Prediction of Early Recurrent Thromboembolic Event and Major Bleeding in Patients With Acute Stroke and Atrial Fibrillation by a Risk Stratification Schema: The ALESSA Score Study.

Prediction of early recurrent thromboembolic event and major bleeding in patients with acute stroke and atrial fibrillation by a risk stratification schema: the ALESSA score study.

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Abstract

Background: This study was designed to derive and validate a score to predict early ischemic events and major bleedings after an acute ischemic stroke in patients with atrial fibrillation (AF).

Methods: The derivation cohort consisted of 854 patients with acute ischemic stroke and AF included in prospective series between January 2012 and March 2014. Older age (HR 1.06 for each additional year, 95% CI 1.00-1.11) and severe atrial enlargement (HR 2.05, 95% CI 1.08-2.87) were predictors for ischemic outcome events (stroke, transient ischemic attack, systemic embolism) at 90 days from acute stroke. Small lesions (≤1.5 cm) were inversely correlated with both major bleeding (HR 0.39, p=0.03) and ischemic outcome events (HR 0.55, 95% CI 0.30-1.00). We assigned to age ≥80 years 2 points and between 70-79 years 1 point; ischemic index lesion >1.5 cm 1 point; severe atrial enlargement 1 point (ALESSA score). A logistic regression with the ROC graph procedure (C statistic) showed an area under the curve of 0.697 (0.632-0.763), p=0.0001 for ischemic outcome events and 0.585 (0.493-0.678), p=0.10 for major bleedings.

Results: The validation cohort consisted of 994 patients included in prospective series between April 2014 and June 2016. Logistic regression with the ROC graph procedure showed an area under the curve of 0.646 (0.529-0.763), p=0.009 for ischemic outcome events and 0.407 (0.275-0.540), p=0.14 for hemorrhagic outcome events.

Conclusions: In acute stroke patients with AF, high ALESSA scores were associated with a high risk of ischemic events but not of major bleedings.

Introduction

Anticoagulation is highly beneficial for long-term secondary stroke prevention in patients with atrial fibrillation (AF); nonetheless, there is a paucity of data addressing when anticoagulation can be effectively and safely initiated after acute stroke. Data from the recently published observational multicenter RAF study (Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation) suggested that the optimal time for initiating anticoagulation treatment for secondary stroke prevention is between 4 to 14 days after an acute stroke (1). However, the specific risk/benefit balance for any given patient and which type of strokes is associated with the highest risk and benefit by early anticoagulation remains unclear. Risk stratification could help to drive clinician decisions on anticoagulant treatment in this clinical setting.

The aim of this prospective multicenter study was to develop and validate a score to predict ischemic events and major bleedings at 90 days from an acute ischemic stroke in patients with AF.

Methods

The risk factors correlated with outcome events were isolated and included in a new risk stratification score from a prospective cohort of patients (derivation cohort). The validation of the results obtained in the derivation cohort was performed in different patients included in prospective series (validation cohort). Patients included in the derivation cohort were not eligible for inclusion in the validation cohort.

Derivation cohort.

The derivation cohort was extracted from the database of the RAF study, a prospective observational study performed between January 2012 and March 2014 which enrolled

consecutive patients with acute ischemic stroke with either known or newly diagnosed AF. The methods and results of RAF study have been described in details (1,2).

On admission, the severity of acute stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS); all investigators were certified about the use of this scale.

AF was classified as paroxysmal (episodes terminating spontaneously within 7 days), persistent (episodes lasting more than 7 days requiring pharmacologic and/or electrical stimulation), or permanent (persisting for more than 1 year, either because cardioversion failed or was not attempted).

A cerebral computed tomography (CT) or magnetic resonance (MR) was performed on admission in all patients to exclude intracranial hemorrhage. A second cerebral CT scan or MR was performed 48–72 h from stroke onset. The sizes of the qualifying infarcts were classified as follows: (a) small, when a lesion was ≤1.5 cm, (b) medium-large when a lesion was >1.5 cm.

Transthoracic echocardiogram was performed within 7 days from index stroke. Left atrial enlargement and its severity was defined following the American Society of Echocardiography guidelines measuring the left atrial diameter or volume taking into account the difference between sexes (3).

Differences in the characteristics of patients with or without outcome events were tested using $\chi 2$ 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.

Description of the risk stratification schema (ALESSA score)

In the cohort of patients included in the RAF study (derivation cohort), older age (HR 1.06 for 1 added year, Standard Error 0.0207, Beta-coefficient 0.055, p=0.0025) and severe atrial enlargement (HR 2.05, Standard Error 0.389, Beta-coefficient 0.989, p= 0.027), were shown to be predictive factors for ischemic outcome events occurring within 90 days from acute stroke. The characteristics of the patients in the derivation cohort with and without outcome events are described in Tables 1 and 2 of online supplemental files. Small lesions (≤1.5 cm) on CT scan or MRI were inversely correlated with both hemorrhagic (HR 0.39, Standard Error 0.491, Beta-coefficient -1.420, p=0.03) and ischemic outcome events (HR 0.55, Standard Error 0.314, Beta-coefficient -0.594, p=0.05) (1,2). Based on the magnitude of the effect (Beta-coefficient) associated with these variables, we assigned to Age ≥80 years 2 points; age between 70-79 years 1 point; the presence of an ischemic index LESion >1.5 cm 1 point and presence of Severe Atrial enlargement 1 point (ALESSA score).

Validation cohort

The validation cohort consisted of 994 ischemic stroke patients with acute stroke and AF seen between April 2014 and June 2016 deriving from several international prospective stroke series. Patients included in the validation cohort were those with a reported echocardiogram within 7 days among 1161 consecutive patients. Inclusion criteria, outcome definition and statistical analysis were as in the derivation cohort.

Patients treated with revascularization (systemic rt-PA and/or intravascular thrombectomy), were assumed as having a final lesion >1.5 cm if they had a NIHSS ≥10 prior to treatment (4).

Definition of outcome events

Outcome events for this study were: ischemic outcome events [combination of stroke, transient ischemic attack (TIA), systemic embolism] and hemorrhagic outcome events (combination of symptomatic intracranial bleeding and major extracranial bleeding) occurring within 90 days. 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. TIA was defined as a transient episode of neurological dysfunction caused by focal brain ischemia without acute infarction at neuroimaging. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ confirmed by imaging, surgery, or autopsy. Hemorrhagic transformation found on neuroimaging 24 to 72 hours after onset was not considered an outcome event, unless they were symptomatic. Major extracranial bleeding was defined as a reduction in the hemoglobin level of at least 2 g per deciliter, requiring a blood transfusion of at least 2 units, or symptomatic bleeding in a critical area or organ (5).

Statistical analysis

Derivation cohort

A descriptive analysis with proportions was used to describe the derivation cohort and the event rates of ischemic outcome events and hemorrhagic outcome events. The 95% confidence interval (CI) of event rates using the binomial approximation was calculated. A logistic regression analysis was performed with ALESSA risk factors as independent variables, and ischemic events and major intra- and extracranial bleeding as dependent variables. The probability that this model would predict the correct classification of individual patients (with or without ischemic or hemorrhagic outcome events) was saved. Thereafter, the probabilities in a receiver-operating characteristic (ROC) curve against ischemic or hemorrhagic outcome events as dependent variables were plotted. The areas under the curves for these ROC curves represent the ability of the ALESSA score

to correctly classify risks for ischemic or hemorrhagic outcome events, which are also referred to as the C-statistic (Harrell's C) (6).

Validation cohort

The same statistical analysis performed in the derivation cohort, was used in the validation cohort.

Results

Derivation cohort

In the RAF cohort (Table 1 online supplemental files), high scores of the ALESSA score (3 and 4) were correlated with ischemic outcome events but not with hemorrhagic outcome events (Figure 1). Patient's characteristics for both cohorts are reported in Table 1. Multivariable analysis confirmed that ALESSA score, as continuous variable, was an independent predictor of ischemic outcome events (OR 1.83 for 1 added point; 95% CI 1.17-2.87, p=0.08) while it was not correlated with hemorrhagic outcome events (OR 1.07 for 1 added point; 95% CI 0.48-2.40, p=0.8). Logistic regression with the ROC graph procedure to obtain the c statistic showed that the area under the curve was 0.697 (0.632-0.763), p=0.0001 for ischemic outcome events and 0.585 (0.493-0.678), p=0.10 for hemorrhagic outcome events (figures 2a and 2b). On multivariate regression analysis, a score higher than 2 was correlated with ischemic outcome events (OR: 2.5, 95% CI 1.4-4.4, p=0.001) while it was not correlated with hemorrhagic outcome events (OR: 1.1, 95% CI 0.5-2.4, P=0.9).

Validation cohort

The features of the validation cohort and the relative differences with the derivation cohort are shown in Table 1. The main differences between derivation and validation cohorts were that the validation cohort had CHA_2DS_2-VASc score lower compared with the derivation cohort and that 88% of the patients in the validation cohort were treated with direct anticoagulants compared to

10% in the derivation cohort. A lower risk of composite outcome event was observed in the validation cohort (4.9%) compared to the derivation cohort (11.5%) (Table 2).

In the validation cohort, high scores of the ALESSA score were correlated with ischemic outcome events but not with hemorrhagic outcome events. (Figure 3). Study outcomes are reported in Tables 1 and 2.

Multivariable analysis confirmed that ALESSA score as continuous variable was an independent predictor of ischemic outcome events (OR 1.69 for 1 added point; 95% CI 1.00-2.85, p=0.048) while it was not correlated with hemorrhagic outcome events (OR 1.19 for 1 added point; 95% CI 0.68-2.09, p=0.5).

Logistic regression with the ROC graph procedure to obtain the c statistic showed that the area under the curve was 0.646 (0.529-0.763), p=0.009 for ischemic outcome events within 90 days and 0.407 (0.275-0.540), p=0.14 for hemorrhagic outcome events (figures 4a and 4b).

On multivariate regression analysis, a score higher than 2 was marginally not associated with ischemic outcome events (OR: 2.07, 95% CI 0.93-4.67, p=0.07) while it was not correlated with hemorrhagic outcome events (OR: 0.7, 95% CI 0.3-1.8, P=0.4).

Discussion

In patients with ischemic stroke with AF, the risk of stroke recurrence has been found to be particularly high in the first two weeks after the acute event (7). Despite this observation, in these patients there are no comparative studies on the optimal timing of starting of anticoagulation. Thus, such a decision hinges upon the assessment of the competing risks for early thromboembolic recurrences and hemorrhagic transformation.

The RAF study suggested that in patients with acute stroke and AF, the best time for initiating anticoagulation treatment for secondary stroke prevention ranges from 4 to 14 days from stroke

onset. In patients with acute stroke and AF, clinicians would like to be able to identify those patients, who may be candidates to prompt anticoagulation, with a risk of early recurrence high enough to justify the risk of cerebral bleeding associated with early anticoagulant treatment. Several risk factors could be used to estimate the risk of recurrence or cerebral bleeding (8). In this study, a novel risk factor-based approach to stroke risk stratification in patients with acute stroke and AF has been validated. Within 90 days from index stroke, patients with ALESSA score between 0 and 2 have a low risk for both ischemic recurrent events and bleeding. During the same period of time, patients with scores 3 or 4 have a statistically significantly increase in the risk of ischemic recurrent events but not of the risk of bleeding. These results may be explained by the fact that the ALESSA score was built picking up from the derivation cohort the variables correlated with ischemic recurrence and not with hemorrhagic transformation. Our clinical interpretation is that patients with score 3 or 4 could have the best benefit from an early anticoagulation. The optimal time of starting anticoagulant treatment might not be the same with all anticoagulants due to the different promptness of action. Indeed, NOACs reach therapeutic level in about 2 hours while vitamin K antagonists may take days to achieve it.

The c-statistic showed a 0.646 predictive value of the ALESSA score for ischemic events. This value, although not outstanding, is of the same order of magnitude of the 0.606 predictive value of the CHA_2DS_2-VASc for long-term risk of thromboembolism in patients with AF (9). Notably, CHA_2DS_2-VASc score is currently considered the best score to choose the type of antithrombotic treatment for long-term stroke prevention in patients with AF. Indeed, in patients with acute stroke and AF, it was found that CHA_2DS_2-VASc score was a predictive factor for ischemic recurrence occurring as early as within 90 days from stroke onset (8). However, in this study CHA_2DS_2-VASc score was a predictive factor, along with ischemic recurrent event, of early symptomatic cerebral bleeding.

Therefore, CHA_2DS_2-VASc score cannot be used to identify those patients with acute stroke and AF who benefit the most of early anticoagulation.

This study has some limitations. The validation cohort had a lower CHA_2DS_2-VASc score compared with the derivation cohort; furthermore, about 88% of the patients in the validation cohort were treated with direct oral anticoagulants compared to about 10% of the patients in the derivation cohort. These differences due to different time periods of data collection, probably lead to a lower rate of outcome events (the combination of ischemic and hemorrhagic events) in the validation cohort compared to the derivation cohort (4.9% versus 10.8% respectively). The low rates of events in the validation cohort may have led to reduce statistical power in the study. However, the study has the advantage to mirror the changes in clinical practice in this clinical setting. In the patients of derivation cohort treated mainly vitamin K antagonists, a key determinant of hemorrhagic risk (and also efficacy of infarct prevention) would be the INR. Unfortunately, the INR at the moment of the outcome event was not available.

Our study has also some strengths as the sample size and the prospective design. In view of the absence of any randomized trial, the ALESSA score based on simple and easily available variables, could assist stroke physicians in better managing acute cerebral ischemia in patients with AF. Furthermore, the score may be used as a selection criteria for trials evaluating early anticoagulation in patients acute stroke and AF.

Conclusions

ALESSA is a novel, simple risk stratification score for patients with acute stroke and AF based on age, lesion size and the presence of severe atrial enlargement. High scores of this schema are associated with the risk of ischemic recurrent events but not with bleeding. Therefore, patients with acute stroke and AF and an ALESSA score higher than 2 are candidates to an early anticoagulation treatment.

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Figure legends

Figure 1

The risk of ischemic outcome events and symptomatic intracranial bleedings / major extracranial bleeding according to ALESSA score in the derivation cohort.

Figure 2

Logistic regression with the ROC (Receiver Operating Characteristic) graph procedure to obtain the c statistic for ischemic outcome events within 90 days (a) and for major intra- and extra-cerebral bleedings (b) in the derivation cohort.

Figure 3

The risk of ischemic outcome events and symptomatic intracranial bleedings / major extracranial bleeding according to ALESSA score in the validation cohort.

Figure 4

Logistic regression with the ROC (Receiver Operating Characteristic) graph procedure to obtain the c statistic for ischemic outcome events within 90 days (a) and for major intra- and extra-cerebral bleedings (b) in the validation cohort.

Table 1: characteristics of patients included in the derivation and validation cohorts

	Derivation cohort (n=854)	**Validation cohort (n=994)**	**p**
Age (mean, years)	76.3 ± 9.5	75.8 ± 10.1	ns
NIHSS (mean)	8.9 ± 7.0	8.1 ± 6.4	ns
			ns
Sex male	398 (46.6%)	457 (46.0%)	ns
Diabetes mellitus	221 (26.0%)	201 (20.2%)	0.004
Hypertension	676 (79.8%)	776 (78.1%)	ns
Hyperlipidemia	282 (33.4%)	361 (36.3%)	ns
History stroke/TIA	205 (24.3%)	250 (25.2%)	ns
Smoking	158 (18.7%)	171 (17.2%)	ns
Alcoholism	57 (6.7%)	50 (5.0%)	ns
History of CHF	167 (19.6%)	159 (16.0%)	0.045
History of MI	142 (16.8)	92 (9.3%)	0.0001
Paroxysmal AF	316 (37.0%)	456 (43.4%)	0.001
Pacemaker	70 (8.2%)	42 (4.2%)	0.004
rtPA and/or thrombectomy	201 (23.5%)	329 (33.0%)	0.0001
Moderate/Severe atrial enlargement	400 (46.9%)	405 (40.7%)	0.008
Small lesion	325 (38.1%)	379 (38.1%)	ns
Alessa score 3-4	295 (34.5%)	408 (41.1%)	0.04
CHA_2DS_2-VASc			
2	17 (2.0%)	37 (3.7%)	
3	55 (6.4%)	97 (9.8%)	
4	105 (12.3%)	146 (14.7%)	
5	221 (25.9%)	254 (25.6%)	
6	240 (28.1%)	318 (32.0%)	
7	149 (17.4%)	106 (10.7%)	
8	60 (7.0%)	29 (2.9%)	
9	7 (0.8%)	7 (0.7%)	
CHA_2DS_2-VASc >4	677 (79.3%)	714 (71.8%)	0.0002
Vitamin k antagonist	493	62	0.0001
Direct anticoagulant	79	878	0.0001
No anticoagulant	282	53	0.0001

Table 2: Endpoints in the derivation and validation cohorts by different oral anticoagulants

	Derivation cohort (n=854)	**Validation cohort (n=994)**
Recurrent ischemic event (90 days)	66 (7.7%)	27 (2.7%)
Ischemic stroke	50	22
TIA	9	4
Systemic embolism	7	1
Hemorrhagic event (90 days)	31 (3.6%)	22 (2.2%)
Symptomatic intracranial bleeding	29	14
Major extracranial bleeding	2	8
Recurrent ischemic event (at 90 days)		
Vitamin k antagonist	35/493 (7.1%)	3/62 (4.8%)
Direct anticoagulant	4/79 (5.1%)	21/878 (2.4%)
Hemorrhagic event (at 90 days)		
Vitamin k antagonist	15/493 (3.0%)	6/62 (9.6%)
Direct anticoagulant	2/79 (2.5%)	21/878 (1.6%)

Figure 1

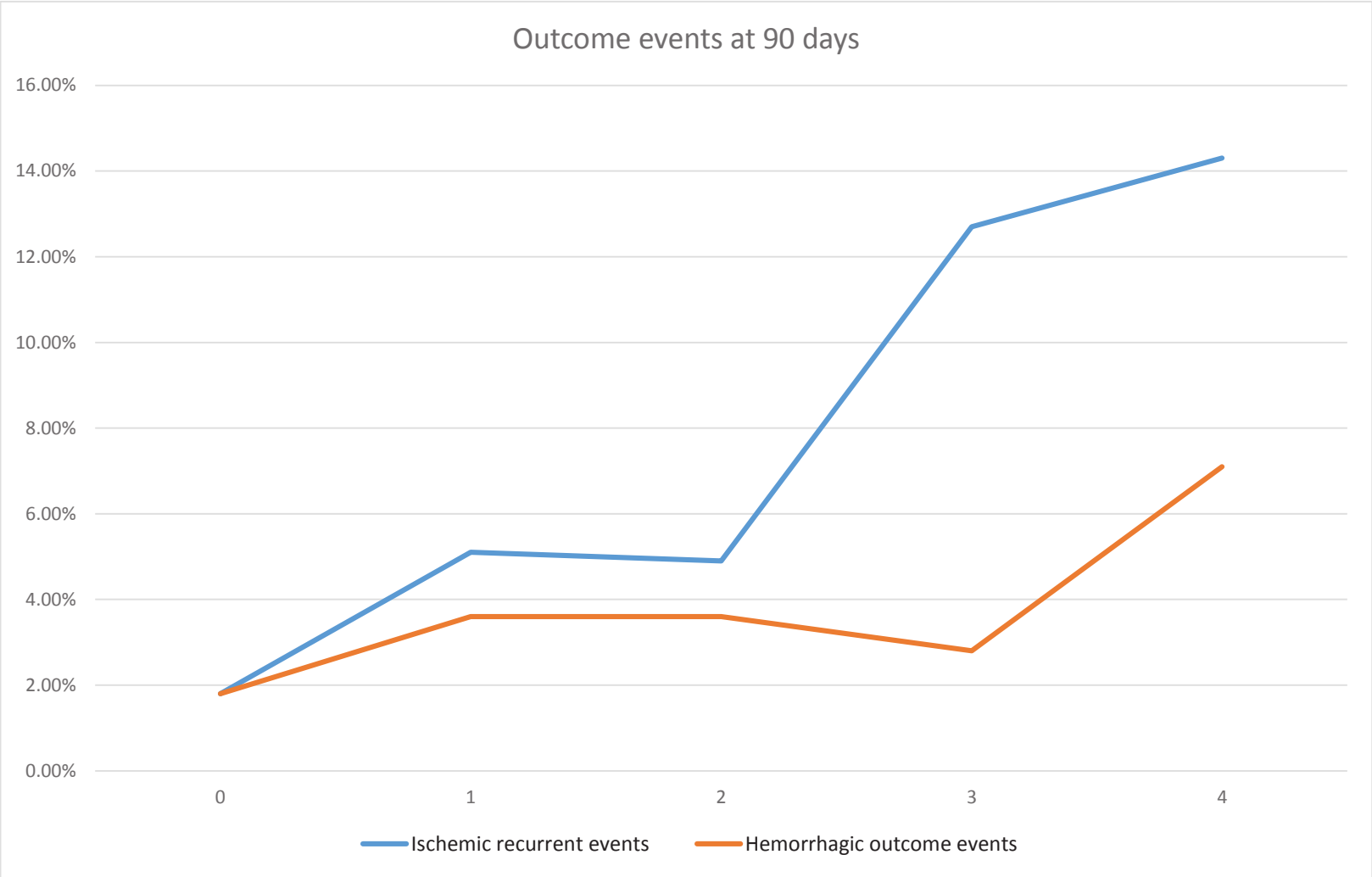
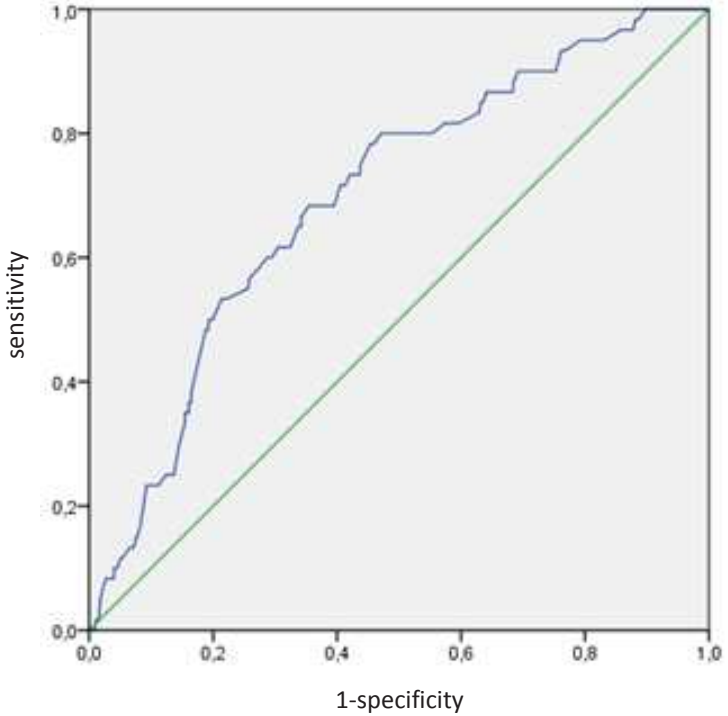
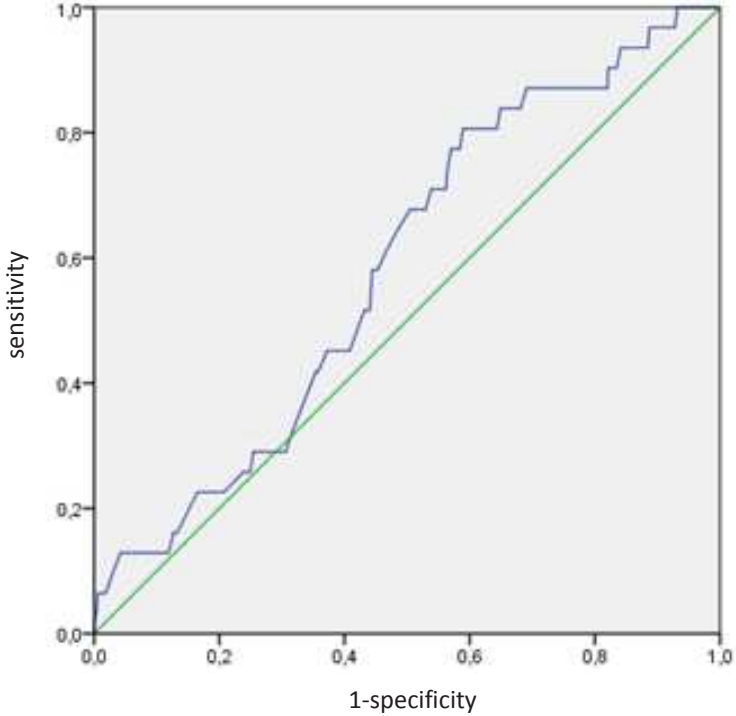

Outcome events at 90 days
16.00%
14.00%
12.00%
10.00%
8.00%
6.00%
4.00%
2.00%
0.00%
0
1
2
3
4
Ischemic recurrent events
Hemorrhagic outcome events

Figure 2 a) and 2 b)

a)



b)



Ischemic outcome events

Area Under the Curve 0.697 (0.632-0.763), p=0.0001

Hemorrhagic outcome events

Area Under the Curve 0.585 (0.493-0.678), p=0.10

Figure 3

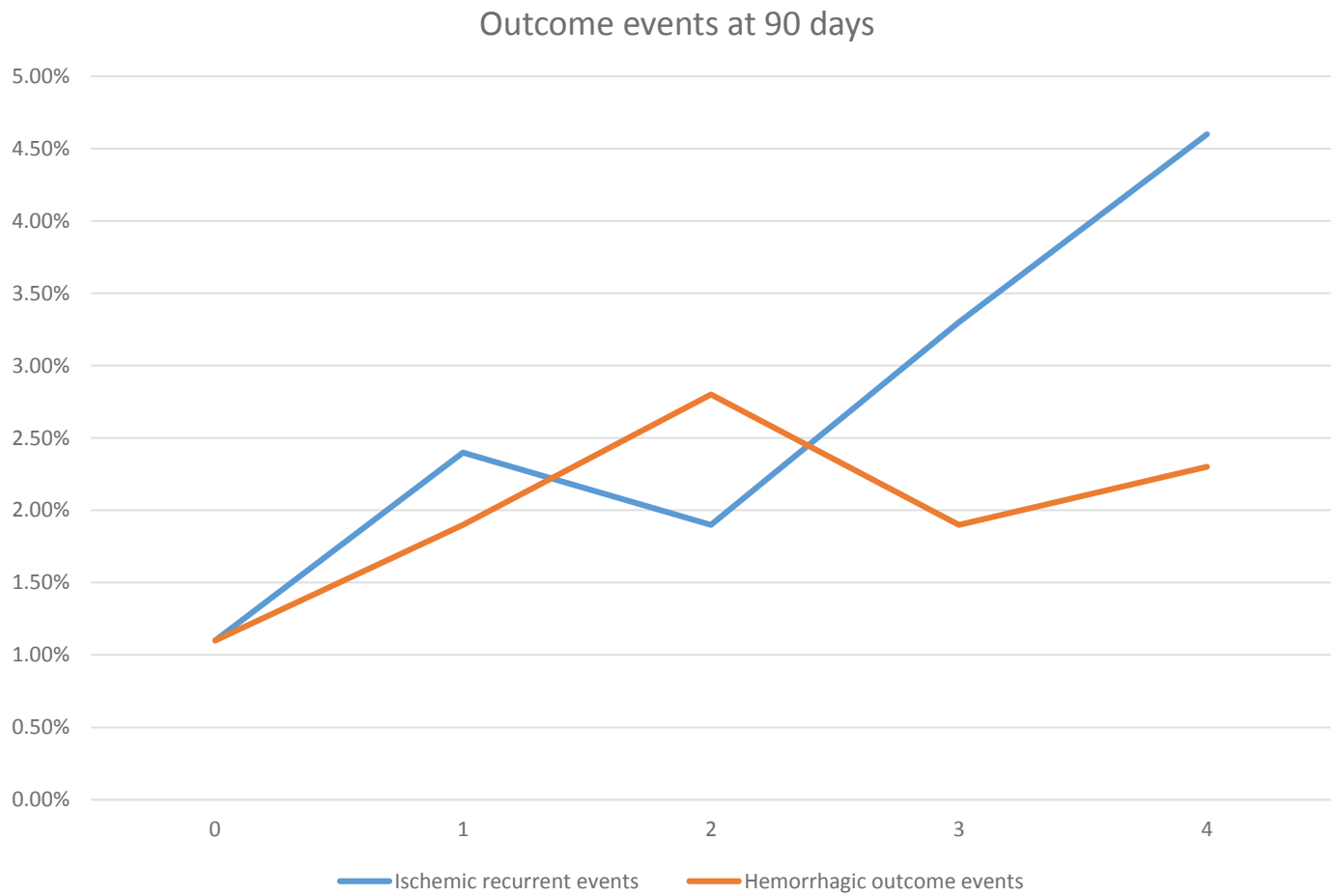
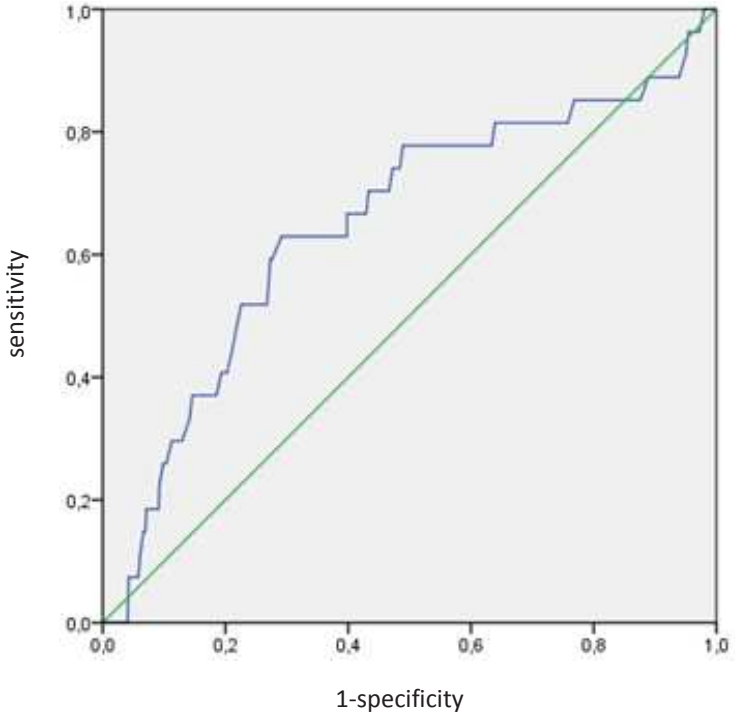

Outcome events at 90 days
5.00%
4.50%
4.00%
3.50%
3.00%
2.50%
2.00%
1.50%
1.00%
0.50%
0.00%
0
1
2
3
4
Ischemic recurrent events
Hemorrhagic outcome events

Figure 4 a) and 4 b)

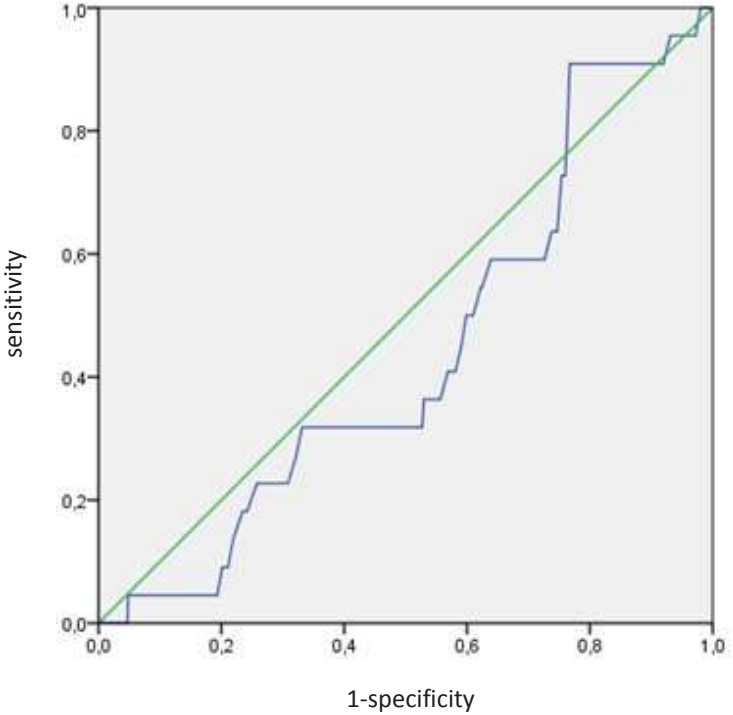
a)



Ischemic outcome events

Area Under the Curve 0.646 (0.529-0.763), p=0.009

b)



Hemorrhagic outcome events

Area Under the Curve 0.407 (0.275-0.540), p=0.14

Supplemental files

	With ischemic outcome events (n=63)	Without ischemic outcome events (n=791)	p
Age (mean, years)	79.3 ± 8.8	76.0 ± 9.5	0.011
NIHSS (mean)	10.3 ± 7.3	8.8 ± 6.9	ns
			ns
Sex male	26 (41.3%)	373 (47.1%)	ns
Diabetes mellitus	22 (34.9%)	199 (25.2%)	ns
Hypertension	56 (88.9%)	620 (78.4%)	ns
Hyperlipidemia	22 (34.9%)	260 (32.9%)	ns
History stroke/TIA	21 (33.3%)	184 (23.3%)	ns
Smoking	19 (30.2%)	198 (25.0%)	ns
Alcoholism	4 (6.4%)	53 (6.7%)	ns
History of CHF	18 (28.6%)	149 (18.8%)	ns
History of MI	10 (15.9%)	132 (16.6%)	ns
Paroxysmal AF	18 (28.6%)	298 (37.7%)	ns
Pacemaker	10 (15.9%)	60 (7.6%)	0.03
rtPA and/or thrombectomy	16 (25.4%)	185 (23.4%)	ns
Moderate/Severe atrial enlargement	23 (36.5%)	174 (22.0%)	0.013
Small lesion	16 (25.4%)	309 (39.1%)	0.03
Alessa score 3-4	38 (60.3%)	257 (32.5%)	0.0001
CHA_2DS_2-VASc >4	55 (87.3%)	622 (78.6%)	ns

Table 1 supplemental file: characteristics of patients in the derivation cohorts with and without ischemic outcome events

	With hemorrhagic outcome events (n=31)	Without hemorrhagic outcome events (n=823)	p
Age (mean, years)	75.1 ± 9.8	76.3 ± 9.5	ns
NIHSS (mean)	9.1 ± 6.6	8.9 ± 7.0	ns
			ns
Sex male	15 (48.4%)	383 (46.5%)	ns
Diabetes mellitus	10 (32.2%)	211 (25.6%)	ns
Hypertension	27 (87.1%)	649 (78.8%)	ns
Hyperlipidemia	10 (32.2%)	272 (33.0%)	ns
History stroke/TIA	4 (12.9%)	201 (24.4%)	ns
Smoking	10 (32.2%)	217 (26.4%)	ns
Alcoholism	4 (12.9%)	53 (6.4%)	ns
History of CHF	8 (25.8%)	159 (19.3%)	ns
History of MI	8 (25.8%)	134 (16.3%)	ns
Paroxysmal AF	10 (32.2%)	306 (37.2%)	ns
Pacemaker	5 (16.1%)	65 (7.9%)	ns
rtPA and/or thrombectomy	6 (19.3%)	195 (23.7%)	ns
Moderate/Severe atrial enlargement	9 (29.0%)	188 (22.8%)	ns
Small lesion	5 (16.1%)	320 (38.9%)	0.01
Alessa score 3-4	11 (35.5%)	284 (34.1%)	ns
CHA_2DS_2-VASc >4	27 (87.1%)	650 (79.0%)	ns

Table 2 supplemental file: characteristics of patients in the derivation cohorts with and without hemorrhagic outcome events