアは，LMWH のみの患者で 11.9 ± 7.6，LMWH の後に経口抗凝固薬の投与を受けた患者で 6.9 ± 5.9，経口抗凝固薬のみの患者で 8.3 ± 6.5 であった。

抗凝固薬の投与を受けなかった患者 263 例中 231 例（87.8％）に抗血小板薬が投与され，32 例は 90 日間の本研究期間中に抗血栓療法を受けなかった。

急性脳卒中の発症後に抗凝固薬の投与を受けた患者と受けなかった患者について，その臨床的特徴をオンラインのデータ補遺（Data Supplement）の表 II に記載する。急性脳卒中の発症後に抗凝固薬の投与を受けなかった患者は，抗凝固薬の投与患者に比べ，平均的に高齢で，病変が大きく，入院時の NIHSS が高かった。

脳卒中発症後 24 ～ 72 時間に実施した神経画像検査で，出血性変化は 134 例（13.0％）に認められた。91 例（8.8％）は出血性梗塞，43 例（4.2％）は脳実質血腫であった。再灌流療法（静脈内または動脈内再灌流法，あるいはその両方）を受けた 230 例（22.4％）のうち，出血性梗塞の 23 例（10.0％）および脳実質血腫の 14 例（6.1％）を含め，37 例（16.1％）に出血性変化を認めた（症候性は 8 例）。全体では，出血性変化の確認後，37 例中 26 例が抗凝固薬の投与を受けた。

発症後 90 日目の時点で，機能的転帰の最終解析が可能であった患者は 1019 例であった（10 例は追跡不能）。510 例（50.0％）が死亡または身体障害（mRS ≧ 3）に至り，111 例が（10.9％）死亡した。

虚血イベントの再発または出血のリスク

患者 123 例において 128 件（12.6％）の転帰イベントが認められた。77 件（7.6％）は虚血性脳卒中または TIA または全身性塞栓症，37 件（3.6％）は症候性頭蓋内出血，14 件（1.4％）は脳外大出血であった。指標にした脳卒中から虚血性脳卒中の再発，症候性頭蓋内出血，TIA，全身性塞栓症までの平均期間はそれぞれ 34.2 ± 31.4，22.5 ± 60.8，43.3 ± 37.9，36.7 ± 36.3 日であった。転帰イベントが発生した患者としなかった患者の臨床的特徴を，オンラインのデータ補遺（Data Supplement）の表 III に記載する。

抗凝固薬を投与された患者 766 例中 90 例（11.7％）に転帰イベントが認められたのに対し，抗凝固薬を投与されなかった患者では 263 例中 38 例（14.4％）であった［P ＝ 0.22，オンラインのデータ補遺（Data Supplement）の図 I］。出血性イベントはそれぞれ 41 例（5.4％）および 10 例（3.8％）（P ＝ 0.31），虚血イベントはそれぞれ 49 例（6.4％）および 28 例（10.6％）に認められた（P ＝ 0.023）。

直接作用型経口抗凝固薬を投与された患者 93 例中 6

例（6.4%）に転帰イベントが認められ，2例（2.1%）は症候性頭蓋内出血，4例（4.3%）は虚血イベントであった。

指標イベントから治療開始までの平均期間は，直接作用型経口抗凝固薬の投与患者で8.5 ± 12.2日，LMWH投与患者で6.5 ± 10.9日，ビタミンK拮抗薬の投与患者で12.1 ± 15.8日であった（国際標準化比2以上）。

虚血イベントの再発または出血のリスクに関連する危険因子

90日以内の転帰イベント（虚血または出血）の発生リスクは，CHA_2DS_2-VAScスコアの増加とともに上昇した。スコア2の患者にイベントは認められず，スコア3では1.7%，スコア4では9.8%，スコア5では10.2%，スコア6では12.3%，スコア7では17.0%，スコア8では20.3%に認められた。

多変量解析の結果，高いCHA_2DS_2-VAScスコア，高いNIHSS（連続またはカテゴリ変数として），大病変，指標とする脳卒中の発症後に使用した抗凝固薬の種類が，複合主要転帰イベントの予測因子であった［オンラインのデータ補遺（Data Supplement）の表IV］。抗凝固薬の種類に関しては，LMWHの次に経口抗凝固薬またはLMWHのみを投与した患者に比べ，経口抗凝固薬のみを投与した患者で転帰が良好であった。LMWHのみの治療は，その他の治療に比べ，転帰イベントの有意なリスク上昇につながった。経口抗凝固薬のみを投与された患者では約7%に転帰イベントが認められたのに対し，LMWHのみまたはその後に経口抗凝固薬を投与された患者では，それぞれ16.8%および12.3%に認められた（$P = 0.003$，図1）。転帰イベントからTIA患者を除いても，結果は同様であった［オンラインのデータ補遺（Data Supplement）の図II］。上記以外の出血性イベントの予測因子として，大病変および脳卒中発症後14 ～ 30日目の抗凝固薬投与が特定された。さらに，高齢および大病変は，虚血イベントの予測因子であった［オンラインのデータ補遺（Data Supplement）の表IV］。

脳卒中発症後の抗凝固療法と虚血イベントの再発または出血のリスク

抗凝固療法の開始日に関連する主要転帰のリスクを評価した無調整の解析を，オンラインのデータ補遺（Data Supplement）の図IIIAに報告する。ビタミンK拮抗薬の投与患者は，国際標準化比が2以上になった日に抗凝固薬を投与されたものとみなした。最もリスクが低かったのは，5 ～ 10日目に抗凝固薬の投与を受けた患者であった。オンラインのデータ補遺（Data Supplement）の図IIIBには，抗凝固療法の開始日に関連する虚血または出血イベントの無調整リスクを報告する。虚血イベントのリスクは15日目まで不変であった。出血イベントのリスクが最も低かったのは5 ～ 10日目の投与開始であった。

この無調整の解析結果に基づき，Cox回帰モデルによる調整を伴う解析では，抗凝固療法の実施時期として7日以内，14日以内，2 ～ 14日目の期間を選択した。年齢，性別，CHA_2DS_2-VAScスコア，病変の大きさ，再灌流療法，入院時のNIHSSで調整した，この解析では，脳卒中発症後4 ～ 14日目の時点で抗凝固薬の投与を開始した患者は，それ以前またはそれ以降に治療を開始した患者に比べ，主要転帰および虚血イベントが有意に減少したことが示唆された（図2Aおよび2B）。同様に，4 ～ 14日目に抗凝固療法を開始した場合脳出血も減少したが，この差は統計学的に有意ではなかった（図2C）。表には，この開始時期を1日ずつ遅らせ，間隔を短くしていった結果を示しており，ハザード比から最もリスクが低いのは12 ～ 14日目であることが明らかとなった。

表には，指標イベントから7日以内に抗凝固薬を投与された患者と，その後に投与された患者とを比較した，Cox回帰分析の結果も示している。また，指標イベントから14日以内に抗凝固薬を投与された患者と，その後に投与された患者とを比較した結果についても同様に示している。

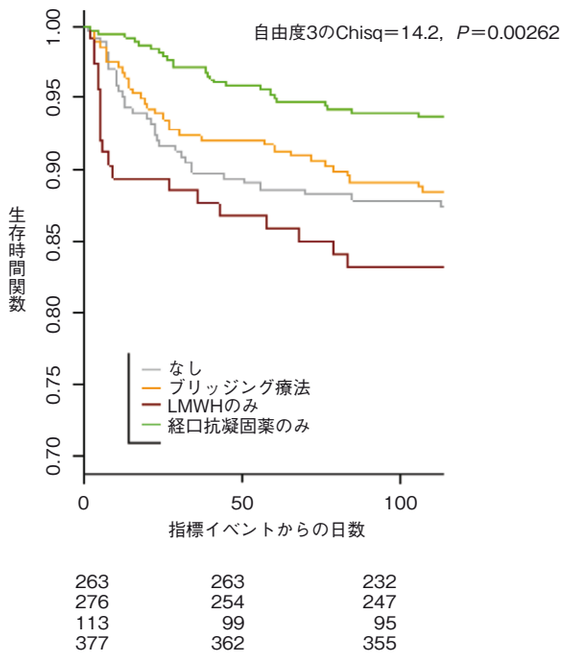
年齢，性別，CHA_2DS_2-VAScスコア，病変の大きさで調整し，抗凝固療法の開始日を時変共変量としたCox比例ハザードモデルでは，抗凝固療法を遅く開始することで，転帰イベントのリスクの平均レベルが高まることが確認された［ハザード比＝3.156，95%信頼区間1.924 ～ 5.176，$P < 0.0001$，オンラインのデータ補遺（Data Supplement）の表V］。

抗凝固薬の種類と投与開始日に関連する虚血イベントの再発または出血のリスク

抗凝固療法の開始日と種類に関連する複合転帰イベントのリスクの差を，図3に報告する。経口抗凝固薬のみを投与された患者は比較的リスクが低く，図3Aのグラフから，二次脳卒中予防に最適な開始タイミングは脳卒中発症後4 ～ 14日目であると考えられる。オンラインのデータ補遺（Data Supplement）の図IVおよびVのグラフは，各種の抗凝固薬の投与患者において，抗凝固療法の開始日に関連して虚血または出血イベントのリスクが異なることを示す証拠である。また，オンラインのデータ補遺（Data Supplement）の図Vから，指標イベントか

ら 2 ～ 3 日目に開始した場合，LMWH のみ，またはワルファリンの前に LMWH を投与した患者で症候性頭蓋内出血のリスクが高いことが示唆される。

指標イベントの発生から 90 日目の時点の機能的転帰に関し，経口抗凝固薬のみを投与された患者の 39.7％（149/375 例）が死亡または身体障害（mRS ≧ 3）となったが，LMWH のみまたは LMWH の後に経口抗凝固薬の投与を受けた患者では，それぞれ 72.3％（81/112 例）および 32.6％（89/273 例）であった。抗凝固療法を受けなかった患者では，73.7％（191/259 例）が死亡または身体障害に至った。



ブリッジング療法：LMWH（低分子量ヘパリン）に続いて経口抗凝固薬を投与

図 1 各種の抗凝固療法を受けた患者の Kaplan-Meier 生存曲線と各期間のリスク症例数（number at risk）（転帰イベント：脳卒中，TIA，症候性頭蓋内出血，全身性塞栓症の複合イベント）。LMWH：低分子量ヘパリン。

病変の大きさと抗凝固療法の開始日に関連する虚血イベントの再発または出血のリスク

大病変は転帰イベントのリスクの上昇に関連した［オンラインのデータ補遺（Data Supplement）の図 VI］。抗凝固療法の開始日に関連する複合転帰イベントのリスクを，小病変または大病変の患者ごとに図 4 に報告する。大病変では，抗凝固薬を 30 日以内に投与した場合，転帰イベントのリスクが上昇したが，小病変では本研究で検討した期間を通じて不変であった。抗凝固療法の開始日に関連する虚血イベントのリスクを，小病変または大病変の患者ごとに，オンラインのデータ補遺（Data Supplement）の図 VII に報告する。

考　察

本研究では，心房細動に伴う急性脳卒中患者における再発イベントの 90 日間のリスクは 7.6％，症候性脳出血の発生率は 3.6％に相当する。今回の結果から，急性虚血性脳卒中の発症後 4 ～ 14 日目の間に抗凝固療法を開始することが，それ以前またはその後の開始に比べ，安全かつ有効であることが示されている。

通常，抗凝固療法の開始時期は病変の大きさによって決められ，これが出血性変化の主な危険因子と考えられている[15]。本研究では，多変量解析の結果，大病変が症候性脳出血の高い発症率および脳卒中の高い再発率に関連していた。実際のところ，小さい虚血性病変がみられる患者は，再発リスクが低い小血管疾患など，心塞栓症以外の基礎的病因を有していた可能性がある[16]。

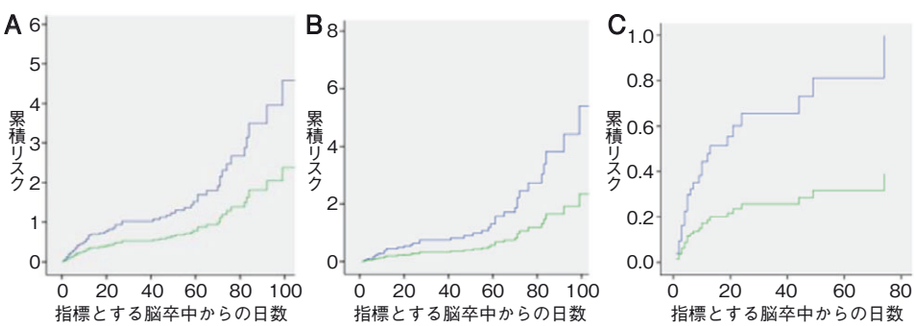
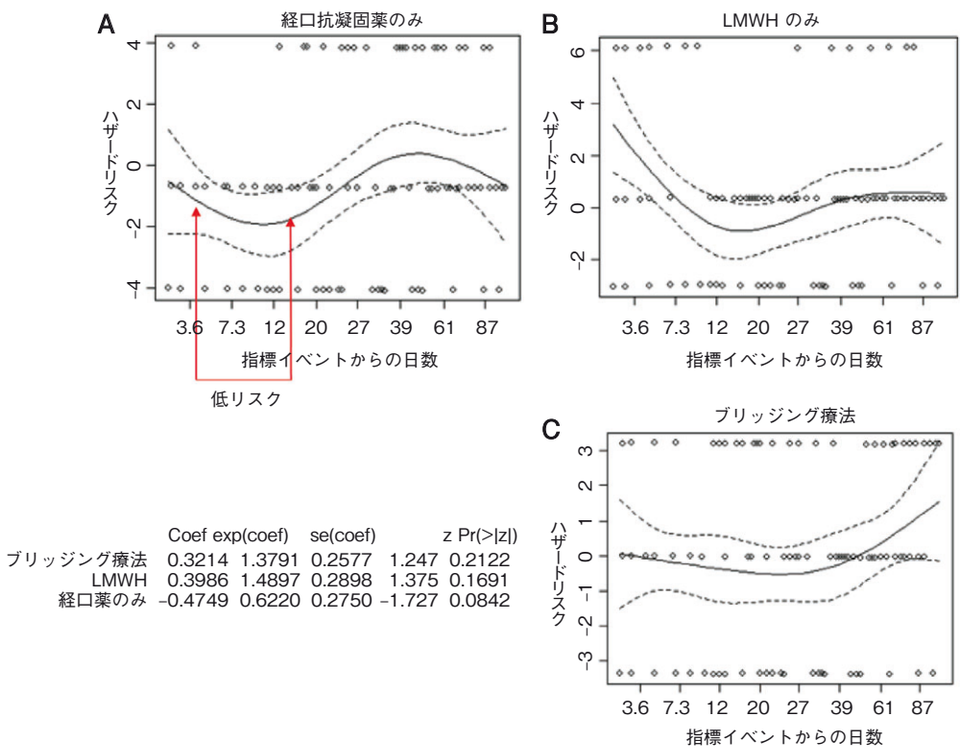


図 2 A, 脳卒中発症後 4 ～ 14 日目に抗凝固薬を投与された患者と他の治療患者における全転帰イベントの比較。ハザード比（HR）＝ 0.53（0.30 ～ 0.93），*P* ＝ 0.025。B, 脳卒中発症後 4 ～ 14 日目に抗凝固薬を投与された患者と他の治療患者における虚血イベント（脳卒中，TIA，全身性塞栓症）の比較。HR ＝ 0.43（0.19 ～ 0.97），*P* ＝ 0.043。C，脳卒中発症後 4 ～ 14 日目に抗凝固薬を投与された患者と他の治療患者における症候性脳出血の比較。HR ＝ 0.39（0.12 ～ 1.19），*P* ＝ 0.09。緑色：脳卒中の発症から 4 ～ 14 日目に抗凝固薬を投与された患者，青色：その他の治療患者（4 日目より前または 14 日目より後に投与）。

表　抗凝固療法を開始した患者におけるハザード比（HR）の比較：脳卒中発症後４～13日目と14日目との比較，急性イベント後７日以内とその後に開始した患者との比較，急性脳卒中発症後14日以内とその後に開始した患者との比較

抗凝固療法の開始時期	全転帰イベント，HR（95% CI）	虚血イベント，HR（95% CI）	出血イベント，HR（95% CI）
7日以内	1.35（0.82～2.22）	1.19（0.76～1.81）	1.72（0.75～4.00）
14日以内	0.71（0.47～2.50）	0.61（0.35～1.06）	1.81（0.75～4.00）
2～14日目	0.67（0.39～1.14）	0.59（0.27～1.29）	0.72（0.29～1.78）
3～14日目	0.58（0.33～1.03）	0.50（0.23～1.12）	0.51（0.18～1.47）
4～14日目	0.53（0.30～0.93）	0.43（0.19～0.97）	0.39（0.12～1.19）
5～14日目	0.47（0.25～0.87）	0.40（0.17～0.86）	0.33（0.10～1.15）
6～14日目	0.42（0.22～0.81）	0.30（0.11～0.80）	0.37（0.10～1.37）
7～14日目	0.43（0.23～0.83）	0.25（0.10～0.65）	0.42（0.11～1.51）
8～14日目	0.42（0.21～0.87）	0.24（0.08～0.69）	0.56（0.15～2.12）
9～14日目	0.43（0.21～0.86）	0.22（0.07～0.62）	0.48（0.13～1.78）
10～14日目	0.30（0.13～0.71）	0.18（0.05～0.63）	0.20（0.02～1.75）
11～14日目	0.29（0.12～0.71）	0.16（0.05～0.56）	0.24（0.03～1.77）
12～14日目	0.21（0.08～0.57）	0.12（0.03～0.45）	0.27（0.03～2.17）
13～14日目	0.38（0.13～1.08）	0.21（0.05～0.85）	0.36（0.04～3.22）
14日目	0.38（0.13～1.11）	0.20（0.05～0.85）	0.36（0.04～3.22）

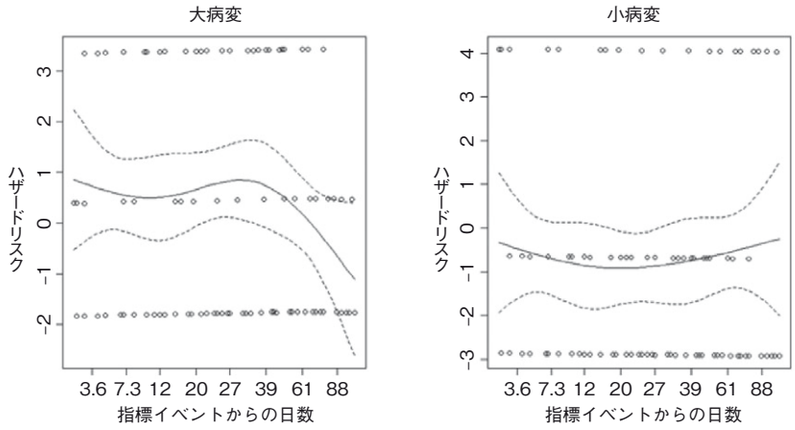


	Coef	exp(coef)	se(coef)	z	Pr(>|z|)
ブリッジング療法	0.3214	1.3791	0.2577	1.247	0.2122
LMWH	0.3986	1.4897	0.2898	1.375	0.1691
経口薬のみ	−0.4749	0.6220	0.2750	−1.727	0.0842

ブリッジング療法：LMWH（低分子量ヘパリン）に続いて経口抗凝固薬を投与

図３　各種の抗凝固療法を受けた患者における抗凝固療法開始日に関連する複合転帰イベントのリスクの差［A：経口抗凝固薬のみ，B：低分子量ヘパリンのみ，C：ブリッジング療法（低分子量ヘパリンの後に経口抗凝固薬を投与）］。抗凝固療法を時変共変量とするCox比例ハザードモデル。ハザードリスク曲線は，推定した比例ハザードの予測値（fitted value）からの標準化残差で示している。

小病変の患者では抗凝固療法をより早期に開始し，大病変の患者では遅らせることにより，安全性は高められるが，有効性に関する利益は小さくなるとの考え方は理に適っている。しかし，PRoFESS試験の対象集団では，指標とした脳卒中のサブタイプが心原性塞栓症または小動脈疾患であった症例の約半数において，再発した脳卒中のサブタイプも指標イベントと同じであったことが報告されている[17]。したがって，抗凝固療法の開始時期を，主に患者のCHA_2DS_2-VAScスコアに基づいて決定することは妥当であると考えられる。実



	coef	exp(coef)		se(coef)	z Pr(>|z|)
大病変	0.4047	1.4988	0.2241	1.805	0.0710
小病変	−0.6143	0.5410	0.2545	−2.414	0.0158 *

図4 小病変および大病変の患者における抗凝固療法開始日に関連する複合転帰イベントのリスクの差。抗凝固療法を時変共変量とした Cox 比例ハザードモデル。ハザードリスク曲線は，推定した比例ハザードの予測値（fitted value）からの標準化残差で示している。

際，本研究では，CHA_2DS_2-VASc が 4 の場合，主要転帰のリスクは 90 日目の時点で 10％と高く，この割合は CHA_2DS_2-VASc スコアの増加とともに線形に上昇した。

本研究において，LMWH のみを投与された患者の占める割合は 14.7％であり，ビタミン K 拮抗薬は 37.8％，直接作用型経口抗凝固薬は 12.1％，そして LMWH の後にビタミン K 拮抗薬（ブリッジング療法）を投与された患者は 36.0％であった。経口抗凝固薬のみを投与された患者は，LMWH の後に経口抗凝固薬または LMWH のみを投与された患者に比べ，出血イベントのリスクが有意に低かった。LMWH のみの治療方針は，最も高い出血リスクに関連した。この知見は，脳卒中の重症度がより高い患者は，嚥下障害を伴う可能性がより高く，経口抗凝固薬の投与率が低かったことに関連すると考えられる。

直接作用型経口抗凝固薬の投与を受けた患者では，症候性頭蓋内出血（2.1％）および虚血イベント（4.3％）のリスクが低かったことから，心房細動患者における虚血性脳卒中の急性期を対象に，さらにこれらの新薬を検討する必要性が示唆される[18]。しかし，低リスクの患者に対してこの治療法が選択されていた可能性も除外できない。

本研究にはいくつかの限界がある。第 1 に，調整した統計モデルにより交絡因子の影響を抑制したものの，今回の非無作為化研究で報告した関連性は間違いなく，数多くの潜在的交絡因子の影響を受けている。第 2 に，転帰イベントの中央判定および虚血病変測定のための血管画像検査の一元化がいずれも行われなかった。第 3 に，抗血栓療法の状況により，脳卒中の再発と無症候性頭蓋内出血の確認において，非盲検化によるバイアスが存在した可能性がある。最後に，抗血栓療法の開始時期に関する選択バイアスの可能性は除外できない。実際に，高齢患者や重度脳卒中患者の大半は，より状態の安定した患者に比べ，治療を受けていないか，治療に遅れがみられた。

本研究の強みは，十分な症例数と前向きデザインである。本研究の知見は，実際の状況を反映している。また，無作為化データが全くないことを踏まえると，脳卒中専門医に対し，心房細動患者の急性脳虚血に対するよりよい管理について，重要な観察的情報を提供していると考えられる。

結論として，心房細動を伴う急性脳卒中患者は，発症後 90 日目の時点における虚血性塞栓性再発および重度出血のリスクが高いことが明らかになった。また，脳卒中の二次予防として抗凝固療法を開始する最適な時期は，急性イベントから 4 ～ 14 日目であることが示唆される。経口抗凝固薬のみを投与された患者の転帰は，LMWH のみまたは経口抗凝固薬の前に LMWH を投与された患者よりも良好であった。さらに，虚血病変が大きい患者は，小病変の患者に比べ，塞栓の再発および脳出血のリスクが高かった。心房細動患者の脳卒中急性期を対象として，直接作用型経口抗凝固薬の有効性を評価する無作為化試験の実施は妥当と考えられる。

謝辞

Thomas Charles Kilcline 氏による編集作業への貢献に対し感謝する。

情報開示

M.Paciaroni は Sanofi-Aventis, Boehringer Ingelheim, Bayer および Pfizer の講演者（speaker bureau）として謝礼金を受領した。G. Agnelli は Boehringer Ingelheim および Bayer の講演者（speaker bureau）として謝礼金を受領した。C. Becattini は Bristol Meyer Squibb および Bayer の講演者（speaker bureau）として謝礼金を受領した。P. Michel は Swiss National Science Foundation および Swiss Heart Foundation から研究助成金，Bayer, Boehringer Ingelheim, Covidien, St. Jude Medical から講演者謝礼金のほか，Pierre-Fabre, Bayer, Bristol Meyer Squibb, Amgen, Boehringer Ingelheim から顧問的立場に対する謝礼金を受領した。J. Putaala は Orion Pharma, Bristol Meyer Squibb, Pfizer, Bayer, Boehringer Ingelheim から心房細動および抗凝固薬に関する講演の謝礼金を受領した。T. Tatlisumak は Lundbeck および Boehringer Ingelheim のコンサルタントまたは顧問的立場として謝礼金を受領した。G. Tsivgoulis は 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）から研究支援を受けた。D. Toni は Boehringer Ingelheim および Bayer から講演者（speaker bureau）および顧問委員として謝礼金を受領した。その他の著者は利益相反がないことを報告している。

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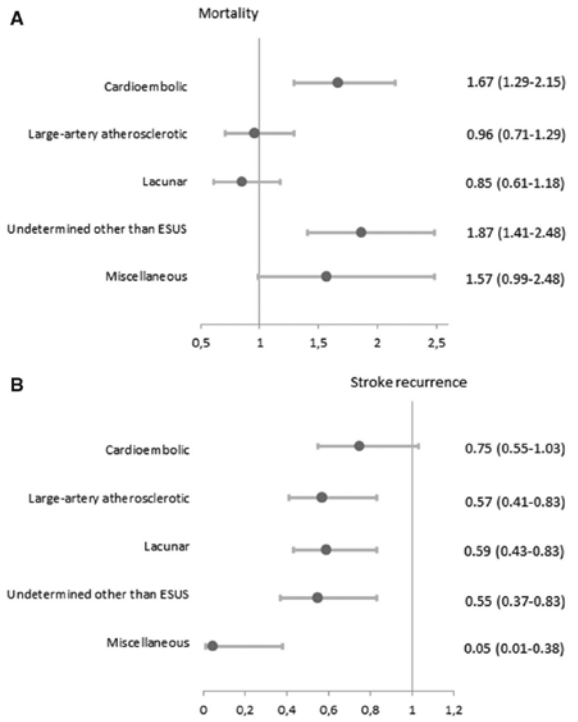

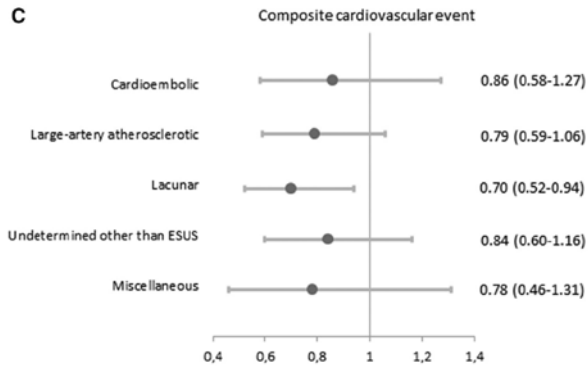

Figure 2. Adjusted hazard ratios of 5-year mortality adjusted to age, sex, National Institute of Health Stroke Scale (NIHSS) score on admission, history of smoking, atrial fibrillation, dyslipidemia, coronary artery disease, heart failure and in-hospital use of aspirin (**A**), stroke recurrence adjusted to age, history of hypertension, smoking, transient ischemic attack, atrial fibrillation, and dyslipidemia (**B**), and composite cardiovascular event adjusted to age, NIHSS score on admission, history of diabetes mellitus, atrial fibrillation, and coronary artery disease (**C**) of stroke types compared with ESUS. ESUS indicates embolic stroke of undetermined source.

Abstract 8

급성허혈뇌졸중과 심방세동을 가진 환자들의 조기 재발 및 뇌출혈

항응고치료의 효과와 시기: RAF 연구

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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(*Stroke*. 2015;46:2175-2182.)

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

배경과 목적

급성심장색전뇌졸중에서 항응고제 투여의 가장 적절한 시기는 명확하지 않다. 저자들은 급성뇌졸중과 심방세동을 가진 환자들에 대한 전향적인 코호트 연구에서 (1) 재발성 허혈 사건 및 중증 출혈에 대한 위험도, (2) 재발 및 출혈에 대한 위험인자 및 (3) 급성뇌졸중 이후의 항응고 치료 및 시작 시점과 연관된 재발 및 출

혈의 위험도를 평가하였다.

방법

이 다기관 연구의 일차 종점은 급성뇌졸중 발생으로부터 90일 이내에 발생한 모든 뇌졸중, 일과성허혈발작, 증상성전신색전, 증상성뇌출혈 및 주요 두개외출혈이었다.

결과

전체 모집된 1029명의 환자 중 123명에서 128건(12.6%)의 사건이 발생하였다: 77명(7.6%)에서는 허혈뇌졸중, 일과성허혈발작 또는 전신색전이 발생하였고, 37명(3.6%)에서는 증상성뇌출혈이 발생하였고, 14명(1.4%)의 환자에서는 주요 두개외출혈이 발생하였다. 뇌졸중 발생 90일째에 50%의 환자들은 사망하였거나 혹은 장애가 남았고(수정랜킨척도 ≥3), 10.9%는 사망하였다. 높은 CHA2DS2-VASc 점수, NIH Stroke 점수, 큰 허혈 병변 및 항응고제의 종류는 일차 종점에 대한 예측인자였다. 보정된 Cox 회귀분석에서 뇌졸중 발생 이후 4일에서 14일 사이에 항응고 치료를 시작하는 것은 4일 이전 혹은 14일 이후에 치료를 시작하는 것에 비해 일차 종점의 유의한 감소와 관련되었다(위험도 0.53, 95% CI, 0.30–0.93). 경구 항응고제 단독으로 치료한 환자들의 7%에서 사건이 발생하였는데, 저분자량헤파린 단독을 사용한 그룹과 경구 항응고제와 저분자량헤파린을 같이 사용한 그룹에서의 사건을 발생률은 각각 16.8%와 12.3%였다(P=0.003).

결론

심방세동 환자에서의 급성뇌졸중은 90일째의 높은 허혈 사건의 재발률 및 주요 출혈 발생률과 연관되어 있다. 이 연구는 높은 CHA2DS2-VASc 점수, NIH Stroke 점수, 큰 병변 및 항응고제의 종류가 재발 및 출혈의 위험 증가에 독립적으로 기여한다는 것을 확인하였다. 또한 연구 결과는 뇌졸중의 이차 예방을 위한 항응고치료 시작의 최적의 시점은 4일에서 14일 사이인 것으로 확인하였다. 더욱이 경구항응고제 단독을 투여받은 환자들은 저분자량헤파린만 사용하거나 경구항응고 시작 전 저분자량헤파린을 사용한 환자들에 비하여 양호한 결과는 보이는 것으로 조사되었다.

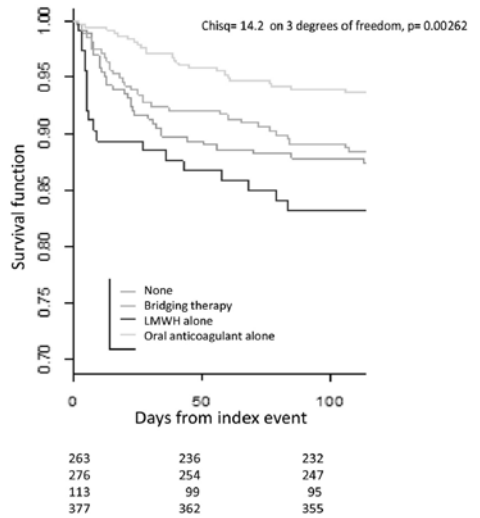


Figure 1. Kaplan–Meier survival curves for patients treated with different types of anticoagulation strategies with numbers at risk during various time intervals (outcome event: combination of stroke, transient ischemic attack, symptomatic intracranial hemorrhage, systemic embolism). LMWH indicates low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

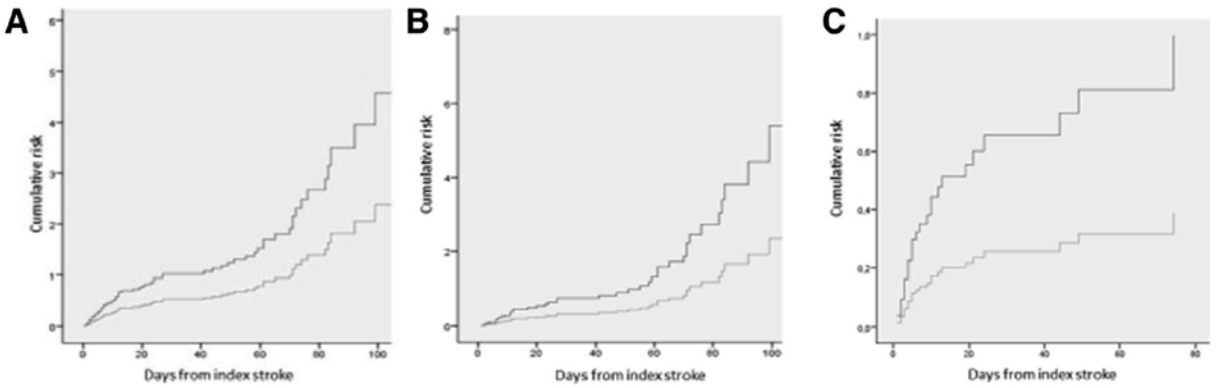
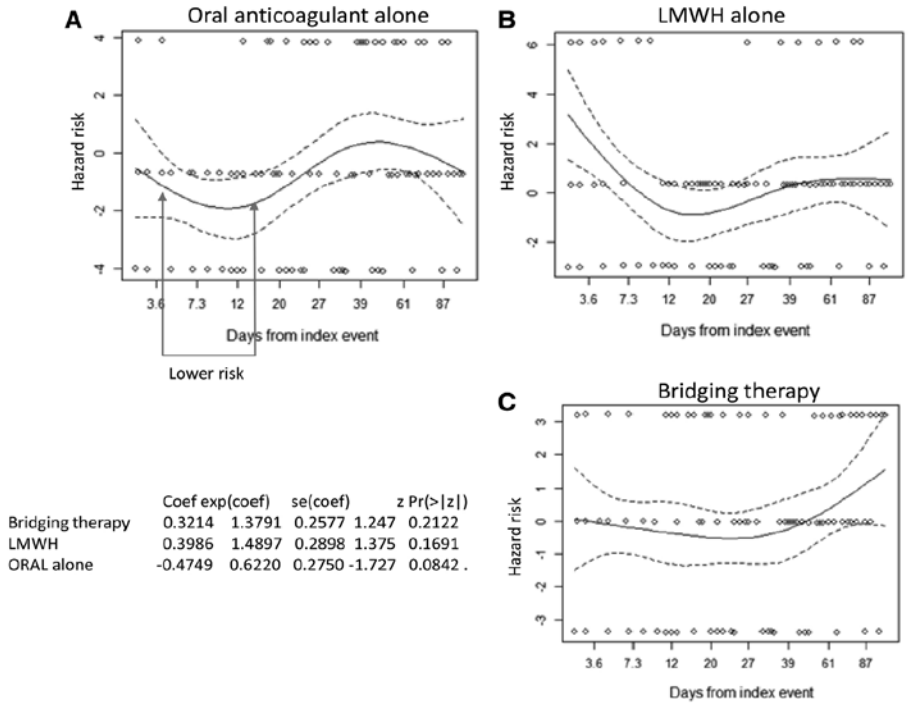


Figure 2. A, All outcome events in patients treated with anticoagulants between days 4 and 14, compared with the other treated patients. Hazard Ratio (HR)=0.53 (0.30–0.93), P=0.025. **B**, Ischemic outcome events (stroke, transient ischemic attack, systemic embolism) in patients treated with anticoagulants 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).



	Coef	exp(coef)	se(coef)	z	Pr(>|z|)
Bridging therapy	0.3214	1.3791	0.2577	1.247	0.2122
LMWH	0.3986	1.4897	0.2898	1.375	0.1691
ORAL alone	-0.4749	0.6220	0.2750	-1.727	0.0842 .

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

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.

Abstract 9

빈스방거병에서 혈관뇌장벽(blood–brain barrier, BBB) 투과도의 장기간 변화

Long-Term Blood–Brain Barrier Permeability Changes in Binswanger Disease

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(*Stroke*. 2015;46:2413-2418.)

Key Words: blood–brain barrier ■ leukoaraiosis ■ magnetic resonance imaging ■ permeability ■ white matter

배경과 목적

열공(lacunes)과 백색질고음영(white matter hyperintensities, WMHs)이 있는 소혈관질환 환자에서는 혈관뇌장벽(blood–brain barrier, BBB)이 파괴된다. WMHs과 국소 BBB 투과도 변화의 관계는 지금까지 연구되지 않았다. BBB 파괴는 정상적으로 보이는 WM와 WMHs 주변부에서 일어난다는 가설을 세웠다. 가설을 시험하기 위해, 빈스방거병과 연관된 광범위한 WMHs가 있는 환자에서 BBB 투과도 측정을 반복하였다.

방법

잘 특성화된 대규모 전향적 혈관인지장애 코호트에서 22명의 빈스방거병 환자들로 구성된 부분집합을 선택하였다. 비교를 위해 16명의 연령이 맞는 대조군을 사용하였다. 비정상 백색질투과도(white matter permeability, WMP)는 역동적 조영증강 자기공명영상(dynamic contrast–enhanced MRI)을 사용하여 수년간 두 차례 측정하였다. WMP 지도는 미리 정해진 역치 이상의 복셀(voxel)로부터 구축되었다. 첫 번째 및 두 번째 방문의 촬영은 함께 등록되었다. WM는 3개 부분으로 나뉘었다: 정상으로 보이는 WM, WMH 주변부(ring), WMH 핵심부(core). 주변부는 WMH 경계의 양측 2 mm로 정의하였다. WMP는 3군데 특정 구역 각각에서 계산하였다. 우리는 개별 변화를 비교하기 위해 대응표본 t 검정, ANOVA, Fisher 정확검정을 사용하였다.