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**Timing of initiation of oral anticoagulants in patients with acute ischemic stroke and atrial fibrillation comparing posterior and anterior circulation strokes.**

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**Background:** The aim of this study in patients with acute posterior ischemic stroke (PS) and atrial fibrillation (AF) were to evaluate (1) the risks of recurrent ischemic event and severe bleeding and (2) these risks in relation with oral anticoagulant therapy (OAT) and its timing.

**Methods:** Patients with PS were prospectively included; the outcome events of these patients were compared with those of patients with anterior stroke (AS) which were taken from previous registries. The primary outcome was the composite of: stroke recurrence, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding and major extracranial bleeding occurring within 90 days from acute stroke.

**Results:** A total of 2,470 patients were available for the analysis: 473 (19.1%) with PS and 1,997 (80.9%) AS. Over 90 days, 213 (8.6%) primary outcome events were recorded: 175 (8.7%) in patients with AS and 38 (8.0%) in those with PS. In patients who initiated OAT within 2 days, the primary outcome occurred in 5 out of 95 patients (5.3%) with PS compared to 21 out of 373 patients (4.3%) with AS (OR 1.07; 95% CI 0.39-2.94). In patients who initiated OAT between days 3 and 7, the primary outcome occurred in 3 out of 103 patients (2.9%) with PS compared to 26 out of 490 patients (5.3%) with AS (OR 0.54; 95% CI 0.16-1.80).

**Conclusions:** Patients with posterior or anterior stroke and AF appear to have similar risks of ischemic or hemorrhagic events at 90 days with no difference concerning the timing of initiation of OAT.

## **Introduction**

Anticoagulant therapy has been proven to be highly effective for secondary stroke prevention in patients with atrial fibrillation (AF) (1). Deciding when to initiate this therapy in patients with acute ischemic stroke and AF is a challenge because the risks of both early recurrent ischemic stroke and hemorrhagic transformation are highest in the days immediately following the acute event (2).

Indeed, there are no definitive data on this issue and current guidelines do not adequately address when to best start oral anticoagulation with even greater uncertainties in patients with acute posterior circulation stroke (3). In fact, it has been described that posterior circulation stroke was associated with a higher early risk for subsequent stroke compared to carotid events; while there was a lower risk of hemorrhagic transformation (4-6).

This international prospective multicenter study included patients with acute ischemic posterior circulation stroke and AF, with the principle aims of evaluating at 90 days from an acute event for (1) the risks of recurrent ischemic embolic event and severe bleeding (both intra and extracranial) as well as (2) the risks of recurrent ischemic embolic event and bleeding in relation to the timing of the start of anticoagulant therapy. Moreover, the rates of ischemic events for patients with anterior or posterior circulation stroke were compared. The data for patients with anterior circulation stroke came from previously published studies. The protocol and the statistical analyses were discussed and approved by all the co-authors before initiating the collect of the data.

## **Methods**

This observational study was performed between October 2018 and June 2019 and included consecutive patients with acute ischemic posterior circulation stroke and previous or newly diagnosed AF without contraindications to anticoagulation. Overall, 19 Stroke Units across Europe, North America and Asia participated. The study was approved by the local institutional review boards, whenever required.

Posterior circulation stroke was defined as any acute stroke occurring in the territories of the posterior cerebral arteries (deep and or superficial), brainstem or cerebellum (7) visible on neuroimaging.

On admission, stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and a cerebral computed tomography examination without contrast or cerebral magnetic resonance imaging (MRI) was performed on all patients to exclude for intracranial hemorrhage. Thrombolysis treatment and/or mechanical thrombectomy were performed as per standard local protocol, in accordance with international guidelines. All participating Stroke Units provided standard Stroke Unit care and monitoring. Physicians were free to decide on any administration of anticoagulant treatment (warfarin, apixaban, edoxaban, dabigatran or rivaroxaban), as well as their timing.

A second brain computed tomography scan or MRI was to be performed 24 to 72 h from stroke onset. 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 (8,9). HT was considered symptomatic whenever it was 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 (10). The sites and sizes of the qualifying infarcts were determined according to standard templates (7): (1) small, when a lesion was  $\leq 1.5$  cm and large, when a lesion was  $>1.5$  cm.

Risk factors and the outcome events of patients with posterior circulation stroke were compared with those of patients with anterior circulation stroke. The latter data came from the RAF and RAF NOACs (Non-vitamin K oral anticoagulants) studies (11,12) that were prospective observational studies carried out between January 2012 and March 2014 at 29 Stroke Units and between April 2014 and June 2016 at 35 stroke units respectively, across Europe, United States and Asia. Both the RAF studies enrolled consecutive patients with acute ischemic stroke and known or newly

diagnosed AF without contraindications to anticoagulation. The same inclusion criteria used for RAF and RAF NOACs was used for the present study.

### **Risk Factors**

Data on risk factors were collected: age, sex, history of hypertension (blood pressure  $\geq 140/90$  mm Hg at least twice before stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus [fasting glucose level  $\geq 126$  mg/dL (7 mmol/L) preprandial on 2 examinations, glucose level  $\geq 200$  mg/dL (11.1 mmol/L) postprandial, or HbA1c  $\geq 6.5\%$ , or under antidiabetic treatment], current cigarette smoking, hyperlipidemia [total cholesterol  $\geq 200$  mg/dL (5.2 mmol/L) or triglycerides  $\geq 140$  mg/dL (1.6 mmol/L) or already under lipid lowering therapy], history of symptomatic ischemic heart disease (myocardial infarction, history of angina pectoris, 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 ( $\geq 300$  g per week), obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), 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  $\geq 5$  mm according to published criteria) were investigated (13). 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 Ratio, activated partial thromboplastin time, systolic blood pressure, and diastolic blood pressure. Data on the use of any antiplatelet, anticoagulants, or revascularization therapy (thrombolytic agents and/or mechanical thrombectomy), before admission, at baseline, and during the follow-up period, were recorded. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score (2 points for a history of stroke or age  $\geq 75$  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 (14).

AF was categorized as: paroxysmal (episodes terminating spontaneously within seven days), persistent (episodes lasting more than seven days or requiring pharmacological and/or electrical cardioversion and permanent (persisting for more than one year, either because cardioversion failed or was not pursued (15). For the purpose of the present study, AF was categorized into two types: paroxysmal AF or sustained (persistent or permanent) AF.

### **Evaluation of Outcome**

Patients were followed-up prospectively by face-to-face, telephone interviews or a review of available medical charts whenever a patient had died during follow-up. Whenever an outcome event occurred, patients were requested to consign any related documentation during a face-to-face visit. Study outcomes were (1) recurrent ischemic cerebrovascular events (stroke or TIA) and symptomatic systemic embolisms; (2) symptomatic cerebral bleedings (intracerebral hemorrhage) and major extracerebral bleeding at 90 days. The primary study 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 Scale score (mRS). Functional outcome was defined as either non-disabling (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 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 extra-cerebral 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 (16).

### **Statistical Analysis**

Patient characteristics are presented as mean and standard deviations for continuous variables and as absolute numbers and percentages for categorical variables. Differences in the characteristics of patients with posterior or anterior circulation stroke were calculated using  $\chi^2$  test for nominal variables and ANOVA for continuous variables. Furthermore, differences in the characteristics of patients with or without outcome event at 90 days were calculated using  $\chi^2$  test for nominal variables whereas ANOVA was used for continuous variables. A multivariable analysis was performed using logistic regression to seek independent predictors of outcome events. The variables included in the model were: age, sex, vascular risk factors, type of anticoagulant, leukoaraiosis, lesion size, type of AF and pacemaker.

Given that data relevant to anterior and posterior circulation strokes were collected over different time periods, a multivariable analysis that adjusted for these time period differences was also performed. For this analysis, the variable “time period of data collection” was classified as 0 for the period 2014-2016 and 1 for the period 2018-2019, and then included in the multivariable model. Moreover, a multivariable model adjusted for any possible effects associated with the different times of initiating the oral anticoagulants was utilized.

Survival function and empirical cumulative hazards function were estimated using Kaplan–Meier estimators for the investigated subgroups 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 (17). Patients were censored at the time of an outcome event, death, or if they were lost to follow-up. In order to best estimate associations, we used odds ratios (OR) for multivariable logistic models; a two-sided  $p$ -value  $< 0.05$  was considered significant.

All statistical analyses were performed using the IBM SPSS Statistics version 25.0 (IBM Corporation, Somers, NY).

The study fulfilled 20/22 items listed in the STROBE for observational studies (18).

## **Results**

A total of 473 patients with posterior circulation stroke were prospectively included; the data of these patients were compared with the data of 1,997 patients with anterior circulation stroke taken from the RAF (969) and RAF NOACs (1028) studies. This population of 2,470 patients (1,306 females, 52.9%) were available for the analysis.

The baseline characteristics of the patients are listed in Table 1. Posterior circulation stroke patients were more likely to have the following: lower baseline NIHSS-score, diabetes mellitus, hypertension, hyperlipidemia, paroxysmal AF, congestive heart failure, implanted pacemaker, history of myocardial infarction and peripheral arterial disease, CHA<sub>2</sub>DS<sub>2</sub>-VASc>4 and large lesion size. Moreover, patients with posterior circulation stroke were also more likely to be on treatment with direct oral anticoagulant after the index stroke; 22 patients with posterior circulation stroke had stenosis  $\geq$ 50% or occlusion of the basilar artery.

## **Outcome Events**

Over 90 days of follow-up, 213 (8.6%) outcome events were recorded: 175/1997 (8.7%) in patients with anterior circulation stroke and 38/473 (8.0%) in patients with posterior circulation stroke. In Table 2 the outcome events are summarized according to anterior or posterior circulation. There were no significant differences between the two groups regarding all types of outcome events (combined, ischemic or hemorrhagic). Considering the entire population, on multivariable analysis, diabetes mellitus (OR 1.66; 95% CI 1.20-2.31), pacemaker (OR 1.73; 95% CI 1.06-2.82), large lesion size (OR 1.81; 95% CI 1.26-2.63) and treatment with warfarin versus NOACs (OR 2.76; 95% CI 1.77-4.29) were associated with combined outcome events, while diabetes mellitus (OR

1.60; 95% CI 1.06-2.44), treatment with warfarin versus NOACs (OR 2.90; 95% CI 1.68-5.03) and NIHSS on admission (OR 1.02 for each point increase; 95% CI 1.00-1.05) were associated with ischemic outcome events. Furthermore, diabetes mellitus (OR 1.63; 95% CI 1.01-2.62), treatment with warfarin versus NOACs (OR 2.23; 95% CI 1.18-4.23) and large lesion size (OR 2.91; 95% CI 1.61-5.20) were associated with hemorrhagic outcome events. Adjusting for different time period collections, no significant differences were evidenced between anterior and posterior circulation strokes, regarding all types of outcome events: OR 0.79 (95% CI 0.10-6.11) for combined end-point, OR 1.23 (95% CI 0.16-9.55) for ischemic end-point and OR 2.11 (95% CI 0.27-16.53) for hemorrhagic end-point.

The outcome events according to the time of oral anticoagulant therapy initiation in patients with anterior or posterior circulation stroke are reported in both Table 3 and Figure 1: 2 out of 95 patients (2.1%) with posterior circulation stroke who initiated oral anticoagulant therapy within 2 days from index stroke had an ischemic endpoint, compared to 16 out of 373 patients (4.3%) with anterior circulation stroke who initiated oral anticoagulant therapy within the same time period (OR 0.48; 95% CI 0.11-2.12). While 1 of the 103 patients (0.9%) with posterior circulation stroke who initiated oral anticoagulant therapy between day 3 and 7 from index stroke, had an ischemic endpoint, compared to 19 out of 490 patients (3.8%) with anterior circulation stroke who initiated oral anticoagulant therapy within the same time period (OR 0.24; 95% CI 0.03-1.84). Furthermore, 3 out of 95 patients (3.1%) with posterior circulation stroke who initiated oral anticoagulant therapy within 2 days from index stroke had a hemorrhagic endpoint compared to 5 out of 373 patients (1.3%) with anterior circulation stroke who initiated oral anticoagulant therapy within the same time period (OR 2.37; 95% CI 0.56-10.11). Whereas 2 of 103 patients (1.9%) with posterior circulation stroke who initiated oral anticoagulant therapy between days 3 and 7 from index stroke had a hemorrhagic endpoint, compared to 8 out of 490 patients (1.6%) with anterior circulation stroke who initiated oral anticoagulant therapy within the same time period (OR 1.19; 95% CI 0.25-5.70). Regarding the combined endpoint (ischemic and hemorrhagic), 5 out of 95 patients (5.3%)

with posterior circulation stroke who initiated oral anticoagulant therapy within 2 days from index stroke had an endpoint, compared to 21 out of 373 patients (4.3%) with anterior circulation stroke who initiated oral anticoagulant therapy within the same time period (OR 0.93; 95% CI 0.34-2.54). While 3 out of 103 patients (2.9%) with posterior circulation stroke who initiated oral anticoagulant therapy between days 3 and 7 from index stroke had an endpoint, compared to 26 out of 490 patients (5.3%) with anterior circulation stroke who initiated oral anticoagulant therapy within the same time period (OR 0.54; 95% CI 0.16-1.80). The risk of any outcome event appeared to be higher after starting anticoagulant therapy >7 days from index stroke for both groups. Adjusting for the different times of oral anticoagulant initiation from index stroke, no significant difference was observed between anterior and posterior circulation strokes regarding combined outcome event (OR 8.31; 95% CI 0.68-100.88). This analysis was not performed for either ischemic or hemorrhagic outcome events, due to the low number of events in both arms.

The outcome events in patients with posterior circulation stroke associated with lesion size are reported in Table 4 and Figure 2: 2 out of 116 patients (1.7%) with small lesion had a hemorrhagic outcome event within 90 days, compared to 18 out of 352 (5.0%) of patients with large lesion (Log rank test,  $p=0.05$ ).

At 90 days, 763 out of 1997 patients (38.2%) with anterior circulation stroke and 187 out of 473 patients (39.5%) with posterior circulation stroke had an mRS>2 (OR 0.95; 95% CI 0.77-1.16); 123 out of 1,997 (6.2%) with anterior circulation stroke and 41 out of 473 patients (8.7%) with posterior circulation stroke died (OR 0.69; 95% CI 0.48-1.00).

## **Discussion**

This study showed that patients with posterior circulation stroke and AF had, at 90 days, an 8.0% risk of combined outcome events that was similar to that of anterior circulation stroke patients (8.7%). The observed risk of ischemic outcome events, though not statistically significant, was lower in patients with posterior circulation stroke, compared to those with anterior circulation

stroke. Moreover, it seems that patients with posterior circulation stroke had a non-statistically significant higher risk for hemorrhagic outcome events, compared to those patients with anterior circulation stroke. With regard to the timing of initiation of oral anticoagulant treatment, the combined outcome event risk in patients with posterior circulation stroke, who had initiated the therapy in the first 7 days, was 8.2%, compared to 10.9% in patients with anterior circulation stroke. Our findings suggest that, when deciding the time to initiate oral anticoagulation, the location of stroke, either anterior or posterior, does not predict the risk of outcome events. Also, the functional final outcome at 90 days using mRS was similar between the two groups, while the NIHSS revealed a less severe stroke syndrome in posterior circulation stroke patients compared to anterior circulation stroke patients. This finding can be attributed to the fact that NIHSS includes more symptoms of the anterior than the posterior circulation; patients with posterior circulation stroke have a score lower despite similar stroke severity (19).

In patients with posterior circulation stroke and AF the risk of intracerebral bleeding in patients with small lesion was low; suggesting an earlier initiation of oral anticoagulant therapy. Several randomized trials are ongoing to further investigate this specific research question (2).

Several studies have reported that patients with posterior and anterior circulation stroke did not differ in terms of the prevalence of vascular risk factors (20-22). Other studies have reported differences in etiology between the two groups (19, 23-26). In our study, patients with posterior circulation stroke appeared to have a higher prevalence of risk factors. Of note, all of the above studies included patients with anterior or posterior circulation stroke without considering etiology while our study included only patients with acute stroke and AF.

Our study has several limitations. First, due to the non-randomized nature of the study, our results may be influenced by several confounders including a selection bias for treatment, even if adjusted statistical models were used in the attempt to control them. Second, a central adjudication of the outcome events was not performed but rather, these events were assessed by the local investigators. Third, in observational studies it is not possible to adjust for physician biases associated with

prescription of oral anticoagulant timings and agents. Another potentially important factor is the difference in time period between posterior strokes and anterior strokes; the former being recent and the latter being from previously published studies with enrolment before 2014 (the RAF and RAF-DOAC studies). There could therefore be important secular trends accounting for different event rates (e.g changes in NOAC use), improved general stroke care (e.g. possibly less bridging), or different oral anticoagulant therapy timing. In fact, regarding changes in oral anticoagulant type use, in the posterior stroke population, which was more recently collected, 66% of the patients were treated with NOACs compared to 55% of the patients in the anterior stroke population. Conversely, 27% of the patients with anterior stroke were treated with warfarin, compared to 19% of the patients in the posterior stroke population.

Furthermore, in the posterior circulation stroke group, compared to the anterior circulation stroke group, a lower number of patients were treated with bridging therapy with full dose of enoxaparin (18% versus 45%). It is plausible that this disparity was influenced by the fact that, in the RAF studies, patients treated with bridging therapy had a worse outcome, compared to those treated without bridging therapy (27). These differences might have influenced the results, even if multivariable models were used in the attempt to adjust them.

There are several ongoing randomized controlled trials to overcome the limitations of these observational data (28) and furthermore, subgroup analyses of these trials are needed to determine how the timing of anticoagulation might interact with ischemic stroke location.

The strengths of our study include its prospective design, the multi-center nature and relatively large sample size.

In conclusion, we observed that patients with posterior or anterior stroke and AF, had similar risks of ischemic and hemorrhagic events at 90 days. The timing of oral anticoagulant initiation did not appear to influence the association between stroke location and outcome events.

## Disclosures

Maurizio Paciaroni received honoraria as a member of the speaker bureau of Aspen, Sanofi-Aventis, Boehringer Ingelheim, Bayer, Bristol Meyer Squibb, Daiiki Sankyo and Pfizer.

Giancarlo Agnelli received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer.

Valeria Caso received honoraria as a member of the speaker bureau and as consultant or advisory board of Boehringer Ingelheim.

Jesse Dawson has received speaker fees from Boehringer Ingelheim, Bayer, Bristol Meyer Squibb, Daiiki Sankyo and Pfizer.

Jukka Putaala received honoraria for lectures related to atrial fibrillation and anticoagulants for Orion Pharma, Bristol Meyer Squibb, Pfizer, Bayer and Boehringer Ingelheim.

Turgut Tatlisumak received honoraria as consultant or advisory relationship by Bayer, Boehringer Ingelheim, Bristol Meyer Squibb, Lumosa Pharm and Portola Phaema.

Kennedy Lees reports fees and expenses for data monitoring committee work and lectures from Boehringer Ingelheim.

Walter Ageno has received speaker's honoraria from, and participated in scientific advisory boards for, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, and has received research support from Bayer and Boehringer Ingelheim.

Danilo Toni received speaker's honoraria and participated in scientific advisory boards for Abbott, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic and Pfizer.

George Ntaios reports speaker fees/advisory board/research support from Bayer, Pfizer, Boehringer Ingelheim and Elpen. All fees are paid to his institution.

Simona Sacco has received honoraria as speaker or as member of advisory boards from Abbott, Allergan, Eli Lilly, Novartis and Teva.

Peter Vanacker received honoraria as a member of the speaker bureau and as advisory board of Boehringer Ingelheim, Bristol Meyer Squibb, Daiichi Sankyo, Medtronic, EG and Pfizer



The other authors have nothing to disclose.

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Table 1: Baseline characteristics stratified by stroke location

	Anterior Stroke (n=1997)	Posterior stroke (n=473)	P
Age (years) mean	76.3±9,7	77.6±9.6	0.6
Median	77.00	79.00	
NIHSS on admission mean	8.5±6.7	6.8±6.9	0.02
Median	6.00	4.00	
Male sex	924 (46.3%)	240 (50.7%)	0.08
Diabetes mellitus	443 (22.2%)	126 (26.6%)	0.04
History of hypertension	1557 (78.0%)	391 (82.7%)	0.02
Hyperlipidemia	675 (33.8%)	190 (40.2%)	0.009
Paroxysmal atrial fibrillation	842 (42.2%)	238 (50.3%)	0.001
History of stroke/TIA	520 (26.0%)	129 (27.3%)	0.5
Current smoker	188 (9.4%)	46 (9.7%)	0.8
Alcohol	127 (6.4%)	55 (11.6%)	0.0008
Congestive heart failure	172 (8.6%)	60 (12.7%)	0.006
History of myocardial infarction	264 (13.2%)	103 (21.8%)	0.0001
History of peripheral artery disease	172 (8.6%)	55 (11.6%)	0.04
Therapy with warfarin after index event	536 (26.8%)	89 (18.8%)*	0.004
- Bridging with full dose enoxaparin	243 (45.3%)	16 (18.0%)	
Therapy with direct anticoagulants after index event	1098 (55.0%)	314 (66.3%)*	0.0001
- Apixaban	338 (30.8%)	129 (41.1%)	
- Dabigatran	405 (36.9%)	90 (28.7%)	
- Edoxaban	0	18 (5.7%)	
- Rivaroxaban	355 (32.3%)	77 (24.5%)	
- Bridging with full dose enoxaparin	112 (10.2%)	18 (5.7%)	
No oral anticoagulants after index event	363 (18.2%)	35 (7.4%)*	0.0001
Mean time of anticoagulant therapy initiation (days)	11.4±15.3	12.3±19.9	0.2
Pacemaker	141 (7.1%)	32 (6.8%)	0.8
Lesion size >1.5 cm	1169 (58.5%)	357 (75.5%)	0.001
Leukoaraiosis	988 (49.5%)	318 (67.2%)	0.0001
rtPA and/or thrombectomy	535 (26.8%)	8 (16.9%)	0.0001
Hemorrhagic transformation (24-72 hours)	214 (10.7%)	75 (15.9%)	0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc > 4	1539 (77.1%)	415 (87.7%)	0.001

\*35 patients missing

Table 2: Association of stroke location (anterior vs. posterior) with outcome events

	Posterior circulation stroke (n=473)	Anterior circulation stroke (n=1997)	Odds ratios (95% Confidence Interval)
Combined endpoint	38 (8.0%)	175 (8.7%)	Unadjusted 0.94 (0.65 – 1.36) Adjusted 0.79 (0.53 – 1.19)
Ischemic endpoint	18 (3.8%)	102 (5.1%)	Unadjusted 0.73 (0.44 – 1.23) Adjusted 0.67 (0.38 – 1.16)
Hemorrhagic endpoint	20 (4.2%)	73 (3.7%)	Unadjusted 1.16 (0.70 – 1.93) Adjusted. 0.93 (0.54 – 1.62)

Table 3: Association of outcome events with the timing of oral anticoagulant therapy initiation after index event stratified by stroke location

Anterior stroke\*

	Combined endpoint	Ischemic endpoint	Hemorrhagic endpoint
0-2 days (n=373)	21 (5.6%)	16 (4.3%)	5 (1.3%)
3-7 days (n=490)	26 (5.3%)	19 (3.8%)	8 (1.6%)
8-14 days (n=373)	30 (8.0%)	14 (3.8%)	17 (4.5%)
>14 days (n=379)	31 (8.2%)	19 (5.0%)	14 (3.7%)
No therapy with oral anticoagulants (n=363)	61 (16.8%)	34 (9.4%)	29 (8.0%)

\*19 patients missing

Posterior stroke\*

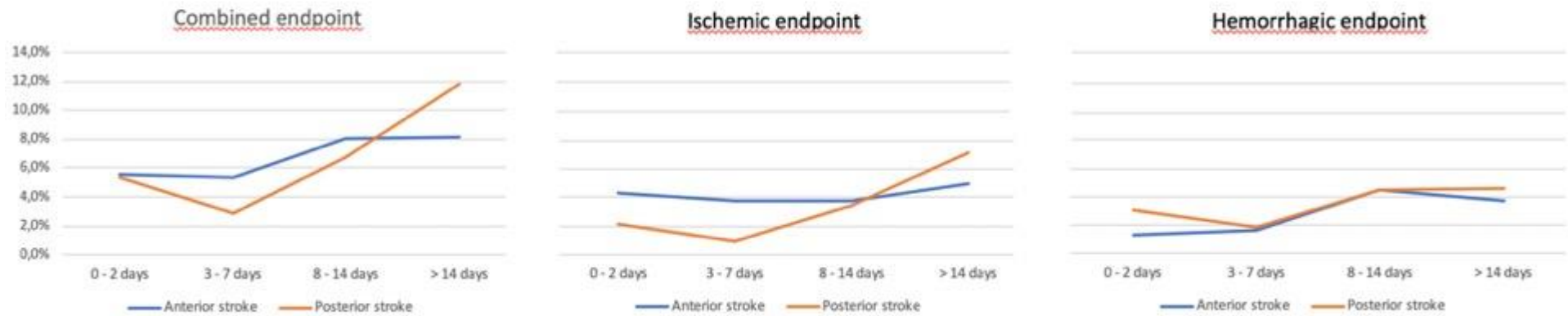
	Combined endpoint	Ischemic endpoint	Hemorrhagic endpoint
0-2 days (n=95)	5 (5.3%)	2 (2.1%)	3 (3.1%)
3-7 days (n=103)	3 (2.9%)	1 (0.9%)	2 (1.9%)
8-14 days (n=88)	6 (6.8%)	3 (3.4%)	4 (4.5%)
>14 days (n=152)	18 (11.8%)	11 (7.2%)	7 (4.6%)
No therapy with oral anticoagulants (n=35)	6 (17.1%)	2 (5.7%)	4 (11.4%)

Table 4: Association of outcome events with lesion size stratified by stroke location

	Small lesion (n=116)	Large lesion (n=352)	Log Rank (Mantel-Cox)
Combined endpoint	7 (6.0%)	30 (8.4%)	0.09
Ischemic endpoint	5 (4.3%)	12 (3.4%)	0.9
Hemorrhagic endpoint	2 (1.7%)	18 (5.0%)	0.05

**Figure 1:** Kaplan-Meier curves of outcome events stratified by timing of initiation of oral anticoagulants in patients with anterior or posterior stroke

**Figure 1**





**Figure 2:** Kaplan-Meier curves of outcome events in patients with posterior stroke stratified by lesion size

**Figure 2**

