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Endovascular treatment for acute ischemic stroke in patients with versus without atrial fibrillation: a matched-control study

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Abstract

Background and objective: The effect of atrial fibrillation (AF) on outcomes of endovascular treatment (EVT) for acute ischemic stroke (AIS) is controversial. This study aimed to investigate the association of AF with outcomes after EVT in AIS patients.

Methods: Subjects were selected from ANGEL-ACT registry (Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke) - a prospective consecutive cohort of AIS patients undergoing EVT at 111 hospitals in China between November 2017 and March 2019, and then grouped according to having a history of AF or not. After 1:1 propensity score matching, the outcome measures including the 90-day modified Rankin Scale (mRS) score, successful recanalization after final attempt, symptomatic intracranial hemorrhage (ICH) within 24 h, and death within 90 days were compared.

Results: A total of 1755 patients, 550 with AF and 1205 without AF, were included. Among 407 pairs of patients identified after matching, no significant differences were found in the mRS score (median: 3 vs. 3 points; $P = 0.29$), successful recanalization (87.2 vs. 85.3%; $P = 0.42$), symptomatic ICH (9.4 vs. 9.1%; $P = 0.86$) and death (16.3 vs. 18.4%; $P = 0.44$) between patients with and without AF.

Conclusion: The findings of this matched-control study show comparable outcomes of EVT in Chinese AIS patients with and without AF, which do not support withholding EVT in patients with both AIS and AF.

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Introduction

Atrial fibrillation (AF), as the most common cause of cardioembolic stroke, is associated with a 4–5 times increased risk of acute ischemic stroke (AIS) and accounts for approximately 30–40% of all acute large vessel occlusion (LVO) [1–8]. Patients with AF-related stroke are older, have greater burden of comorbidities and worse neurological deficits, thus have a higher probability of disability or mortality after usual care [9–12]. Furthermore, intravenous thrombolysis (IVT) is less effective on both recanalization and clinical outcome but also increases the risk of intracranial hemorrhage (ICH) in patients with AF. The poor response to IVT could be partly explained by the pathophysiology of AF-related stroke, such as the gaps between patients with and without AF in terms of embolic size and components, collateral status, infarct core volume, and stroke progression [13, 14].

Endovascular treatment (EVT) represented by mechanical thrombectomy with stent-retriever or aspiration catheter has become the standard treatment for selected patients with AIS due to intracranial proximal LVO [15]. However, limited data and conflicting results exist regarding the role of AF on procedural and clinical outcomes after EVT [16–21]. To address this issue and on the hypothesis that the modification of AF was attributed to the effect of case mix; in other words, AF might not independently affect any outcome in EVT-treated patients after adjusting for possible confounders. We therefore performed a matched-control analysis based on a prospective nationwide registry database to assess whether the technical success and functional outcomes differ in LVO patients with and without AF after receiving EVT.

Methods

Study population

Data were extracted from ANGEL-ACT (Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke), a prospective nationwide registry of 1793 consecutive patients with AIS caused by LVO undergoing EVT in 111 hospitals in China between November 2017 and March 2019. Full methods of the registry, such as inclusion/exclusion criteria and data collection standards, have been reported earlier [22]. The protocol was approved by the ethics committees of all centers, and all participants (or legal representatives) provided written informed consent. The study procedures were in accordance with the 1964 Helsinki declaration and its later amendments.

In this analysis, patients with missing baseline or procedure data in Table 1 were excluded, and the remainder cases were divided into two groups based on whether they had pre-existing AF, identified by previous medical records.

Outcome measures

The primary outcome was the 90-day modified Rankin Scale (mRS) score assessed by trained and independent investigators. The secondary outcomes included successful recanalization (modified Thrombolysis in Cerebral Infarction [mTICI] of 2b–3) after first and final attempt, complete recanalization (mTICI of 3) after final attempt, [23] the proportions of mRS 0–1, 0–2 and 0–3 at 90 days. The safety outcomes were intra-procedural complications (e.g., new territorial embolization, arterial perforation, arterial dissection, vasospasm requiring treatment and in-stent thrombosis), any ICH, parenchymal hematoma type 2 (PH2) and symptomatic ICH within 24 hours according to the Heidelberg Bleeding Classification, [24] and death within 90 days.

Statistical analysis

Data were displayed as median (interquartile range [IQR]) or frequency (percentage). Univariable comparisons of baseline characteristics between patients with and without AF were performed using Mann-Whitney or Pearson's chi-square tests. To improve the comparability between the two groups, a 1:1 propensity score matching (PSM) was performed by using a caliper distance of 0.05 [25]. For comparing the outcomes between both groups, the odds ratios (OR) or common OR with their 95% confidence intervals (CI) were calculated using a binary or ordinal logistic regression model, if applicable. Significance level was set to $\alpha = 0.05$ (2-sided). Statistical analyses were conducted with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Among 1793 patients enrolled in the ANGEL-ACT registry, 38 patients were excluded due to missing baseline or procedure information, a total of 1755 patients were included in this analysis, including 550 cases with AF and 1205 without AF. After PSM, 814 patients were identified (Fig. 1).

As shown in Table 1, there were significant differences in many baseline and procedure characteristics between pre-matched patients with and without AF. For example, patients with AF were 8 years older, had 3 points higher NIHSS scores, were more frequently given anticoagulants before stroke onset, and received more passes of thrombectomy than those without AF; while patients with AF had lower proportions of male, current smoker, and vertebro-basilar artery occlusion, were less often given tirofiban during the procedure and emergency angioplasty/stenting, and experienced 65 min shorter onset-to-puncture time than those without AF (all P -values < 0.01). After PSM, all baseline and procedure characteristics between groups were well-balanced (Table 1).

Table 1 Baseline and procedure characteristics of patients with AF versus without AF

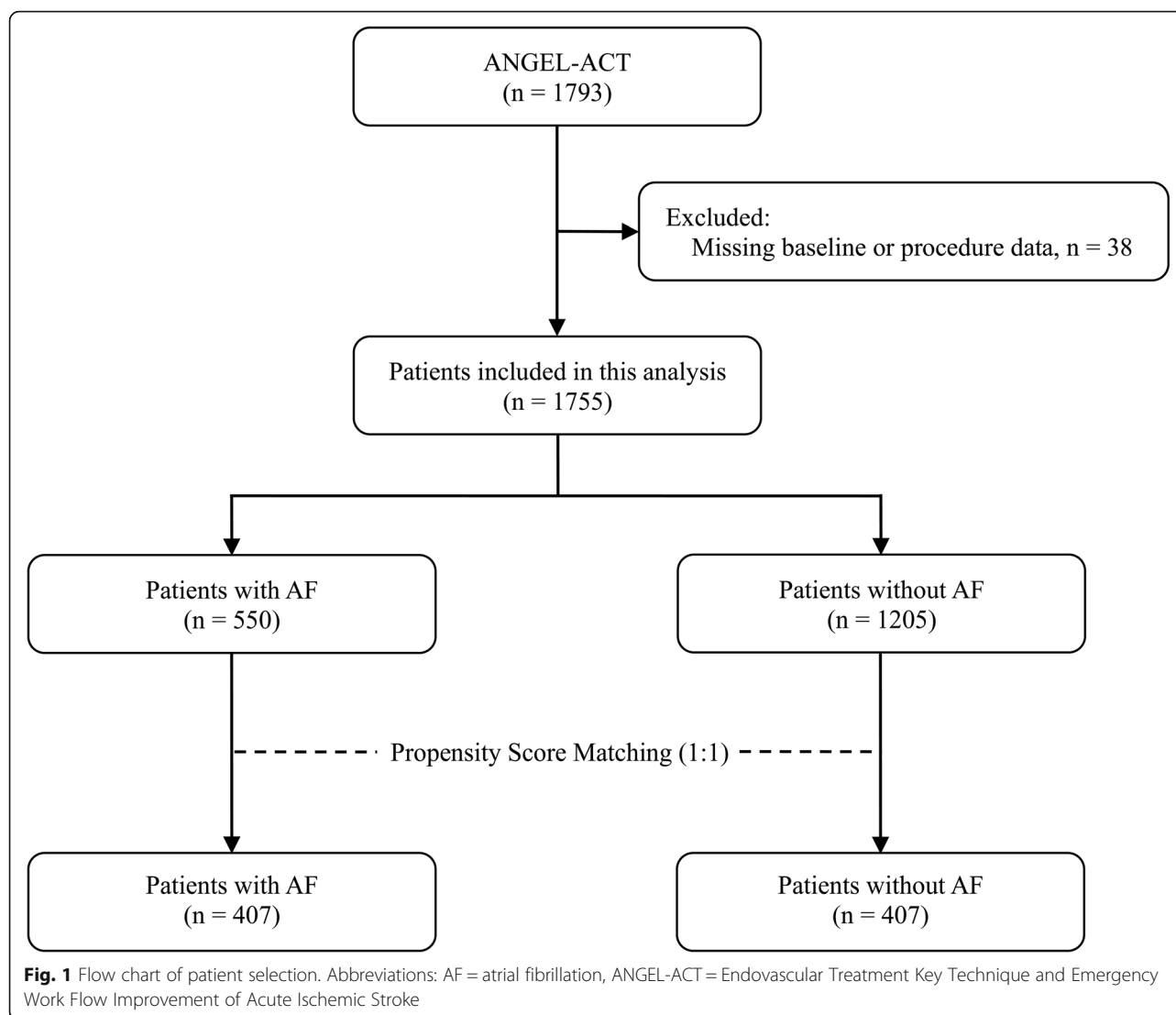
Baseline and procedure variables	Pre-matched population (n = 1755)				Post-matched population (n = 814)			
	With AF (n = 550)	Without AF (n = 1205)	SD (%)	P-value	With AF (n = 407)	Without AF (n = 407)	SD (%)	P-value
Age, median (IQR), years	71 (64–78)	63 (54–70)	72.0	< 0.01	69 (62–76)	68 (61–75)	4.3	0.32
Male sex	246 (44.7)	910 (75.5)	66.2	< 0.01	213 (52.3)	221 (54.3)	3.9	0.57
History of hypertension	333 (60.6)	673 (55.9)	9.5	0.07	232 (57.0)	245 (60.2)	6.5	0.35
History of diabetes mellitus	99 (18.0)	225 (18.7)	1.8	0.74	73 (17.9)	82 (20.2)	5.6	0.42
Prior ischemic stroke	130 (23.6)	207 (17.2)	16.1	< 0.01	85 (20.9)	88 (21.6)	1.8	0.80
Pre-stroke mRS score \geq 1	84 (15.3)	146 (12.1)	9.2	0.07	55 (13.5)	60 (14.7)	3.5	0.61
Cigarette smoking			56.5	< 0.01			7.3	0.27
Never Smoker	420 (76.4)	629 (52.2)			291	285		
Ex-smoker	44 (8.0)	89 (7.4)			37	28		
Current smoker	86 (15.6)	487 (40.4)			79	94		
Systolic blood pressure, median (IQR), mmHg	145 (130–160)	145 (132–162)	7.5	0.21	145 (130–160)	145 (130–160)	2.1	0.95
NIHSS score, median (IQR)	18 (14–22)	15 (11–21)	29.5	< 0.01	17 (13–21)	17 (13–22)	2.6	0.87
ASPECTS, median (IQR) ^a	10 (7–10)	9 (7–10)	13.1	< 0.01	10 (7–10)	10 (7–10)	1.5	0.91
Occlusion site			46.4	< 0.01			9.1	0.20
Internal carotid artery	166 (30.2)	279 (23.2)			111 (27.3)	116 (28.5)		
Middle cerebral artery M1 segment	266 (48.4)	493 (40.9)			197 (48.4)	187 (45.9)		
Middle cerebral artery M2 segment	59 (10.7)	91 (7.6)			47 (11.6)	39 (9.6)		
Vertebro-basilar artery	49 (8.9)	313 (26.0)			42 (10.3)	60 (14.7)		
Other intracranial arteries ^b	10 (1.8)	29 (2.4)			10 (2.5)	5 (1.2)		
Prior use of antiplatelet agents	101 (18.4)	187 (15.5)	7.8	0.14	75 (18.4)	73 (17.9)	1.3	0.86
Prior use of anticoagulants	51 (9.3)	20 (1.7)	34.0	< 0.01	19 (4.7)	15 (3.7)	4.9	0.48
Prior intravenous thrombolysis	145 (26.4)	368 (30.5)	9.3	0.07	115 (28.3)	102 (25.1)	7.2	0.30
Type of anesthesia			16.8	0.01			4.1	0.55
Local anesthesia only	265 (48.2)	500 (41.5)			190 (46.7)	184 (45.2)		
Local anesthesia plus sedation	92 (16.7)	190 (15.8)			68 (16.7)	60 (14.7)		
General anesthesia	193 (35.1)	515 (42.7)			149 (36.6)	163 (40.1)		
Stent-retriever thrombectomy	385 (70.0)	834 (69.2)	1.7	0.74	284 (69.8)	289 (71.0)	2.7	0.70
Aspiration thrombectomy	14 (2.6)	40 (3.3)	4.6	0.38	13 (3.2)	15 (3.7)	2.7	0.70
Stent-retriever plus aspiration thrombectomy	124 (22.6)	180 (14.9)	19.6	< 0.01	83 (20.4)	77 (18.9)	3.7	0.60
Pass number of thrombectomy, median (IQR)	2 (1–3)	1 (1, 2)	40.8	< 0.01	2 (1–3)	2 (1–3)	1.4	0.79
Emergency angioplasty/stenting	45 (8.2)	471 (39.1)	78.1	< 0.01	45 (11.1)	57 (14.0)	8.9	0.20
Intra-arterial thrombolysis	33 (6.0)	111 (9.2)	12.1	0.02	31 (7.6)	31 (7.6)	0.0	1.00
Intra-procedural use of tirofiban	201 (36.6)	712 (59.1)	46.3	< 0.01	167 (41.0)	186 (45.7)	9.3	0.18
Intra-procedural use of heparin	251 (45.6)	606 (50.3)	9.3	0.07	187 (46.0)	178 (43.7)	4.5	0.53
Onset-to-puncture time, median (IQR), min	260 (195–370)	325 (225–484)	30.8	< 0.01	284 (200–390)	290 (210–410)	6.0	0.22
Puncture-to-recanalization time, median (IQR), min	80 (50–120)	89 (54–135)	11.2	0.01	79 (50–120)	87 (53–128)	5.3	0.19

Abbreviations: AF atrial fibrillation, ASPECTS Alberta Stroke Program Early CT Score, IQR interquartile range, mRS modified Rankin Scale, NIHSS National Institutes of Health Stroke Scale, pc-ASPECTS posterior circulation Alberta Stroke Program Early CT Score, SD standardized difference

Values are numbers with percentages in parentheses, unless indicated otherwise

^aASPECTS for anterior circulation stroke, and pc-ASPECTS for posterior circulation stroke

^bincluding anterior cerebral artery A1/A2 segments, posterior cerebral artery P1 segment



Comparisons of outcome measures between patients with and without AF were presented in Table 2. Before matching, there was no significant difference in recanalization rates between the two groups, but patients with AF had a higher 90-day mRS score ($P < 0.01$) and higher risks of intra-procedural complications ($P = 0.02$), hemorrhagic transformations within 24 hours (all $P < 0.01$), and death within 90 days ($P = 0.01$), whereas they had lower proportions of mRS 0–1, 0–2, and 0–3 points at 90 days (all $P < 0.01$). After matching, the difference in the primary outcome - 90-day mRS score no longer existed between patients with and without AF (median: 3 vs. 3 points; $P = 0.29$). In addition, all differences in secondary and safety outcomes that differed between both groups before matching also disappeared.

Discussion

This real-world registry study in China found that patients with AF were older, had more severe symptoms on admission, a lower proportion of posterior circulation occlusions, and a shorter time from onset to puncture. After matching for baseline characteristics using propensity scores, AF was not independently associated with 90-day functional outcomes, recanalization rates, and intra-procedural complications.

A subgroup analysis of the MR CLEAN trial (Multi-center Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) showed a trend towards a decreased treatment effect of EVT in patients with AF. However, the sample size of AF patients in their study was rather small, thus no definite conclusion could be drawn [16]. A subsequent meta-analysis from the HERMES collaboration (Highly

Table 2 Outcome measures of patients with AF versus without AF

Outcome variables	Pre-matched population (n = 1755)				Post-matched population (n = 814)			
	With AF (n = 550)	Without AF (n = 1205)	Univariable analysis		With AF (n = 407)	Without AF (n = 407)	Univariable analysis	
			Effect size (95% CI)	P-value			Effect size (95% CI)	P-value
Primary outcome								
mRS at 90 d, median (IQR)	4 (1–5)	3 (0–5)	0.59 (0.47–0.74) ^a	< 0.01	3 (0–5)	3 (1–5)	1.16 (0.82–1.52) ^a	0.29
Secondary outcomes								
Successful recanalization after first attempt ^c	267/550 (48.6)	588/1205 (48.8)	0.99 (0.81–1.21) ^b	0.92	209/407 (51.4)	190/407 (46.7)	1.21 (0.92–1.59) ^b	0.18
Successful recanalization after final attempt ^c	479/550 (87.1)	1065/1205 (88.4)	0.89 (0.65–1.20) ^b	0.44	355/407 (87.2)	347/407 (85.3)	1.18 (0.79–1.76) ^b	0.42
Complete recanalization after final attempt ^d	376/550 (68.4)	789/1205 (65.5)	1.14 (0.92–1.41) ^b	0.24	279/407 (68.6)	264/407 (64.9)	1.18 (0.88–1.58) ^b	0.27
mRS 0–1 at 90 d	174/518 (33.6)	521/1162 (44.8)	0.62 (0.50–0.77) ^b	< 0.01	143/387 (37.0)	143/386 (37.1)	1.00 (0.74–1.33) ^b	0.98
mRS 0–2 at 90 d	195/518 (37.6)	565/1162 (48.6)	0.64 (0.52–0.79) ^b	< 0.01	160/387 (41.3)	155/386 (40.2)	1.05 (0.79–1.40) ^b	0.74
mRS 0–3 at 90 d	252/518 (48.7)	676/1162 (58.2)	0.68 (0.55–0.84) ^b	< 0.01	208/387 (53.8)	192/386 (49.7)	1.17 (0.89–1.56) ^b	0.27
Safety outcomes								
Intra-procedural complications ^e	63/550 (11.5)	95/1205 (7.9)	1.51 (1.08–2.12) ^b	0.02	43/407 (10.6)	36/407 (8.8)	1.22 (0.76–1.94) ^b	0.41
Any ICH within 24 h	158/516 (30.6)	222/1163 (19.1)	1.87 (1.48–2.37) ^b	< 0.01	106/384 (27.6)	95/388 (24.5)	1.18 (0.85–1.62) ^b	0.32
PH2 within 24 h ^f	35/516 (6.8)	41/1163 (3.5)	1.99 (1.25–3.17) ^b	< 0.01	25/384 (6.5)	23/388 (5.9)	1.11 (0.62–1.98) ^b	0.74
Symptomatic ICH within 24 h ^f	54/513 (10.5)	70/1156 (6.1)	1.83 (1.26–2.65) ^b	< 0.01	36/381 (9.4)	35/386 (9.1)	1.05 (0.64–1.71) ^b	0.86
Death within 90 d	100/518 (19.3)	162/1162 (13.9)	1.48 (1.12–1.94) ^b	0.01	63/387 (16.3)	71/386 (18.4)	0.86 (0.59–1.25) ^b	0.44

Abbreviations: AF atrial fibrillation, CI confidence interval, ICH intracranial hemorrhage, IQR interquartile range, mRS modified Rankin Scale, mTICI modified Thrombolysis in Cerebral Infarction, OR odds ratio, PH2 parenchymal hematoma type 2

Data are shown as the event number/total number (%), unless otherwise indicated

^aThe common OR values were calculated using an ordinal logistic regression model and indicated the odds of improvement of 1 point on the mRS at 90 days

^bThe OR values were calculated using a binary logistic regression model

^cDefined as mTICI of 2b–3

^dDefined as mTICI of 3

^eIncluding new territorial embolization, arterial perforation, arterial dissection, vasospasm requiring treatment and in-stent thrombosis

^faccording to the Heidelberg Bleeding Classification

Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) demonstrated no interaction between AF and functional outcomes after EVT, but found a trend towards a lower rate of symptomatic ICH in AIS patients with AF (3.4% in AF patients vs. 4.5% in non-AF patients), which might be related to the lower percentage of pre-treatment with IVT (76.3% in AF patients vs. 90.6% in non-AF patients). This is probably mainly due to the fact that patients with AF are more likely to taking oral anticoagulants, which is a contraindication for the administration of tPA [17]. Conversely, a post-hoc analysis of a multi-center head-to-head clinical trial revealed that AF was an independent risk factor for any ICH in AIS patients undergoing stent-retriever thrombectomy, which was partly attributable to the adjusted anticoagulation status and more retrieval attempts by mediation analyses [18]. Furthermore, a national registry

study assessing post-thrombectomy outcomes found no difference in either in-hospital or discharge outcomes between matched patients with or without AF, [19] whereas two other studies suggested faster procedural time, fewer passes, higher rates of first pass effect, successful reperfusion and good functional outcome with AF-related stroke [20, 21].

Previous observations found patients with AIS caused by AF tend to have more bleedings and worse outcomes after EVT than those without AF [16, 18]. However, special cautions should be taken when interpreting these results, such a statement could lead to misconceptions to suspecting or even denying EVT to patients with AF. We may expect that AIS caused by a sudden embolus from the cardiovascular circulation can progress faster than AIS caused by progressive carotid or intracranial artery stenosis, where there may be time for

development of collaterals [26]. In this study, patients with AF were treated about 1 hour earlier (median time from onset to puncture: 260 min vs. 325 min) compared to those without AF, suggesting a faster infarct growth rate and a stronger time dependence of reperfusion therapy in AF-related stroke.

Strengths of this study were the large sample size of enrolled patients ($n = 1755$) and the high prevalence of AF (31.3%), resulting in more reliable estimations. Also, comparison of outcomes after PSM was a strength. Finally, all radiological and clinical outcomes in this analysis were centrally adjudicated by the independent imaging core laboratory or clinical events committee, except those intra-procedural complications were locally scored by site investigators. Nevertheless, our study has some limitations. First, the collateral status has been shown to be an excellent predictor of stroke outcomes, [27] so a major limitation of this study is the lack of assessment of collateral status, which has been postulated as a possible reason for difference in functional outcomes post-EVT of LVO patients with vs. without AF [28, 29]. Second, this study was conducted in Chinese population, where the prevalence of intracranial atherosclerotic disease (ICAD) is very high [30]. In this context, an underlying ICAD stenotic lesion is often cited as a possible reason for immediate re-occlusion after thrombectomy that results in bailout intracranial angioplasty or stenting, thus potentially having an impact on the outcomes [31]. Our findings should be interpreted with caution and could not easily be extrapolated to other populations. Third, patients with AF may have more comorbidities (e.g., decreased ejection fraction, valvular heart disease, other organ failure), larger infarct core, and different texture of thrombus compared to those without AF. However, these variables were not collected in the ANGEL-ACT registry, so their confounding effects could not be ruled out. Finally, no information on antithrombotic therapy from post-procedure to discharge, treatment adherence and rehabilitation training after discharge was recorded, therefore limiting comments on the association between them and functional outcomes.

Conclusion

The present study found no difference in the radiological and clinical outcomes following EVT between Chinese AIS patients with and without AF, implying AF status should not hamper the decision making to proceed to EVT. Furthermore, our results were in contrast to the increased hemorrhage rates and worse functional outcomes observed in AF-related stroke treated with supportive care or IVT. It is known that thrombolysis is less used in patients with AF-related LVO and, if used, has

only limited effect. Thus, the fact is EVT might be the best chance for these patients.

Abbreviations

AF: Atrial fibrillation; AIS: Acute ischemic stroke; ANGEL-ACT: Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke; ASPECTS: Alberta Stroke Program Early CT Score; CI: Confidence interval; EVT: Endovascular treatment; HERMES: Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials; ICH: Intracranial hemorrhage; IQR: Interquartile range; IVT: Intravenous thrombolysis; LVO: Large vessel occlusion; MR CLEAN: Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS: Modified Rankin Scale; mTICI: Modified Thrombolysis in Cerebral Infarction; NIHSS: National Institutes of Health Stroke Scale; OR: Odds ratio; pc-ASPECTS: Posterior circulation Alberta Stroke Program Early CT Score; PH2: Parenchymal hematoma type 2; PSM: Propensity score matching; SD: Standardized difference

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Authors' contributions

XT, DM and ZM designed the study; XT, SL and WL wrote the main manuscript text and prepared figures; ZR and RL made the critical revision of manuscript; AW performed the statistical analysis; BJ, XZ, XH, GL and GM conducted the study and acquired the data; YW, YW and ZM supervised the study; DM and ZM analyzed and interpreted the data. All authors reviewed the manuscript. The author(s) read and approved the final manuscript

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author Dapeng Mo (bjttmodp@163.com) or Zhongrong Miao (zhongrongm@163.com) upon reasonable request.

Declarations

Ethics approval and consent to participate

The protocol was approved by the ethics committees of Beijing Tiantan Hospital and each participating site. Each participant or his/her representative gave written informed consent before being enrolled in the study. The study procedures were in accordance with the 1964 Helsinki declaration and its later amendments.

Consent for publication

Not applicable.

Competing interests

The authors have no financial conflicts of interest.

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