Influences of Intravenous Thrombolysis with Recombinant Tissue-type Plasminogen Activator on the Outcome of Atrial Fibrillation Patients with Acute Ischemic Stroke: A Case a Case-control Study of 227 Patients

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Research

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Abstract

Background: It is a debatable topic about the benefit of intravenous (IV) thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) for atrial fibrillation (AF) patients with acute ischemic stroke (AIS). This study aimed to identify whether IV rt-PA could improve the short-term outcome of patients with AF-AIS.

Methods: Medical data of patients with AIS onset within 72hs admitted in the department of neurologic of our hospital between January 1st, 2015 and December 31, 2020 were extracted. The AF-AIS patients were selected and divided into IV rt-PA group (group A) and non-rt-PA group (group B). The baseline characteristics, imaging changes and modified Rankin Scale (mRS) score (≤ 2 as good prognosis, > 2 as poor, = 6 as death) at discharge were obtained to compare the differences between the two groups. Logistic regression was used to analyze the factors influencing on the outcome.

Results: Among a total of 1663 AIS patients, there were 280 had AF, of them 227 AF-AIS cases were conformed to the inclusion criteria, including 45 in group A and 182 in group B. All of AF-AIS patients, 48.0% had larger size of infarction and 62.1% had National Institute of Health stroke scale (NIHSS)score more than 10, the differences in the size and NIHSS between the two groups were not significant. A total of 51 cases (22.5%) died during hospitalization, the difference between group A and group B was not obvious (20.0% vs. 23.1%, *P*=0.658). The cumulative poor outcome (including deaths) at discharge was 75.3%, the difference between the two groups was also not significant (77.8% vs. 74.7%, *P*=0.671). The incidence of hemorrhagic transformation (HT) in group A was higher than that of in group B (40.0% vs. 21.4, P=0.010), the same was true for parenchymal hematoma (PH) in group A than group B (22.2% vs. 5.5%, *P* = 0.001). On univariate analysis, poor outcome was significantly associated with infarct size, NIHSS and PH, but not thrombolysis. The proportion of PH in patients with poor outcome between the two groups was also not remarkable. On adjusted multiple logistic regression analysis, both baseline infarction size [(*P*=0.013, odds ratio (OR) =4.558, 95% 95% confidence interval (CI): 1.373- 15.133] and NIHSS (*P*<0.001, OR=1.348, 95% CI=1.219-1.491) but not thrombolysis or PH entered into the final model as significant independent risk factors of poor outcome.

Conclusion: Patients with AF-AIS had larger infarction size, higher NIHSS score, higher rate of mortality and worse outcome, for them, the IV rt-PA increased the incidence of PH except significantly improved their short-term prognosis.

Background

Atrial fibrillation (AF) is an independent risk factor for acute ischemic stroke (AIS), and about 20% of AIS is associated with AF in China [1]. AF might be newly detected in nearly a quarter of patients with stroke or transient ischemic attack [2], and in up to one third of cryptogenic stroke and in up to one fourth of patients with embolic stroke of undetermined source [3]. Patients with AF-AIS have more severe nerve injury, higher fatality and mortality [1]. It is the most effective therapy to improve the prognosis using intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) within 4.5 hours after onset of AIS [4, 5]. AF is not a contraindication to IV rt-PA in patients with AIS, but the effect and potential risk of hemorrhagic transformation (HT) remains controversial. Some researchers found that the outcome of IV rt-PA in patients with AF was even worse compared to those without AF [6, 7]. However, Shahripour et al. [8] recently reported

their study results on the International Stroke Conference 2021 that AF did not have a significant impact on rates of symptomatic intracranial hemorrhage (sICH) in AIS patients treated with IV rt-PA or endovascular treatment, or both, compared to other stroke subtypes. The purpose of our study is to explorer the difference of the short-term outcome between IV rt-PA and non-rt-PA in patients with AF-AIS, and to analyze the possibility of rt-PA benefit and associated affect factors.

Materials And Methods

Study subjects

According to the baseline characteristics, imaging changes, received IV rt-PA or not, the AF-AIS cases were selected for comparative analysis of the prognosis. Because it is a retrospective study, it does not involve patient's safety and privacy, then no ethical review.

Inclusion criteria

Patients who meet the diagnostic criteria of AIS [5] and complicated with AF, and the course from stroke symptoms onset to admission were no more than 72h.

Exclusion criteria

1) Patients without AF; 2) Patients with the final diagnosis of transient ischemic attack; 3) Patients with previously nervous system injury left a modified Rankin Scale (mRS) score ≥2; 4) Patients received intra-arterial treat; 5) Patients with mechanical value; 6) Patients with coagulation abnormal; 7)Patients with severe cardiac / pulmonary / renal insufficiency or malignant tumor.

Grouping and main treatment

According to whether or not to receive IV rt-PA within 4.5 hours after the occurrence of AF-AIS, patients were divided into rt-PA group (A) and control group (B). All patients of group A met the IV thrombolytic standard [5]. For patients in group A, rt-PA (from Shanghai Boehringer Ingelheim Pharmaceutical Co., Ltd., approval number: national medicine standard J20090089, specification 50mg × 1 bottle) was given following the guideline [5], i.e. 0.9 mg/kg, maximum ≤ 90mg, 10% of the total IV, the remaining was pumped into over 1h. The subsequently treatment was the same as that of group B, if no HT found 24h later after rt-PA. Patients in group B was treated with medicines of anti-platelet aggregation or anticoagulation, statins and improving blood circulation immediately after admission.

Definition of major indicators

The diagnosis of AF was based on medical history and was confirmed by electrocardiogram and /or continuous electrocardiogram monitoring. Glasgow coma scale (GCS) was used to evaluate the state of consciousness, which was divided into two grades: score of 15-13 and < 13. National Institutes of Health Stroke Scale (NIHSS) was used to evaluated the degree of nerve injury, which was also divided into two grades: score of ≦10 and > 10 [9]. Based on the max diameter of infarction area involved anterior or posterior

circulation appeared on brain MRI or CT, small-, medium- and large-sized AIS was <1.5, 1.5-3.0 and >3.0 cm, respectively [10,11]. The mRS score ≦ 2 as good prognosis, > 2 as poor, = 6 as death).

Subtypes of HT was defined as following: hemorrhagic infarction (HI)-1 with scattered, heterogeneous petechiae along the margins of the infarct; HI-2 with more confluent but still heterogeneous petechiae within the infarcted area; parenchymal hematoma (PH)-1 with a homogeneous hematoma covering <30% of the infarcted area and only mild space-occupying effect; and PH-2 with a dense hematoma >30% of the lesion volume with significant space- occupying effect [12].

Outcomes

Functional outcome was assessed using mRS score at discharge.

Statistical analyses

Measurement data were expressed as “x±s” if the data were distributed normally; otherwise, the data were expressed as “M (Q1~Q3)”. Baseline grouped measurement data that met the normality and homogeneity of variances criteria were analyzed using analysis of variance (ANOVA) test; otherwise, the nonparametric Mann-Whitney U test was used. Chi-Square or rank sum tests were used for categorical data. Prognostic factors were analyzed using binary logistic regression (Backward conditional method). All analyses were performed with SPSS 26.0 (©Copyright IBM Corporation 2016, IBM Corporation Software Group Route 100 Somers, NY 10589, USA). P <0.05 was considered to be a statistically significant difference.

Results

General result

There were 1663 consecutive patients with AIS were retrieved in our electronic medical record system over 6 years, of them 280 (16.8%) had AF. After enrollment, a total of 227 AF-AIS conformed to the criteria were available for this study, including 45 cases in group A and 182 cases in group B. A known AF and AF detected after onset of AIS were 175 and 52, respectively (Figure. 1)

Baseline characteristics

Twenty-point five percent of AF-AIS patients received IV rt-PA thrombolysis. The age of group A (70.2 ± 11.8, range 48-90) was significantly younger than that of group B (76.7 ± 10.7, range 41-98), and infarction located in anterior circulation were significantly more than that in posterior circulation (P < 0.027). There was no obvious difference in other baseline data between the two groups (Table 1).

Hemorrhagic transformation

Neither HI nor PH was further separated into corresponding subtypes, such as HI-1 and HI-2, or PH-1 and PH-2, due to the small size of sample. The rate of HT in group A was nearly twice as high as that in group B (40.0% vs. 21.4%, P = 0.010). The incidence of PH in group A was significantly higher than that in group B (22.2% vs.

5.5%, P = 0.001). The median time of detected PH was 12.5 (5.5, 22.5) hours in group A and 35.5 (11.0, 180.0) hours in group B. It suggests that IV rt-PA increase the risk of PH. The difference of HI between the two groups was not obvious (Table 2).

Outcomes

The cumulative mortality was 22.5% (Table 3), the difference between group A and group B was not significant (20.0% vs. 23.1%, P = 0.658, OR = 1.200, 95% CI: 0.535-2.691). Media time of death was 12 (5, 25) days. Media time of hospitalization was 18 (13, 29) days. The total rate of poor outcome at discharge was 75.3%, there was also no significant difference between the two groups (77.8% vs. 74.7, P = 0.671, OR = 0.845, 95% CI: 0.388-1.839).

On univariate analysis (Table 4), the poor prognosis rate of patients with medium and large size of infarction reached 68.3% and 94.5%, respectively, which was significantly higher than that of 45.5% of small size of infarction (all P < 0.001). The poor outcome rate of patients with GCS < 13 score was significantly higher than that of GCS 13-15 score (96.1% vs. 58.1%, P < 0.001), and so was NIHSS >10 score compared with NIHSS≦10 score (94.3% vs. 44.2%, P < 0.001). There was a positive correlation between the size of infarction and NIHSS (Spearman's rho test, r = 0.539，P < 0.001). These results confirmed that larger size of infarction, higher NIHSS score or lower GCS score were the risk factors of poor prognosis for AF-AIS patients.

A total of 20 (8.8%) AF-AIS patients developed PH, each group had 10 cases, and all of them got a poor outcome (Table 4), including 4 of deaths in each group (Table 5). The poor outcome rate of patients with PH was significantly higher than that of patients without PH (100% vs. 72.9, P = 0.005). As for poor outcome, the difference between group A and group B were not significant in the proportion of infarct size, NIHSS and PH (Table 4), as well as in age, gender, known AF or newly detected AF after stroke onset, baseline blood pressure and blood glucose, so on (some data were not listed).

The poor prognosis rate of anterior circulation infarction was significantly higher than that of posterior circulation infarction (79.8% vs. 50.0, P < 0.001, Table 4). Patients with larger size infarction and with NIHSS score > 10 were mainly in anterior circulation, in addition, all of the 20 cases with PH occurred in anterior circulation (Table 6).

On multiple logistic regression analysis using the Backward LR method, after adjusted age and other confounding factors, both the size of infarction (P = 0.013, OR = 4.558, 95% CI: 1.373-15.133) and NIHSS (P < 0.001, OR = 1.348, 95% CI: 1.219-1.491) but not rt-PA or PH entered into the final model as significant independent predictors for poor outcome (Table 7). The model accuracy of prediction was 87.2%. The area under the receiver operating characteristic (ROC) curve of infarction size and NIHSS was 0.789 and 0.896, respectively (Figure 2, Table 8). The best cutoff value of NIHSS was 9.5, its sensitivity was 83%, and specificity was 82%.

Discussion

In this study, the incidence of AF in patients with AIS was 16.8%, which was in accordance with the incidence of 16.9% reported by Mehrpour et al [7]. The total rate of poor outcomes was 75.3%, including 22.5% of deaths;

there was no significant difference between the two groups. The high morbidity and mortality of AF-AIS were consistent with other reports: Mehrpour et al. [7] studied 118 Iranian AIS received IV rt-PA (24 with AF, 94 no AF), the poor outcome of AF patients was significantly higher than that of non-AF patients (79.2% vs. 41.5%, P = 0.001) at 3 months. Findler et al. [6] studied 214 AIS patients who received IV rt-PA (63 with AF, 151 no AF) from 27 Israeli hospital, more patients had favorable outcome in non-AF group than in AF group (P = 0.058, OR = 2.217, 95% CI: 0.973 - 5.05). Alkhouli et al. [13] investigated a total of 930,010 AIS patients between 2003 and 2014 in the National Inpatient Samplein the United States, found that 18.2% of these patients had AF, the mortality rate was higher in patients with AF compared with patients without AF (9.9% vs. 6.1%; P < 0.001). Above results suggest that AF is a risk factor for poor outcome of AIS, and IV rt-PA could not improve the prognosis of AF-AIS.

Our data analysis also shown no significant difference in the outcome of the known AF and the newly discovered AF after stroke onset, it was consistent with the report by Hsich et al. [14].

The study of histological composition of clots retrieved from cerebral arteries in AIS patients confirmed that the clots from cardio-embolism, being formed in regions of stasis or slow flow in the atrium, had a significantly higher proportion of red blood cells and a lower proportion of fibrin, while thrombi occurring in atherosclerotic large arteries were mainly composed of fibrin and platelets [15]. The target of rt-PA is fibrin in thrombus, so the embolus of AF is more resistant to rt-PA, i.e. the so-called "rt-PA resistance", it might partially explain why the IV rt-PA efficacy for AF-AIS is not ideal.

HT is an important complication of AIS, especially with the use of anticoagulants and thrombolytic agents. The rates of rt-PA-related symptomatic intracranial hemorrhage (sICH) in AIS patients were 3.8-22.6% [16, 17]; however, the rates in AF-AIS patients reached 22.0-33.0% [18, 19].

Jensen et al. [20] performed a multicenter, randomized, placebo-controlled trial, to study HT after IV rt-PA thrombolysis in patients with wake-up stroke. Of the 483 patients, HI and PH were 19.7% and 4.4%, respectively. Analyzing their data based on with and without AF, among 59 cases with AF, 47.5% developed HT and 8.5% had PH; by contrast among 424 cases without AF, only 3.8% had PH. Multiple logistic regression analysis identified IV rt-PA (P = 0.003, OR = 2.08, 95% CI: 1.28-3.40), baseline NIHSS score (P < 0.001, OR = 1.11, 95% CI: 1.05-1.17), lesion volume (P = 0.005, OR = 1.03, 95% CI: 1.01-1.05), and AF (P < 0.001, OR = 3.02, 95% CI: 1.57-5.80) were associated with any HT.

Our data shown that the incidence of HT in group A was significantly higher than that in group B (40.0% vs. 21.4%, P = 0.010). According to HT classification analysis, the incidence of PH in group A was significantly higher than that in group B (22.2% vs. 5.5%, P = 0.001), but not HI. These results indicate that AF-AIS have a high incidence of HT, and rt-PA increases the risk of PH.

An earlier study [21] found that the majority of sICH occurred within the first 24 hours after the start of rt-PA therapy and 80% of fatal hemorrhage occurred within the first 12 hours. It suggests that sICH occurred after 36 hours could be considered unrelated to rt-PA treatment. Of our patients, the shortest time of PH after IV rt-PA in group A appeared at 2 hours, the median time was 12.5 (5.5, 22.5) hours, and the median time of PH in group B was 35.5 hours (11.0, 180.0), which supports that the earlier PH is related to IV rt-PA therapy.

The blood-brain barrier (BBB) forms the interface between cerebral vessels and nerve tissue to ensure the normal material exchange between blood and nerve tissue. The integrity of BBB depends on the tight junction between endothelial cells and basement membrane. Following AIS, there is the loss of BBB tight junction integrity, which leads to increased paracellular permeability and results in vasogenic edema and HT [22]. A study by Kidwel et al. [23] shown that after the use of rt-PA in AIS patients, abnormal high signals of fluid attenuated inversion recovery MRI sequence appeared in the sulcus containing cerebrospinal fluid in the area of occlusive vessels, suggesting that rt-PA have neurovascular toxic effect of BBB disruption and the development of ICH. It is known that rt-PA can induce activation of matrix metalloproteinase-9 (MMP-9), Montaner et al. [24] studied 41 patients with AIS involving the middle cerebral artery territory who received rt-PA within 3 hours after stroke onset, and found that the baseline levels of serum MMP-9 had a graded response with the degree of HT. The high activity of this enzyme further damages the matrix and leads to worse HT [25].

Mere HI may be understood as a marker of successful recanalization into partially ischemic damage area with no adverse clinical effect while massive HT, especially PH2, is to be associated with poor outcome [20]. Another study by Nogueira et al. [26 found that both of HI (P < 0.0001, OR = 2.23, 95% CI: 1.53-3.25) and PH (P<0.0001, OR =6 .24, 95% CI: 3.06-12.75) were close related with functional outcome, however only PH was associated with a higher mortality (P < 0.0001, OR = 3.53, 95% CI: 2.19-5.68). In our study, we found that there was no correlation between HI and adverse prognosis in any groups, while the poor outcome rate of 10 patients with PH in each group was 100%, including 40% of deaths, it indicating that PH was associated with worse clinical outcome.

Baseline neurological severity was one of the risk factors independently associated with sICH in the NINDS trial (OR = 1.8, 95% CI: 1.2–2.9) [27]. In a multicenter t-PA Acute Stroke Survey, baseline NIHSS was a risk factor for all rt-PA related ICH and remained an independent predictor in each multivariate statistical model [28].

Size of infarction, or infarction volume, an important factor associated with prognosis, is correlated strongly with NIHSS score [29]. Our data analysis was consistent with it, the correlation coefficient between infarct size and NIHSS grade was 0.539 (P < 0.001), and for patients with lager size of infarction and NIHSS >10 score, the poor outcome was 94.5% and 94.3%, respectively. On multivariate Logistic regression analysis, both baseline infarction size (P = 0.013, OR = 4.558, 95% CI: 1.373-15.133) and NIHSS (P < 0.001, OR =1.348, 95% CI: 1.219-1.491) but not rt-PA entered into the final model as significant risk factors of poor prognosis. The result suggests that infarction size and NIHSS were risk factors of poor outcomes, and IV rt-PA could not improve the prognosis of patients with AF-AIS.

Researches indicate that different from the AIS patients with intracranial large artery stenosis or cerebral microvascular disease which has better collateral compensation, AF-AIS is a sudden vascular occlusion due to cardiogenic embolism, there is no time to establish adequate collateral compensation, therefore AF patients have greater infarct growth, larger infarcts, more frequent PH, worse functional outcome and higher mortality compared to patients with no AF [19, 30].

Our univariate analysis also showed that the outcome in anterior circulation infarction was significantly worse than that of posterior circulation (79.8%, vs. 50.0%, P < 0.001). It might be because patients with anterior circulation infarction have a higher proportion of large size of infarction and higher NIHSS score, in addition, all of 20 patients with PH occurred in anterior circulation.

Conclusions

In summary, our data analysis of AF-AIS patients shows that the large size of infarction accounts for 48% and NIHSS >10 sore accounts for 62.1%. The total mortality is 22.5% and the poor prognosis (including cases of deaths) is 75.3%. All of these results have no significant intergroup differences. However, the incidence of PH in group A is obviously higher than that of in group B. On adjusted multiple logistic regression analysis, both baseline infarction size and NIHSS but not rt-PA or PH entered into the final model as significant independent risk factors of poor outcome. That is, for AF-AIS patients, IV rt-PA increases the incidence of PH except significantly improved their short-term prognosis. This study's advantage is all of AIS patients companying with AF. However, it is a single-center, small-sample retrospective study and without an evaluation of long-term outcome. Therefore, the representativeness of the results may be limited and need to be further determined by larger sample randomized controlled trials. Recent studies [31-33] have reported that the prognosis of patients with AF-AIS treated with direct intra-arterial thrombectomy therapy is better than that of IV rt-PA thrombolysis or bridging therapy. This may open up a new treatment method for improving the prognosis of AF-AIS.

Abbreviations

AF-AIS: atrial fibrillation - acute ischemic stroke; BBB: blood-brain barrier; CI: confidence interval; HI: hemorrhagic infarction; HT: hemorrhagic transformation; IV: intravenous; MMP-9: matrix metalloproteinase-9; mRS: modified Rankin Scale; NIHSS: National Institute of Health stroke scale; OR: odds ratio; PH: parenchymal hematoma; rt-PA: recombinant tissue-type plasminogen activator; sICH: symptomatic intracerebral hemorrhage; TC: triglyceride

Declarations

Ethics approval and consent to participate: It is a retrospective study, it does not involve patient's safety and privacy, then no ethical review.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: HXW, NZ, GQW and YHH designed the study. HXW and NZ retrieved and collected the data. NZ and GQW analyzed the data. NZ and GQW drafted the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Clinical baseline characteristics of atrial fibrillation patients with acute ischemic stroke

Characteristics	Total (n=227)	Group A (n=45)	Group B (n=182)	F/Z Statistic	*P*
Age, mean±SD	75.4±11.2	70.2±11.8	76.7±10.7	F=1.504	<0.001
≦70, n (%)	73 (32.2)	19 (42.2)	54 (29.7)	Z= -1.611	0.107
> 70, n (%)	154 (67.8)	26 (57.8)	128 (70.3)		
Sex female, n (%)	125 (55.1)	21 (46.7)	104 (57.1)	Z= -1.262	0.207
male, n (%)	102 (44.9)	24 (53.3)	78 (42.9)		
DM no, n (%)	163 (71.8)	36 (80.0)	127 (69.8)	Z= -1.361	0.173
yes, n (%)	64 (28.2)	9 (20.0)	55 (30.2)		
Hlip no, n (%)	194 (85.5)	37 (82.2)	157 (85.5)	Z= -0.687	0.492
yes, n (%)	33 (14.5)	8 (17.8)	25 (14.5)		
HBP no, n (%)	62 (27.3)	14 (31.1)	48 (26.4)	Z= -0.637	0.524
yes, n (%)	165 (72.7)	31 (68.9)	134 (73.6)		
SBP, mean±SD	150.2±23.9	150.7±27.3	150.1±23.1	F=1.110	0.878
DBP, mean±SD	86.7±14.6	89.3±16.5	86.0±14.1	F=0.633	0.181
GCS , mean±SD	11.6±3.6	12.6±3.3	11.4±3.6	Z= -1.816	0.069
15-13 sore, n (%)	124 (54.6)	30 (66.7)	94 (51.6)		
12-3 sore, n (%)	103 (45.4)	15 (33.3)	88 (48.4)		
NIHSS, mean±SD	12.8±6.9	12.8±6.4	12.7±7.1	F=1.981	0.060
≦10 sore, n (%)	86 (37.9)	19 (42.2)	67 (36.8)		
>10 sore, n (%)	142 (62.1)	26 (57.8)	115 (63.2)		
Glucose (mmol/L)	8.0±4.2	7.9±4.0	8.0±4.3	F=0.074	0.879
TC (mmol/L)	4.0±1.0	4.0±1.0	4.0±1.0	F=0.219	0.948
TG (mmol/L)	1.1±0.7	1.1±0.7	1.1±0.7	F=1.579	0.787
LDL-C (mmol/L)	2.4±0.9	2.3±0.8	2.4±1.0	F=2.890	0.346
Site anterior, n (%)	193 (85.0)	43 (95.6)	150 (82.4)	Z= -2.207	0.027
posterior, n (%)	34 (15.0)	2 (4.4)	32 (17.6)		
Size small, n (%)	55 (24.2)	12 (26.7)	43 (23.6)	Z= -1.029	0.304
medium, n (%)	63 (27.7)	15 (33.3)	48 (26.4)		
lager, n (%)	109 (48.0)	18 (40.0)	91 (50.0)		

Group A: receive intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA);

Group B: no rt-PA.

F: statistic of Levene's test with *P* value calculated by one-way ANOVA; Z: statistic of nonparmetric test with *P* value calculated by Mann-Whitney U. DM: history of diabetes mellitus; HLip: history of hyperlipidemia; HBP: history of hypertension; SBP: systolic pressure; DBP diastolic pressure; GCS: Glasgow coma scale; NIHSS National Institutes of Health Stroke Scale; TC: total cholesterol; TG triglyceride; LDL-C: low-density lipoprotein cholesterol; Site: infarction location in anterior or in posterior circulation system; Size: infarction volume of small, medium and larger

Table 2 Comparison of hemorrhagic transformation

Hemorrhagic transformation		Total (n=227)	Group A (n=45)	Group B (n=182)	χ^2	*P*	OR	95% CI	
								Lower	Upper
HT	no, n (%)	170 (74.9)	27 (60.0)	143 (78.6)	6.617	0.010	0.409	0.204	0.819
	yes, n (%)	57 (25.1)	18 (40.0)	39 (21.4)					
HI	no, n (%)	190 (83.7)	37 (82.2)	153 (84.1)	0.090	0.764	0.877	0.371	2.074
	yes, n (%)	37 (16.3)	8 (17.8)	29 (15.9)					
PH	no, n (%)	207 (92.1)	35 (77.8)	172 (94.5)	12.566	0.001	0.203	0.079	0.526
	yes, n (%)	20 (7.9)	10 (22.2)	10 (5.5)					

Group A: intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA); Group B: no rt-PA. X^2: Pearson Chi-Square; OR: odds ratio; CI: confidence interval; HT: hemorrhagic transformation; HI: hemorrhagic infarction; PH: parenchymal hematoma.

Table 3 Comparison of prognosis

Prognosis		Total (n=227)	Group A (n=45)	Group B (n=182)	χ^2	*P*	OR	95% CI	
								Lower	Upper
Dead	yes, n (%)	51 (22.5)	9 (20.0)	42 (23.1)	0.196	0.658	1.200	0.535	2.691
	no, n (%)	176 (77.5)	36 (80.0)	140 (76.9)					
mRS >2	yes, n (%)	171 (75.3)	35 (77.8)	136 (74.7)	0.181	0.671	0.845	0.388	1.839
	no, n (%)	56 (24.7)	10 (22.2)	46 (25.3)					

Group A: intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA); Group B: no rt-PA. X^2: Pearson Chi-Square; OR: odds ratio; CI: confidence interval; HT: hemorrhagic transformation; mRS: modified Rankin scale, >2 indicated poor prognosis.

Table 4 Analysis of factors related to outcome

Factors	All n=227 (%)			Group A, n=45 (%)		Group B, n=182 (%)			
	mRS>2	mRS≦2	*P*	mRS>2	mRS≦2	mRS>2	mRS≦2	*Z*	*P*
Age ≦70	51 (69.9)	22 (30.1)	0.189	14 (73.7)	5 (26.3)	37 (68.5)	17 (31.5)	-0.419	0.675
>70	120 (77.9)	34 (22.1)		21 (80.8)	5 (19.2)	99 (77.3)	29 (22.7)	-0.383	0.702
AF Known	129 (73.7)	46 (26.3)	0.301	25 (79.1)	7 (21.9)	104 (72.7)	39 (27.3)	-0.625	0.532
New	42 (80.8)	10 (19.2)		10 (76.9)	3 (23.1)	32 (82.1)	7 (17.9)	-0.402	1.000
Site Anterior	154 (79.8)	39 (20.2)	<0.001	34 (79.1)	9 (20.9)	120 (80.0)	30 (20.0)	-0.134	0.894
Posterior	17 (50.0)	17 (50.0)		1 (50.0)	1 (50.0)	16 (50.0)	16 (50.0)	0.000	1.000
Size small	25 (45.5)	30 (54.5)	0.013[a]	7 (58.3)	5 (41.7)	18 (41.9)	25 (58.1)	-1.004	0.315
medium	43 (68.3)	20 (31.7)	<0.001[b]	10 (66.7)	5 (33.3)	33 (68.7)	15 (31.3)	-0.150	1.000
larger	103 (94.5)	6 (5.5)	<0.001[c]	18 (100)	0 (0.0)	85 (93.4)	6 (6.6)	-1.116	0.587
GCS 13-15	72 (58.1)	52 (41.9)	<0.001	21 (70.0)	9 (30.0)	51 (54.3)	43 (54.7)	-1.515	0.130
3-12	99 (96.1)	4 (3.9)		14 (93.3)	1 (6.7)	85 (96.6)	3 (3.4)	-0.601	1.000
NIHSS ≦10	38 (44.2)	48 (55.8)	<0.001	11 (57.9)	8 (42.1)	27 (40.3)	40 (59.7)	-1.355	0.175
>10	133 (94.3)	8 (5.7)		24 (92.3)	2 (7.7)	109 (94.8)	6 (5.2)	-0.491	0.640
HI no	144 (75.5)	46 (24.5)	0.717	27 (73.0)	10 (27.0)	117 (76.5)	36 (23.5)	-0.445	0.657
yes	27 (73.0)	10 (27.0)		8 (100)	0 (0.0)	19 (65.5)	10 (34.5)	-1.918	0.079
PH no	151 (72.9)	56 (27.1)	0.005	25 (71.4)	10 (28.6)	126 (73.3)	46 (26.7)	-0.221	0.825
yes	20 (100.0)	0 (0.0)		10 (100)	0 (0.0)	10 (100.0)	0 (0.0)	0.000	1.000

Group A: intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA); Group B: no rt-PA; Z: statistic of nonparametric test with *P* value calculated by Mann-Whitney U; mRS: modified Rankin scale (score≦2 as good prognosis, score>2 as poor); AF: atrial fibrillation; Known: AF was diagnosed

before stroke; New: AF was discovered after stroke onset; Site: infarction location in anterior or in posterior circulation system; Size: infarction volume of small, medium and larger; GCS: Glasgow coma scale; NIHSS National Institutes of Health Stroke Scale; HT: hemorrhagic transformation prognosis; for groups cooperation [a] small vs. medium; [b] medium vs. larger; [c] larger vs. small (infarction size comparation between subgroups).

Table 5 Relationship between hemorrhagic transformation and dead

	All, n=227 (%)			Group A, n=45 (%)		Group B, n=182 (%)			
Factors	Dead	Survival		Dead	Survival	Dead	Survival	*Z*	*P*
HI no	45 (23.7)	145 (76.3)	0.320	8 (21.6)	29 (78.4)	37 (24.2)	116 (75.8)	-0.328	0.743
yes	6 (16.2)	31 (83.8)		1 (12.5)	7 (87.5)	5 (17.2)	24 (82.8)	-0.318	1.000
PH no	43 (20.8)	164 (79.2)	0.056	5 (14.3)	30 (85.7)	38 (22.1)	134 (77.9)	-1.035	0.301
yes	8 (40.0)	12 (60.0)		4 (40.0)	6 (60.0)	4 (40.0)	6 (60.0)	0.000	1.000

Group A: intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA); Group B: no rt-PA; Z: statistic of nonparametric test with *P* value calculated by Mann-Whitney U; HI: hemorrhagic infarction; PH: parenchymal hematoma.

Table 6 Comparison of between anterior circulation and posterior circulation infarction

Characteristics		Site of infarction		*Z*	*P*
		Anterior, n (%)	Posterior, n (%)		
Size	small, n (%)	41 (21.2)	14 (41.2)	-3.237	0.001
	medium, n (%)	51 (24.6)	12 (35.3)		
	lager, n (%)	101 (52.2)	8 (23.5)		
NIHSS ≦10 sore, n (%)		66 (34.2)	20 (58.8)	-2.723	0.006
	>10 sore, n (%)	127 (65.8)	14 (41.2)		
PH	no, n (%)	173 (89.6)	34 (100.0)	-1.961	0.091
	yes, n (%)	20 (10.4)	0 (0.0)		

Site: infarction location in anterior or in posterior circulation system; Z: statistic of nonparametric test with *P* value calculated by Mann-Whitney U; Size: infarction volume of small, medium and larger; NIHSS: National Institutes of Health Stroke Scale; PH: parenchymal hematoma.

Table 7 Multiple adjusted logistic analysis for risk factors of poor prognosis

Variables	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI	
							Lower	Upper
Size			7.387	2	0.025			
Size (1)	0.016	0.484	0.001	1	0.974	1.016	0.393	2.625
Size (2)	1.517	0.612	6.139	1	0.013	4.558	1.373	15.133
NIHSS	0.299	0.051	33.977	1	<0.000	1.348	1.219	1.491
Constant	-1.093	0.810	1.821	1	0.177	0.335		

Method: Backward LR, Entry = 0.05, Removal = 0.10; CI: confidence interval; Size: small, Size (1): middle, Size (2): large of infarction; NIHSS: National Institutes of Health Stroke Scale.

Tab.8 Area under receiver operating characteristic (ROC)

Variables	Area	S.E	*P*	95% CI	
				Lower	Upper
Size	0.789	0.034	< 0.001	0.723	0.855
NIHSS	0.896	0.022	< 0.001	0.852	0.941

CI: confidence interval; Size: infarction volume; NIHSS: National Institutes of Health Stroke Scale.

Figures

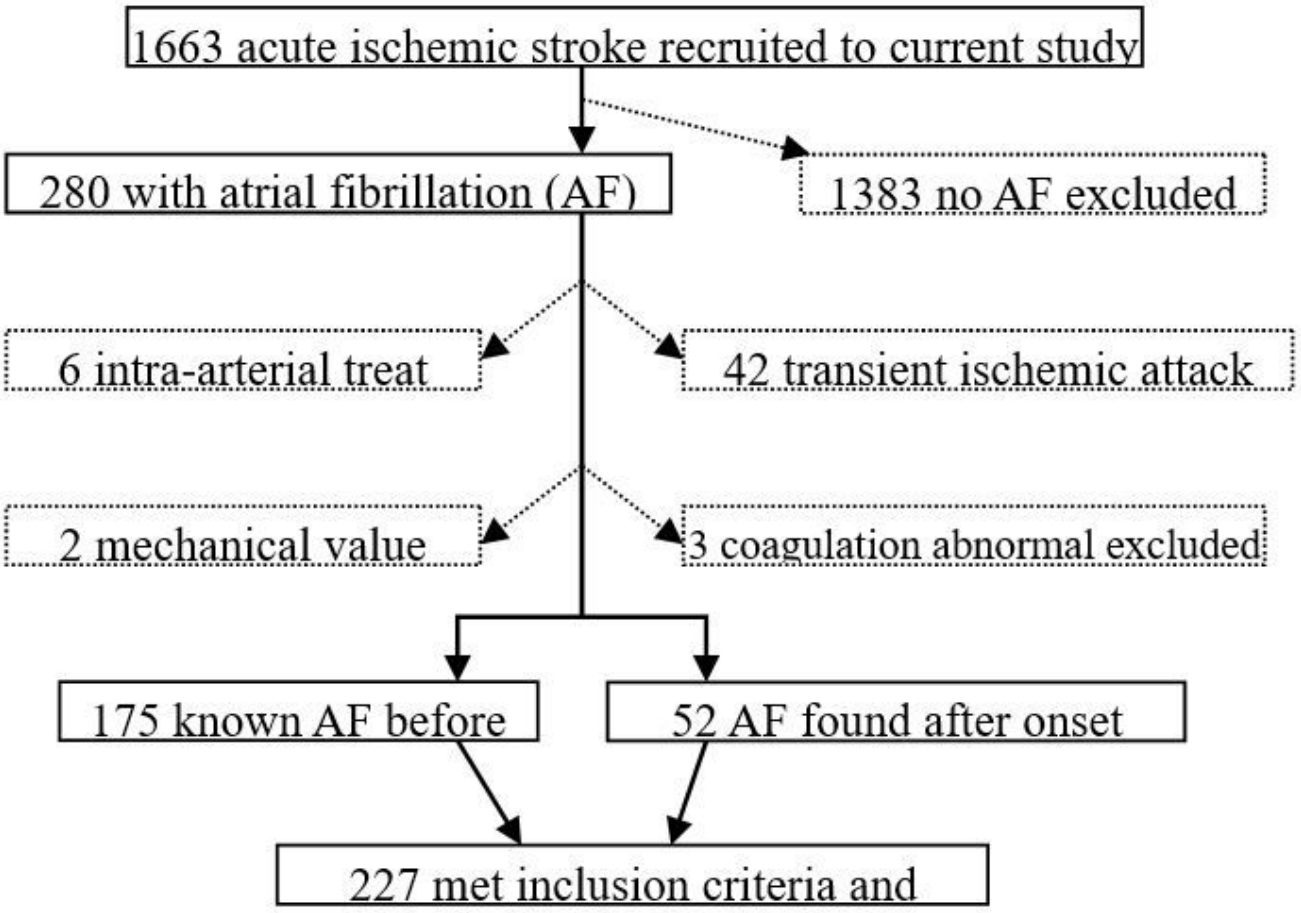

Figure 1

Trial profile

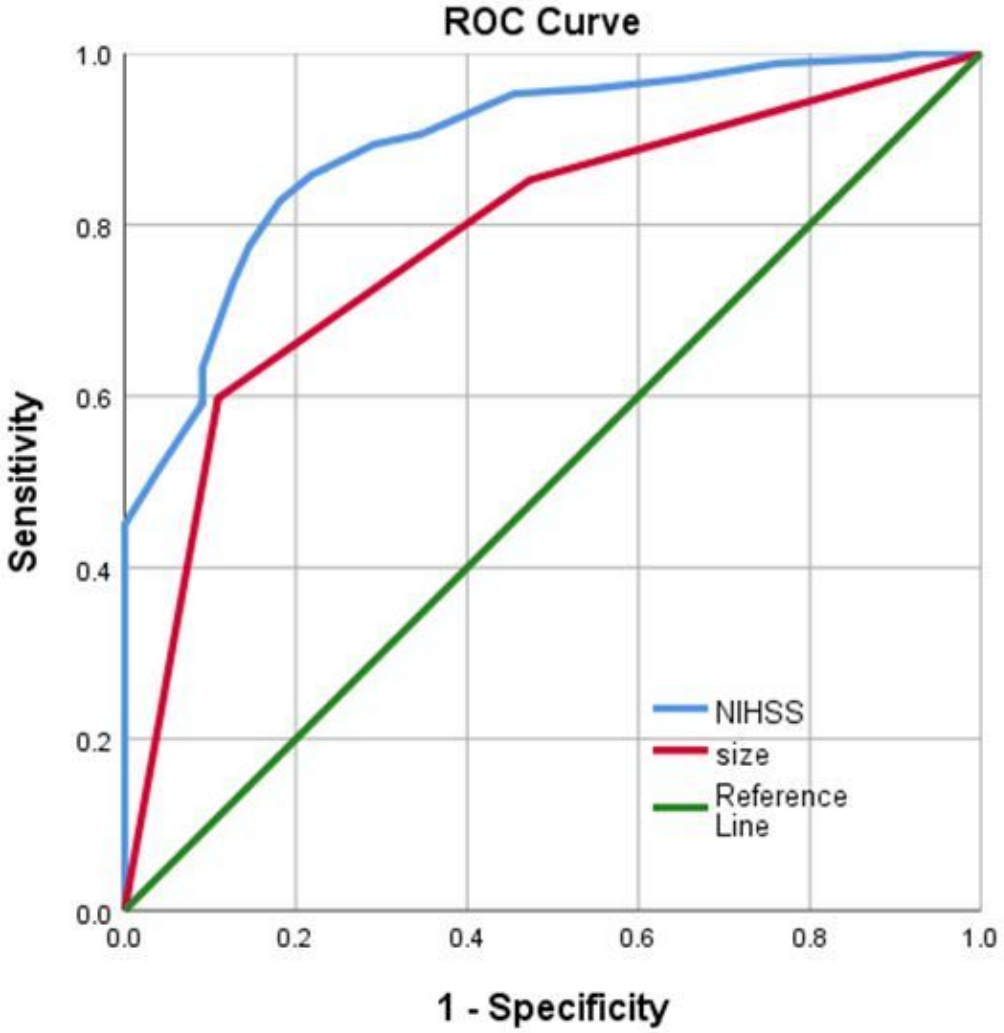

Figure 2

Receiver Operating Characteristic (ROC)