Stroke

CLINICAL AND POPULATION SCIENCES

Safety of Anticoagulation in Patients Treated With Urgent Reperfusion for Ischemic Stroke Related to Atrial Fibrillation

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BACKGROUND AND PURPOSE: The optimal timing for starting oral anticoagulant after an ischemic stroke related to atrial fibrillation remains a challenge, mainly in patients treated with systemic thrombolysis or mechanical thrombectomy. We aimed at assessing the incidence of early recurrence and major bleeding in patients with acute ischemic stroke and atrial fibrillation treated with thrombolytic therapy and/or thrombectomy, who then received oral anticoagulants for secondary prevention.

METHODS: We combined the dataset of the RAF and the RAF-NOACs (Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin K Oral Anticoagulants) studies, which were prospective observational studies carried out from January 2012 to March 2014 and April 2014 to June 2016, respectively. We included consecutive patients with acute ischemic stroke and atrial fibrillation treated with either vitamin K antagonists or nonvitamin K oral anticoagulants. Primary outcome was the composite of stroke, transient ischemic attack, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding within 90 days from the inclusion. Treated-patients were propensity matched to untreated-patients in a 1:1 ratio after stratification by baseline clinical features.

RESULTS: A total of 2159 patients were included, 564 (26%) patients received acute reperfusion therapies. After the index event, 505 (90%) patients treated with acute reperfusion therapies and 1287 of 1595 (81%) patients untreated started oral anticoagulation. Timing of starting oral anticoagulant was similar in reperfusion-treated and untreated patients (median 7.5 versus 7.0 days, respectively). At 90 days, the primary study outcome occurred in 37 (7%) patients treated with reperfusion

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and in 146 (9%) untreated patients (odds ratio, 0.74 [95% CI, 0.50–1.07]). After propensity score matching, risk of primary outcome was comparable between the 2 groups (odds ratio, 1.06 [95% CI, 0.53–2.02]).

CONCLUSIONS: Acute reperfusion treatment did not influence the risk of early recurrence and major bleeding in patients with atrial fibrillation–related acute ischemic stroke, who started on oral anticoagulant.

Key Words: anticoagulants ■ atrial fibrillation ■ secondary prevention ■ thrombectomy ■ thrombolytic therapy

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
LMWH	low-molecular weight-heparin
NOAC	nonvitamin K oral anticoagulant
OR	odds ratio
VKA	vitamin K antagonist

The optimal starting time of anticoagulant treatment after an acute ischemic stroke in patients with nonvalvular atrial fibrillation (AF) remains highly debated. In these patients, current guidelines, which are mostly based on observational studies and consensus opinions, recommend using the lesion size and the stroke severity to decide when to start oral anticoagulant.[1–3]

Because of paucity of data, urgent reperfusion therapies are not currently taken into account in the decision on whether and when oral anticoagulation should be initiated after AF-related acute ischemic stroke. Acute reperfusion treatments by systemic thrombolysis and/or mechanical thrombectomy are associated with a better outcome, yet with a non-negligible risk of hemorrhagic transformation.[4,5] Antithrombotic therapy within the first 24 hours after systemic thrombolysis (with or without mechanical thrombectomy) is not currently recommended,[2] and, after this time interval, the optimal timing of starting oral anticoagulant treatment remains to be defined. In small observational studies, early introduction of nonvitamin K oral anticoagulant (NOACs) in patients with acute stroke appeared to be safe in patients treated with acute reperfusion therapy.[6–8]

We aimed at assessing the incidence of early recurrence and major bleeding in patients with acute ischemic stroke and AF treated with thrombolytic therapy and/or thrombectomy, who then received oral anticoagulants for secondary prevention.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. We pooled the datasets of the RAF and the RAF-NOACs (Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin K Oral Anticoagulants) studies, which were prospective observational studies carried out from January 2012 to March 2014 and April 2014 to June 2016, respectively. Both studies enrolled consecutive patients with acute ischemic stroke and known or newly diagnosed AF without permanent contraindications to oral anticoagulant. The RAF study included patients treated with either vitamin K antagonists (VKAs) or NOACs, and the RAF-NOACs study only patients treated with NOACs. The design and methods of the 2 studies have been previously described.[9,10]

For the purpose of this analysis, we compared clinical features and outcomes of patients treated and untreated with acute reperfusion treatment. Acute reperfusion therapies included systemic thrombolysis (intravenous rt-PA) and/or intraarterial thrombectomy that were delivered as per standard local protocol as considered appropriate by local investigators. Standard stroke unit care, monitoring, and treatment were provided according to current international recommendations for acute ischemic stroke. Attending physicians made decisions regarding the type of anticoagulant to be prescribed for secondary stroke prevention, as well as the day of initiation of anticoagulant treatment. Types of anticoagulant prescribed for secondary stroke prevention were (1) VKAs alone or with bridging therapy with low-molecular weight-heparin (LMWH), (2) NOACs alone or with bridging therapy with LMWH, (3) LMWH alone, or (4) no anticoagulant treatment. Bridging therapy with LMWH was defined as any temporary full dose of LMWH (eg, 100 UI/kg of enoxaparin twice a day) started before or with VKAs, to cover the time needed by these last agents to reach the therapeutic effect or as any full dose (given for at least 24 hours) of LMWH before the use of a NOAC.[11] Follow-up visits or telephone contacts were prospectively performed.

The study was approved by the local institutional review boards, if required. Informed consent was provided by study participants in countries where this was required by law.

Outcomes

The primary outcome was the composite of stroke, transient ischemic attack, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding within 90 days from the inclusion in the study.[9,10] Secondary outcomes were (1) any ischemic event; (2) any hemorrhagic event; (3) all-cause death; and (4) disability using the modified Rankin Scale. Ischemic events included ischemic stroke, transient ischemic attack, and symptomatic systemic embolism. Symptomatic cerebral bleeding and major extracerebral bleeding were considered as hemorrhagic events.

Stroke was defined as an acute episode of focal neurological deficit of vascular origin in a site consistent with the territory of a major cerebral artery and categorized as ischemic or hemorrhagic. Transient ischemic attack 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. Cerebral bleeding was considered symptomatic if associated with a decline in neurological status quantified as an increase of 4 points of the NIHSS or leading to death. Extracerebral major bleeding was defined according to the ISTH criteria, which consist of a reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ or fatal bleeding.[12] All-cause death was defined as death from any cause during the study period. Disability was assessed using the modified Rankin Scale. Disability functional outcome was defined as a modified Rankin Scale score of 3 to 5.

Statistical Analyses

We compared baseline characteristics of reperfusion-treated and untreated patients using the $\chi 2$ test for categorical variables or the Mann-Whitney *U* test for continuous variables. Patient's characteristics were summarized as mean±SD if normally distributed and as median and interquartile range if not normally distributed for continuous variables and as absolute numbers and percentages for categorical variables.

The risk of study outcomes between reperfusion-treated and untreated patients was compared using logistic regression analysis. Results were reported as odds ratios and 95% CIs. A multivariable analysis was performed using logistic regression to determine independent predictors of the primary outcome, any ischemic event, and any hemorrhagic event. The independent variables of interest included in the multivariable models were permanent AF, current smoker, lesion size, type of reperfusion treatment, type of oral anticoagulant therapy, and CHA_2DS_2-VASc score.

The risk of study outcomes over time in reperfusion-treated and untreated patients was compared using Cox proportional hazards regression models. All associations were presented as hazard ratios and corresponding 95% CIs. These analyses were adjusted for the following risk factors: permanent AF, current smoker, lesion size, oral anticoagulant type, and CHA_2DS_2-VASc score. Patients were censored at the time of an outcome event or death. A 2-sided $P<0.05$ was considered significant.

Furthermore, a propensity score matching was used to balance the differences in baseline characteristics between reperfusion-treated and untreated patients. The propensity scores for treatment status were estimated from a logistic regression model, which included the following covariables: age, sex, NIHSS at admission, hypertension, diabetes, dyslipidemia, paroxysmal AF, current smoker, history of congestive heart failure, previous stroke or transient ischemic attack, the use of oral anticoagulant, the use of LMWH (with or without bridging). Patients treated with acute reperfusion therapies were matched to untreated patients in a 1:1 ratio. Standardized difference was used to assess the balance of covariates after matching, and a standardized difference <10% was considered acceptable.[13,14] Logistic regression analysis was used to compare primary and secondary outcomes in each propensity score–matched cohort.

All statistical analyses were performed using the IBM SPSS Statistics version 23.0 (IBM Corporation, Armonk, NY).

RESULTS

A total of 2159 patients were included in the RAF and RAF-NOACs trials, of which 564 (26%) patients were treated with acute reperfusion therapy. Of these, 471 patients were treated with systemic thrombolysis and 57 patients with endovascular thrombectomy. The remaining 36 patients received both systemic thrombolysis and endovascular thrombectomy. The characteristics of the patients are summarized in Table 1.

Patient treated with acute reperfusion therapies were younger than untreated patients (74.5±10.1 versus 76.9±9.6; $P<0.001$) and had more often paroxysmal AF ($P<0.001$), history of diabetes mellitus ($P<0.001$), previous stroke ($P<0.001$), and a CHA_2DS_2-VASc score equal or more than 5 ($P<0.001$). Neurological impairment assessed by NIHSS on admission, as well as the size of the lesion were significantly higher in patients

Table 1. Main Characteristics of the Study Patients

Overall Patients, 2159	r-tPA/IA, 564 (26%)	No Reperfusion Therapies; 1595 (74%)	*P* Value
Demographics			
Age	74.54±10.1	76.96±9.6	<0.001
Female	260 (46%)	735 (46%)	0.961
Risk factors			
Diabetes mellitus	94 (17%)	388 (24%)	<0.001
Hypertension	431 (77%)	1258 (79%)	0.171
Hyperlipidemia	184 (33%)	540 (34%)	0.640
Paroxysmal AF	284 (50%)	646 (41%)	<0.001
Previous stroke	104 (19%)	464 (29%)	0.001
Current smoking	50 (9%)	156 (10%)	0.560
Alcoholism	30 (5%)	112 (7%)	0.198
Chronic heart failure	84 (15%)	285 (18%)	0.118
Previous MI	68 (12%)	231 (15%)	0.157
Peripheral arterial disease	39 (7%)	143 (9%)	0.135
Aortic atheroma	44 (8%)	123 (8%)	0.711
Pacemaker	36 (6%)	114 (7%)	0.630
CHA_2DS_2-VASc ≥5	406 (72%)	1264 (79%)	0.0001
Clinical and radiological characteristics			
Lesion <1.5 cm	154 (27%)	666 (42%)	<0.001
NIHSS at admission, median (IQR)	10.0 (10)	4.0 (7)	<0.001
Treatment			
Resumption of oral anticoagulation	505 (90%)	1287 (81%)	0.147
NOAC	384 (76%)	841 (65%)	<0.001
Warfarin	121 (22%)	446 (28%)	<0.001
Starting anticoagulation time (d), median (IQR)	7.5 (10)	7 (11)	0.287

AF indicates atrial fibrillation; IA, intra-arterial thrombectomy; IQR, interquartile range; NIHSS, National Institutes of Health; NOAC, nonvitamin K oral anticoagulant; and r-tPA, recombinant tissue-type plasminogen activator.

treated with reperfusion than those untreated (both $P<0.001$). Before the acute stroke, 50 of 564 (8.9%) patients treated with urgent reperfusion and 487 of 1595 (30.5%) untreated patients were on oral anticoagulants (Table I in the Data Supplement).

After acute stroke, 1792 patients received oral anticoagulant therapy, of which 505 of the 564 (90%) patients who were initially treated with acute reperfusion therapies. Oral anticoagulants were commenced in 1287 of 1595 (81%) patients untreated with reperfusion ($P=0.147$). Timing of starting oral anticoagulant was similar in reperfusion-treated and untreated patients (median 7.5 [interquartile range 10] versus 7.0 [interquartile range 11] days, respectively, $P=0.287$). NOACs were used in 76% of patients treated with reperfusion and in 65% of untreated patients ($P<0.001$; Table 1). After acute stroke, bridging therapy with LMWH before anticoagulant treatment was used in 95 of 564 (17%) patients treated with reperfusion therapies and 277 of 1595 (17%) patients non receiving reperfusion therapies, NOAC alone was started in 336 treated (60%) and in 770 (48%) untreated patients, although no anticoagulant treatment in 5% and 13% of patients, respectively. The type of anticoagulant started after the index event and the respective rates of outcomes are shown in Table II in the Data Supplement.

Study Outcomes

At 90 days, the primary study outcome occurred in 37 (7%) patients treated with reperfusion treatment and in 146 (9%) untreated patients (odds ratio [OR], 0.74 [95% CI, 0.50–1.07]; Table 2). Risk of primary outcome was 1.23 (95% CI, 0.52–2.92) in patients treated with intra-arterial thrombectomy and 0.68 (95% CI, 0.46–1.02) in patients treated with both rt-PA and intraarterial thrombectomy as compared with untreated patients.

Twenty-four (4%) patients in the treated group and 82 (5%) patients in the untreated group had an ischemic event (OR, 0.82 [95% CI, 0.51–1.31]). No significant differences were observed as to symptomatic hemorrhagic intracerebral and extracerebral events between treated and untreated patients (2% versus 4%, respectively; OR, 0.56 [95% CI, 0.31–1.03]). Extracerebral hemorrhages occurred in 3 (0.5%) patients in the treated group and in 20 (1.2%) patients in the untreated group. Seven patients in the untreated group experienced both an ischemic and hemorrhagic event. Hemorrhagic transformation at 24 to 72 hours occurred in 63 (11%) patients treated with reperfusion therapies and in 176 (11%) untreated patients (OR, 1.01 [95% CI, 0.75–1.38]; Table 2).

Compared with untreated patients, patients treated with reperfusion therapies had similar rates of all-cause death (4% versus 7%, OR, 0.65 [95% CI, 0.42–1.00]) and disability (modified Rankin Scale score 3–5; 32% versus 31%, OR, 1.07 [95% CI, 0.87–1.31]).

By restricting the analysis to patients treated only with i.v. thrombolysis, we found that patients receiving i.v. thrombolysis had a significant lower risk of the primary outcome compared with untreated patients (OR, 0.61 [95% CI, 0.40-0.94]; Table III in the Data Supplement).

In the Cox regression analyses, the risk of primary outcome over time was similar in patients treated and not treated with reperfusion treatments (adjusted HR, 0.90 [95% CI, 0.55–1.47]; Figure). No differences were observed in term of risk of an ischemic event (adjusted HR, 0.89 [95% CI, 0.47–1.70]) as well as risk of a hemorrhagic event (adjusted HR, 0.61 [95% CI, 0.30–1.30]) between the 2 groups.

Multivariable Analysis

In the multivariable analysis, the presence of lesion larger than 1.5 centimeters in brain imaging (OR, 1.84 [95% CI, 1.2–2.7]), and the CHA_2DS_2-VASc score (OR for each

Table 2. Rate of Primary and Secondary Study Outcomes in Patients Treated or Untreated With Acute Reperfusion Therapies

Overall; 2159	r-tPA/IA; 564 (26%)	No Reperfusion Therapies; 1595 (74%)	Odds Ratio (95% CI)
Primary outcome			
Any ischemic and any hemorrhagic event	37 (7%)	139 (9%)	Unadjusted OR, 0.74; 95% CI, 0.50–1.07
			Adjusted OR, 0.85; 95% CI, 0.53–1.36
Secondary outcomes			
Any ischemic event	24 (4%)	82 (5%)	Unadjusted OR, 0.82; 95% CI, 0.51–1.31
			Adjusted OR, 1.01; 95% CI, 0.56–1.72
Any hemorrhagic event	13 (2%)	64 (4%)	Unadjusted OR, 0.56; 95% CI, 0.31–1.03
			Adjusted OR, 0.60; 95% CI, 0.29–1.26
Mortality	26 (4%)	111 (7%)	Unadjusted OR, 0.65; 95% CI, 0.42–1.00
			Adjusted OR, 0.47; 95% CI, 0.29–0.78
Disability (mRS 3–5)	182 (32%)	492 (31%)	Unadjusted OR, 1.07; 95% CI, 0.87–1.31
HT 24–72	63 (11.2%)	176 (11%)	Unadjusted OR, 1.01; 95% CI, 0.75–1.38

HT indicates hemorrhagic transformation; IA, intra-arterial thrombectomy; mRS, modified Rankin Scale; OR, odds ratio; and r-tPA, recombinant tissue-type plasminogen activator.

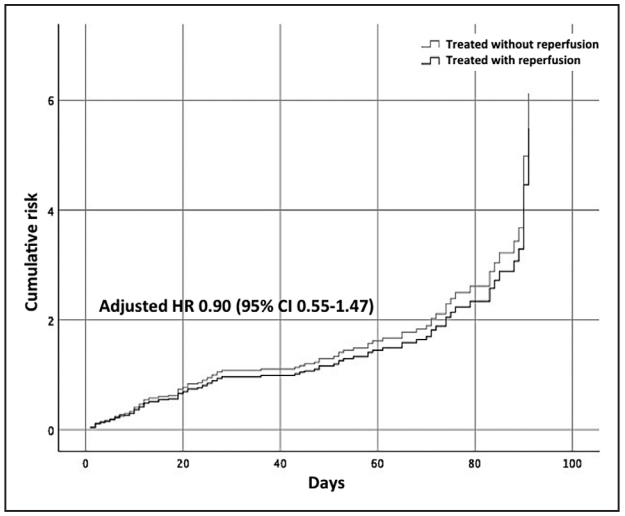

Figure. Cumulative risk of the primary study outcome.

increasing point 1.24 [95% CI, 1.06–1.43]) resulted to be independent predictors of increased risk for the primary study outcome. In contrast, the use of NOACs was associated with a significant reduced odd of the primary outcome (OR, 0.42 [95% CI, 0.29–0.65]; Table 3). Acute reperfusion treatment was not associated with the primary outcome (OR, 0.87 [95% CI, 0.54–1.38]).

Factors associated with an ischemic event and with a hemorrhagic event are shown in Table 3. The use of NOACs was independently associated with lower risk of an ischemic event (OR, 0.38 [95% CI, 0.24–0.66]) and of a hemorrhagic event (OR, 0.55 [95% CI, 0.28–0.94]).

Propensity Score–Matched Cohort

After propensity score 1:1 matching, 304 patient-pairs were formed. No differences were observed in patients treated with and without acute reperfusion therapies after matching (Table 4). In the matched populations, the risk of the primary outcome was comparable between reperfusion-treated and untreated patients (OR, 1.06 [95% CI, 0.53–2.02]; Table 5). No differences were observed in the risk of an ischemic event or a hemorrhagic event between the 2 groups.

DISCUSSION

Our study showed that the rates of patients with acute ischemic stroke with AF who initiated oral anticoagulation was similar in subjects receiving or not receiving acute reperfusion therapies, while the median elapsed time interval from the index event was 7 days. At 90 days, patients treated with or without reperfusion had a similar risk of the composite outcome as well as of any ischemic or hemorrhagic event. The use of NOACs was associated with an improved efficacy and safety profile compared with VKAs both for ischemic and hemorrhagic outcomes.

Table 3. Multivariate Analysis of the Primary Outcome and of Any Ischemic and Any Hemorrhagic Event

	OR	95% CI	*P* Value
Primary outcome			
Paroxysmal AF	0.77	0.51–1.11	0.212
Lesion <1.5 cm	0.57	0.37–0.87	0.008
Current smoker	0.74	0.33–1.64	0.454
r-tPA/IA	0.87	0.55–1.38	0.556
CHA_2DS_2-VASc	1.24	1.06–1.44	0.006
NOACs vs VKAs	0.44	0.29–0.65	<0.001
Any ischemic event			
Paroxysmal AF	0.66	0.39–1.12	0.125
Lesion <1.5 cm	0.70	0.49–2.85	0.183
Current smoker	0.72	0.33–1.64	0.454
r-tPA/IA	0.98	0.55–1.76	0.961
CHA_2DS_2-VASc	1.29	1.07–1.56	0.008
NOACs vs VKAs	0.40	0.24–0.66	<0.001
Any hemorrhagic event			
Paroxysmal AF	0.97	0.53–1.78	0.922
Lesion <1.5 cm	0.43	0.22–0.84	0.013
Current smoker	0.21	0.03–1.54	0.125
r-tPA/IA	0.67	0.32–1.38	0.274
CHA_2DS_2-VASc	1.11	0.88–1.39	0.379
NOACs vs VKAs	0.52	0.29–0.95	0.033

AF indicates atrial fibrillation; IA, intra-arterial thrombectomy; NOAC, nonvitamin K oral anticoagulant; r-tPA, recombinant tissue-type plasminogen activator; and VKC, vitamin K antagonist.

Our study is a prospective observational study that enrolled 2159 patients of which 564 were treated with reperfusion strategy. We observed that patients treated with acute reperfusion therapies had higher baseline NIHSS and lower lesion volume and comorbidities compared with untreated patients. However, to overcome these different patient's features among the 2 study groups, we performed a propensity score matching. We found that the similar risk of primary outcome observed in the treated and untreated population was independent of the influence of comorbidity, as shown by its persistence after adjustment for baseline features according to a propensity score matching 1:1. Interestingly, when we included in the analysis only patients treated with i.v. thrombolysis alone, these patients had a significant lower risk of primary outcome than patients non receiving reperfusion therapy. In this view, we think that starting early anticoagulant treatment after acute stroke in these patients would be a reasonable option.

Our study provides novel observation about the start of anticoagulation in these patients and confirms previous findings of smaller studies as shown by a recent review.[15] The early introduction (within the first 2 weeks) of rivaroxaban or dabigatran in 34 patients with AF-related ischemic stroke treated with intravenous rt-PA appeared to be safe.[6] None of these patients experienced symptomatic

Table 4. Characteristics of the Patients After Propensity Score Matching

	r-tPA/IA (n=304)	No Reperfusion Therapies (n=304)	*P* Value
Age (y, mean)	75.6±9.4	75.1±9.7	0.5
Female sex	165 (54.3%)	157 (51.6%)	0.6
NIHSS at admission (mean)	8.9±5.0	8.3±6.9	0.2
Diabetes mellitus	65 (21.4%)	53 (17.4%)	0.3
Hypertension	235 (77.3%)	234 (77.0%)	1.0
Dyslipidemia	96 (31.6%)	96 (31.6%)	1.0
Paroxysmal AF	146 (48.0%)	147 (48.4%)	1.0
Current smoker	26 (8.6%)	27 (8.9%)	1.0
History of stroke/TIA	76 (25.0%)	65 (21.4%)	0.3
History of CHF	45 (14.8%)	54 (17.8%)	0.4
Use of oral anticoagulant	251 (82.6%)	258 (84.9%)	0.5
Use of LMWH (with/without bridging)	65 (21.5%)	78 (25.5%)	0.2

AF indicates atrial fibrillation; IA, intra-arterial thrombectomy; LMWH, low-molecular weight-heparin; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; and TIA, transient ischemic attack.

hemorrhagic transformation or a symptomatic recurrent ischemic event. Reassurance regarding the early initiation of rivaroxaban in patients with AF-associated minor ischemic stroke was also shown in a small randomized-controlled clinical trial from Korea.[16] Similarly, in a retrospective study of 35 patients with stroke treated with urgent reperfusion, NOACs were started within a median of 6 days after stroke. At 90 days, one patient had a symptomatic cerebral hemorrhage.[7] Moreover, in a prospective cohort of 73 patients with ischemic stroke receiving thrombolysis, early initiation of NOACs (within 2–4 days) after thrombolytic therapy appeared to be associated with lower risk of hemorrhagic events compared with VKAs. However, there was no significant difference (0 versus 5.6%, *P*=0.240) due to the limited number of the included patients.[8] Preventing stroke and avoiding hemorrhagic transformation represents the cornerstone of secondary prevention in nonvalvular AF-related acute ischemic stroke, and reperfusion treatment is usually considered to increase the risk of hemorrhagic complications in the early phase of stroke. Our study suggests that reperfusion treatment does not influence the clinical outcomes of patients with AF-related acute ischemic stroke, as acute reperfusion therapies did not emerge as independent predictors of any ischemic and/or hemorrhagic outcome. Interestingly, in our study, the presence of a small lesion in brain imaging and high CHA_2DS_2-VASc score were inversely correlated to the primary outcome. Therefore, we think that patients with a high CHA_2DS_2-VASc score and a small lesion size could safely start early anticoagulant treatment with NOACs, particularly if they were treated with thrombolytic treatment.

Moreover, we found that the use of NOAC alone without bridging therapy with LMWH was the best treatment option in these patients. None of the NOAC phase III randomized-controlled clinical trials included patients who had experienced a recent ischemic stroke (within the first weeks).[17–20] However, in a meta-analysis of these clinical trials of AF patients with previous transient ischemic attack or stroke, NOACs were associated with a significant reduction of stroke, stroke or systemic embolism, hemorrhagic stroke, and intracranial bleeding compared with VKAs.[21] Our results expand previous findings confirming the highest safety and efficacy profile of NOACs over VKAs even in patients with AF-related acute ischemic stroke treated with urgent reperfusion therapy, supporting the observations of other datasets.[22,23]

Our study had several limitations. First, this was not a randomized study and therefore the results were possibly influenced by some confounders. Indeed, the different time periods of data collection, the non randomized selection of the individual anticoagulant treatment and their doses could have influenced our results. However, the study has the advantage to reflect the changes and the real-life experiences in clinical practice in this clinical setting. Second, the number of study outcome events was relatively low, leading to a reduction of statistical power of the study. In this view, the

Table 5. Risks of Primary and Secondary Outcome After Propensity Score Matching Between Patients Treated With or Without Acute Reperfusion Therapies

	r-tPA/IA (n=304)	No Reperfusion Therapies (n=304)	Odds Ratio (95% CI)	*P* Value
Primary outcome	20 (6.6%)	19 (6.3%)	1.06 (95% CI, 0.53–2.02)	0.9
Any ischemic event	13 (4.3%)	11 (3.6%)	1.19 (95% CI, 0.52–2.70)	0.7
Any hemorrhagic event	7 (2.3%)	10 (3.3%)	0.69 (95% CI, 0.26–1.84)	0.6

IA indicates intra-arterial thrombectomy; and r-tPA, recombinant tissue-type plasminogen activator.

results of sub-group analyses should be regarded with caution. Third, the possibility of selection bias regarding the starting time of anticoagulant therapy cannot be excluded. Fourth, the number of patients who were treated with endovascular reperfusion therapies was limited (<100 cases), and this needs to be taken into account when interpreting our findings.

CONCLUSIONS

In conclusion, our study suggests that acute reperfusion therapies seem not to influence the risk of early recurrence and major bleeding in patients with AF-related acute ischemic stroke, who subsequently started oral anticoagulant treatment. Therefore, acute reperfusion treatment should not refrain stroke physicians from an early initiation of oral anticoagulation for secondary stroke prevention when the potential benefits outweigh the perceived risks. Further studies, preferably randomized trials, are needed to better investigate this issue.

ARTICLE INFORMATION

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