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Original Article

Influence of atrial fibrillation on prognosis of thrombolytic therapy in stroke patients: a meta-analysis

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Abstract: Objective: This is a meta-analysis to evaluate the effects of atrial fibrillation (AF) on prognosis of thrombolytic therapy in stroke patients. Methods: CochraneLibrary, PubMed, EMbase, CNKI, VIP, and CBM were searched for cohort studies concerning the outcomes of intravenous thrombolytic therapy in the stroke patients with and without AF. Literature screening, quality assessment, and data extraction were independently performed by 2 reviewers. Meta-analysis was performed with the RevMan5.2 software. Results: Totally 13 cohort studies (with 7000 patients) were included in this analysis. Our results from the meta-analysis showed that, the improvement of neurological function in both the early [OR=0.68; 95% CI, (0.44, 1.04); *P*=0.08] and late [OR=0.59; 95% CI, (0.47,0.74); *P*<0.00001] periods after thrombolysis in the acute stroke patients with AF was obviously inferior to the patients without AF. Moreover, AF could significantly elevate the incidences of intracranial hemorrhage [OR=1.42; 95% CI, (1.14, 1.77); *P*=0.001] and symptomatic hemorrhage [OR=1.64; 95% CI, (1.27, 2.11); *P*<0.00001], after thrombolysis, in the stroke patients. Furthermore, meta-analysis showed that AF was associated with increased mortality after thrombolysis in acute stroke patients [OR=1.95; 95% CI, (1.65, 2.29); *P*<0.00001]. Conclusion: AF impacts the neurological function improvement after thrombolytic therapy, and increases the incidence of hemorrhage, as well as the mortality, after thrombolytic therapy, in acute stroke patients.

Keywords: Stroke, thrombolytic therapy, atrial fibrillation (AF), meta-analysis

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and one of the main causes of cardioembolic stroke [1]. It has been shown that, the risk of stroke might be increased by 4-5 times for the patients with AF. Moreover, the risk of spontaneous hemorrhagic transformation after stroke would also be elevated in the sepatients, with poor neurological function outcomes [2, 3]. Appropriate antithrombotic therapy is of great importance in the treatment of AF, which could significantly reduce the incidences of cerebral adverse events [4, 5]. However, controversial findings have been obtained for the effectiveness of the thrombolytic agents in treating AF.

A previous study has shown that, thrombolytic therapy could significantly improve the neurological function in patients with AF [6]. On the other hand, some other studies have indicated no benefits for the thrombolytic therapy in patients with cerebral infarction and AF [7]. Moreover, a multicenter study suggests that, compared with non-thrombolytic treatments, thrombolytic therapy lead to neither beneficial nor adverse outcomes in patients with AF [8]. Furthermore, some other studies evaluate the correlation of advanced age, neurological deficits, high aortic occlusion, and other stroke risk factors prognosis of thrombolysis in patients with AF, and they find that AF does not independently affect the outcomes of thrombolysis [9-11].

Since there is no consensus on whether stroke patients with AF could benefit from thrombolysis, AF has not been included in the exclusion criteria for the thrombolytic therapy. A previous study has shown that, in severe stroke patients, AF is a predictor for favorable neurological outcomes within 3 m after thrombolysis [12]. Based on the sefindings, it is of great importance to investigate the safety and efficacy of thrombolytic therapy in acute ischemic stroke patients accompanied with AF.

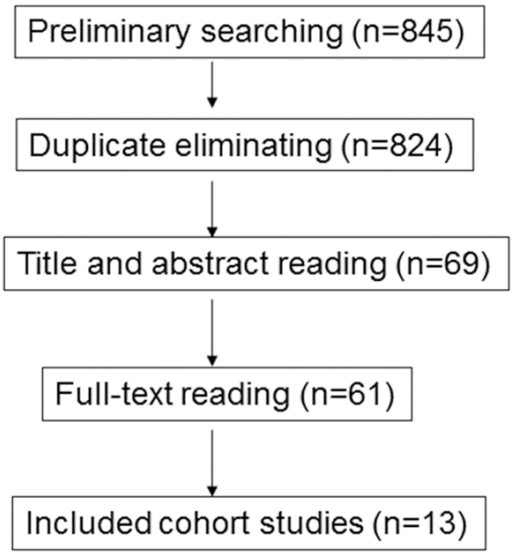

Figure 1. Literature searching flow chart.

In this study, a system atic meta-analysis was performed to evaluate the effects of AF on prognosis of thrombolytic therapy in acute stroke patients. Whether AF might be the risk factors for hemorrhage after thrombolysis and prognosis of thrombolysis was investigated.

Materials and methods

Inclusion and exclusion criteria

Only cohort studies were included in this meta-analysis. All the sestudies concerned the patients with acute ischemic stroke (onset within 14 d), who were diagnosed according to the WHO diagnostic criteria for stroke, based on the auxiliary diagnostic detection of CT or MRI. Exposure factor was AF, and the sestudies compared the outcomes of thrombolytic therapy between the acute ischemic stroke patients with and without AF. Exclusion criteria were as follows: (1) studies in which the outcome variables could not be analyzed and compared with other studies; (2) summaries and reviews from which data could not extracted; and (3) studies concerning the association between AF and multiple cerebrovascular diseases, in which the ischemic stroke can not be evaluated independently.

Outcome variables

Outcome variables included (1) symptomatic intracranial hemorrhage after thrombolysis; (2) short-term neurological function improvement after thrombolysis, which was defined as the National Institutes of Health Stroke Scale (NIHSS) score <2 or the scorere duction of more than 8 [13]; (3) long-term neurological function improvement after thrombolysis, which was defined as the mRS score ≤2 within 3 m after disease onset [14]; and (4) mortality.

Search strategy

Cochrane Library (2015 version 2), PubMed (1978-2015 September), EMbase (1974-2015 September), CNKI (1978-2015 September), VIP (1989-2015 September), and CBM (1978-2015 September) were searched for publications, with the following keywords: AF, stroke, cerebrovascular disorder, brain infarction, brain ischemic, tissue plasminogen activator, thrombolytic therapy, and fibrinolytic agent. Cohort studies were included to compare the outcomes for thrombolytic therapy between the stroke patients with and without AF. Studies in the reference list and related reviews had also been retrieved.

Literature screening, quality assessment, and data extraction

Literature screening, quality assessment, and data extraction were independently performed by 2 reviewers. Once disagreement occurred, a third reviewer would be involved, and the final decision should be made with the consensus of all reviewers. Data extraction mainly included (1) researchers, magazines, and publishing time; (2) study design; (3) basic characteristics of patients in control and experimental groups (case number, sex ratio, and age); (4) exposure factors, such as AF detection methods and time; (5) outcomes. The study subject population, intergroup comparability, and outcome measurement and evaluation were assessed, according to the Newcastle-Ottawa Scale (NOS) [15], with the highest score of 9.

Statistical analysis

Meta-analysis was performed with the RevMan5.2 software (CochraneIMS, Oxford, UK) [16]. Mean difference (MD) and odds ratio (OR) were used as the effect size measures for continuous and categorical variables, respectively. The χ^2 test was performed to examine the study heterogeneity (α=0.1). If there was no statistical heterogeneity (P>0.10, $I^2 \leq$ 50%), the fixed-effect model was used for meta-analysis; on the contrary, the random-

Table 1. Study characteristics in the meta-analysis

Studies	Study type	Patients with AF/all patients	Meanage, y (AF/non-AF)	NIHSS baseline, median (IQR) (AF/non-AF)	Time from symptom onset to treatment, min (AF/non-AF)	Study area	Study language
Kimura *et al.*, 2009 [11]	Retrospective	44/85	77.2/69.4	17.3/12.3	148.3/147.6	Japan	English
Sanak *et al.*, 2010 [10]	Retrospective	66/157	68.1/66.5	13.0/10.0	146.3/145.5	Czech	English
Awadh *et al.*, 2010 [18]	Retrospective	74/228	76/66.4	14/14	162.7/173.3	Scotland	English
Zhang *et al.*, 2010 [6]	Retrospective	22/53	68.3/60.7	12.0/9.1	203.7/196.7	China	English
Seet *et al.*, 2011 [17]	Retrospective	76/214	78.9/71.5	13/12	138.3/143.5	Singapore	English
Huang *et al.*, 2012 [19]	Retrospective	26/86	72.08/62.33	14.27/12.80	136.54/150.67	China	Chinese
Frank *et al.*, 2012 [8]	Retrospective	992/4064	73.9/67.1	14/11	NR	Multicenter	English
Sung *et al.*, 2013 [12]	Retrospective	72/143	68.3/64.6	NR	NR	China	English
Saposnik *et al.*, 2013 [7]	Retrospective	316/1689	NR	14/10	NR	Canada	English
You *et al.*, 2013 [22]	Retrospective	45/162	69.2/62.5	15.11/13.25	185.0/186/2	China	Chinese
Padjen *et al.*, 2013 [21]	Retrospective	155/734	78/64	NR	148/153	U.S.A.	English
Lou *et al.*, 2014 [20]	Retrospective	137/330	71.7/63.4	13/9	234.0/245.6	China	Chinese
Zhang *et al.*, 2015 [23]	Retrospective	47/109	64.6/63.6	8.7/7.1	<180 min	China	Chinese

Note: NR, not reported.

Table 2. Methodological quality assessment of studies in the meta-analysis

Studies	A	B	C	D	E	F	G	H	Score
Kimura *et al.*, 2009 [11]	1	1	0	1	1	1	1	1	7
Sanak *et al.*, 2010 [10]	1	1	1	1	1	1	1	1	8
Awadh *et al.*, 2010 [18]	1	1	0	1	2	1	1	1	8
Zhang *et al.*, 2010 [6]	1	1	1	1	1	0	1	1	7
Seet *et al.*, 2011 [17]	1	1	1	1	1	1	1	1	8
Huang *et al.*, 2012 [19]	1	1	1	1	1	0	1	1	7
Frank *et al.*, 2012 [8]	1	1	0	1	1	1	1	1	7
Sung *et al.*, 2013 [2]	1	1	1	1	1	1	1	1	8
Saposnik *et al.*, 2013 [7]	1	1	1	1	1	0	1	1	7
You *et al.*, 2013 [22]	1	1	0	1	1	0	1	1	6
Padjen *et al.*, 2013 [21]	1	1	0	1	1	0	1	1	7
Lou *et al.*, 2014 [20]	1	1	1	1	1	0	1	1	7
Zhang *et al.*, 2015 [23]	1	1	1	1	1	0	1	1	7

Note: A. Representativeness of exposed group (1 point); B. Representativeness of unexposed group (1 point); C. Determination of exposure factors (1 point); D. Certainty on none outcome variables at study beginning (1 point); E. Considering the comparability of exposed and unexposed groups (2 points); F. Outcome variable evaluation (1 point); G. Follow-up period long enough (1 point); and H. Follow-up data integrality (1 point).

effect model was applied. Descriptive analysis was conducted for findings with large heterogeneity or unable to find sources.

Results

Literature search results

Literature search process and results were shown in **Figure 1**. Preliminary search yielded 845 potentially eligible articles. After eliminating the duplicates, based on the inclusion an dexclusion criteria, 13 cohort studies (with 7000 patients) were included in this analysis [6-23]. Characteristics of these 13 studies were collected in **Table 1**, and the methodological quality assessment results were shown in **Table 2**.

Effect of AF on neurological function improvement after thrombolysis

In the seinvolved studies, there were 4 cohort studies concerning the association between AF and early neurological function improvement after thrombolysis, and 12 cohort studies regarding the relationship between AF and late neurological function improvement after thrombolysis. Due to the substantial heterogeneity of the sestudies, the fixed-effect model was used for analysis. Meta-analysis results showed that, the improvement of neurological function in the early period after thrombolysis in the acute stroke patients with AF was obviously inferior to the group without AF [OR=0.68; 95% CI, (0.44, 1.04); P=0.08] (**Figure 2**). Similar results were obtained for the analysis of neurological function improvement in the late period after thrombolysis, i.e., the late neurological function improvement after thrombolysis in stroke patients with AF was significantly inferior to the group without AF [OR=0.59; 95% CI, (0.47, 0.74); P<0.00001] (**Figure 2**). Taken together, these results suggest that the neurological function improvement after thrombolysis in stroke patients with AF is inferior to the patients without AF.

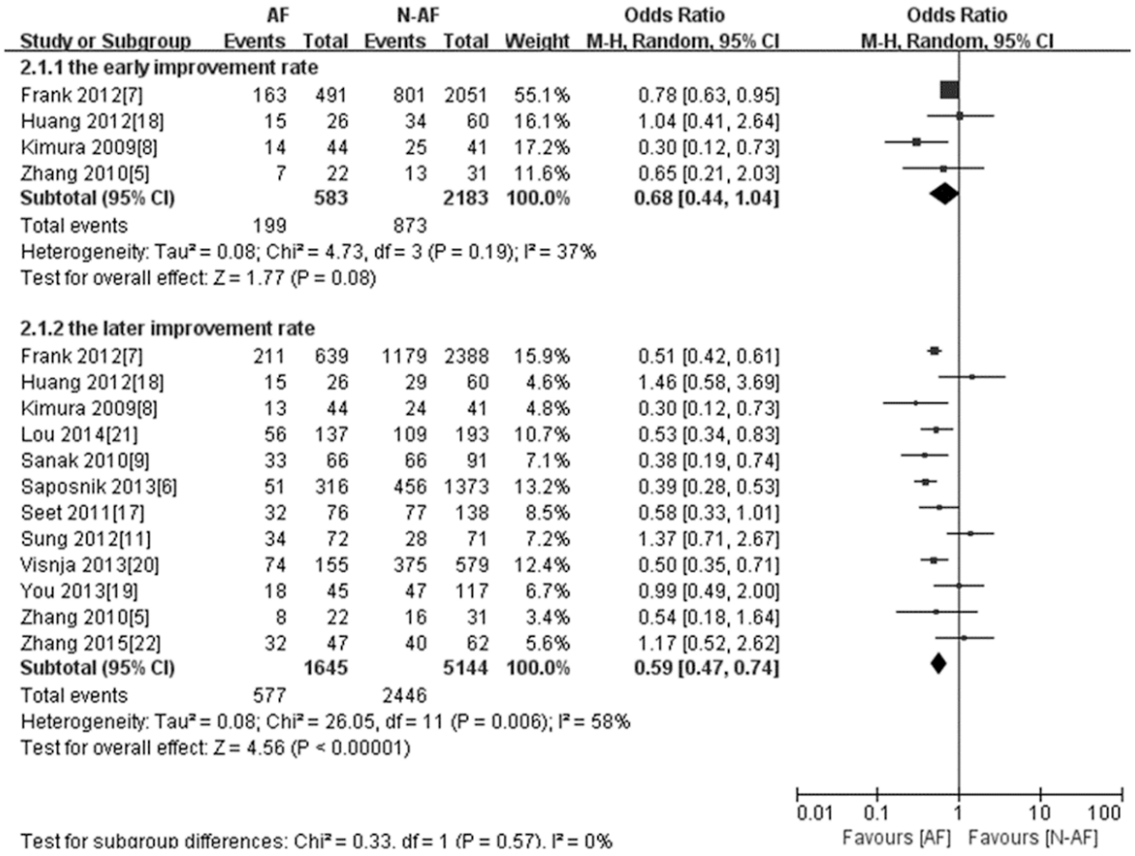

Figure 2. Effect of AF on neurological function improvement after thrombolysis.

Effect of AF on hemorrhage after thrombolysis

All these 13 cohort studies had reported about the correlation between AF and hemorrhage after thrombolysis, in which 5 were associated with the intracranial hemorrhage after thrombolysis. Due to the limited heterogeneity between these studies, the fixed-effect model was applied herein. Our results from the meta-analysis showed that, compared with the group without AF, significant elevated incidences of intracranial hemorrhage [OR=1.42; 95% CI, (1.14, 1.77); *P*=0.001] and symptomatic hemorrhage [OR=1.64; 95% CI, (1.27, 2.11); *P*< 0.00001], after thrombolysis, were observed in the acute stroke patients with AF (**Figure 3**). These results suggest that AF significantly elevate the incidence of hemorrhage after thrombolysis in stroke patients.

Effect of AF on mortality after thrombolysis

In these cohort studies, 9 analyzed the correlation between AF and mortality after thrombolysis. According to that I^2<50%, the fixed-effect model were used to obtain the effect size measures. Meta-analysis showed that, the mortality after thrombolysis in the acute stroke patients with AF was significantly higher than the patients without AF [OR=1.95; 95% CI, (1.65, 2.29); *P*<0.00001] (**Figure 4**). These results suggest that AF is significantly associated with the increased mortality after thrombolysis in stroke patients.

Discussion

Thrombus accompanied with AF may lead to cardioembolism, which usually occurs in the carotid system [24-26]. Middle cerebralartery (MCA) is an atural extension of the internal carotidartery, which provides blood supply to important brain regions, including the frontal, temporal, and parietal lobes, as well as the basal ganglia. MCA has relatively less branches, subsequently resulting in reduced branch compensation. Lacking chronic ischemic process leads to the limited adapt ability of MCA to brain ischemia. Therefore, MCA occlusion

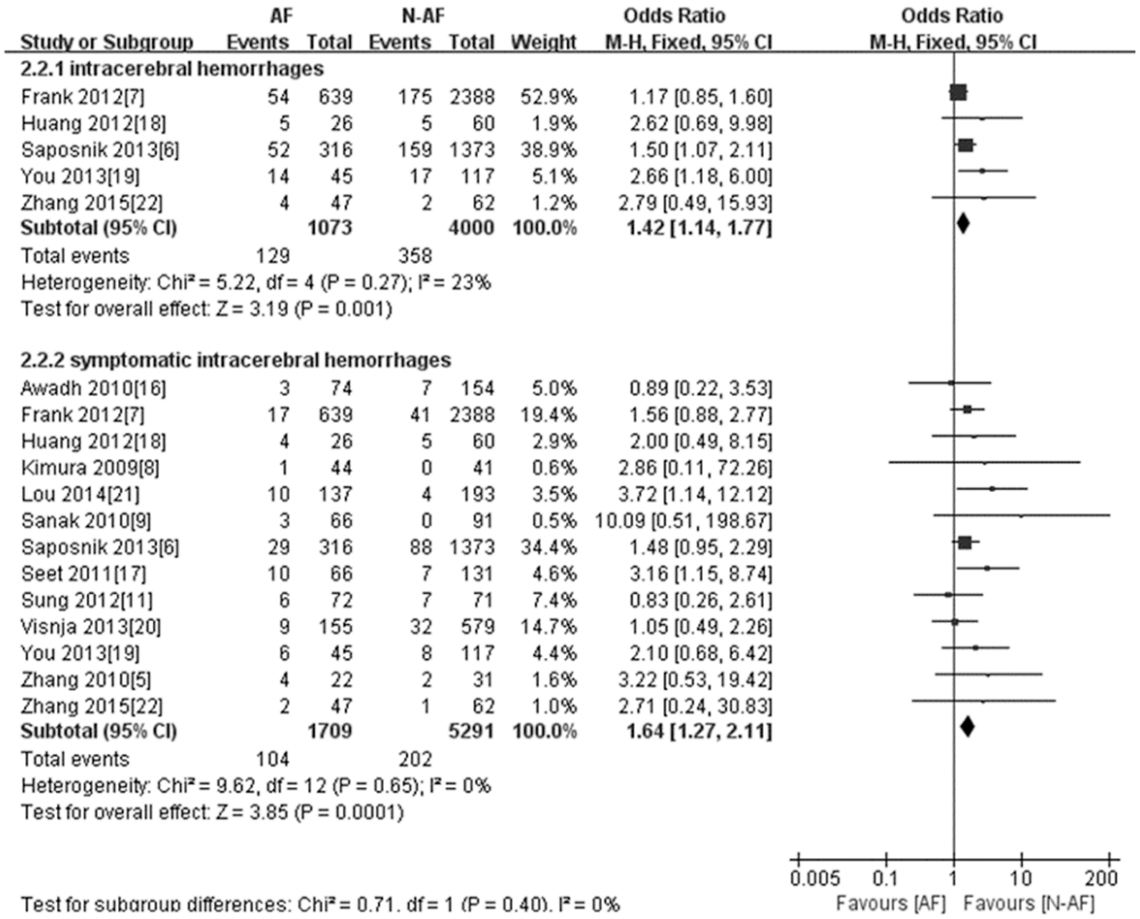

Figure 3. Effect of AF on hemorrhage after thrombolysis.

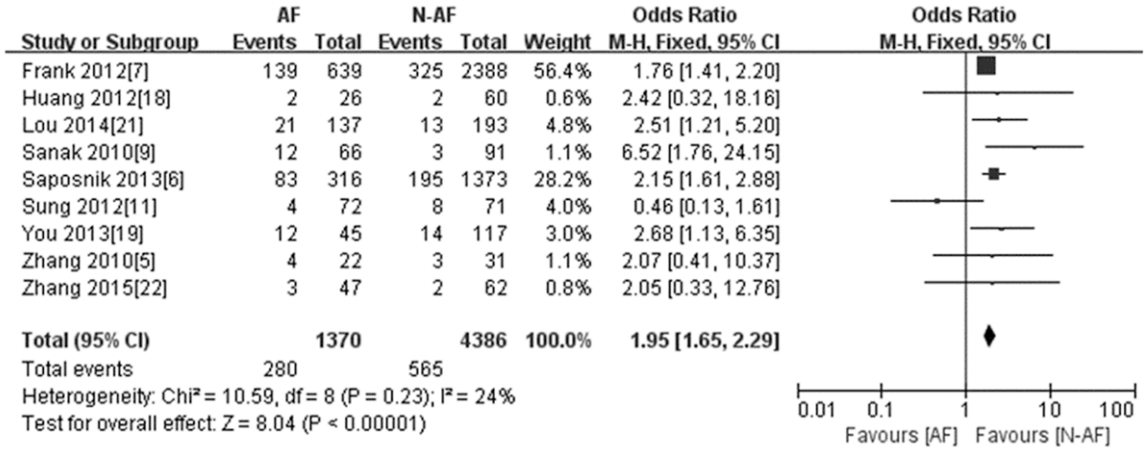

Figure 4. Effect of AF on mortality after thrombolysis.

would inevitably cause massive cerebral infarction, with high hemorrhagic infarction rate and mortality. Thrombolytic therapy has been regarded as the most effective treatment for the acute ischemic stroke within time window, which could significantly improve the short- and long-term disease prognosis [27-29].

A previous study has shown that, thrombus induced by atrial fibrillation is larger than that

caused by atherosclerosis, with higher proportion of old thrombus [8]. Moreover, the risk for hemorrhagic transformation is higher in the ischemic stroke patients with AF. Therefore, it is interesting to investigate and compare the safety and efficacy of the intravenous thrombolytic therapy for patients with and without AF. In this study, our results showed that, the neurological function improvement in both the early and late periods after thrombolysis in the acute stroke patients with AF was obviously inferior to the group without AF. Moreover, the incidences of intracranial hemorrhage and symptomat ichemorrhage, as well as mortality, after thrombolysis, were significantly increased in the patients with AF. Based on these findings, we suggest that, the hemorrhage risk should be carefully evaluated for the acute ischemic stroke patients accompanied with AF, to overcome the adverse prognosis.

Poor prognosis of thrombolysis for stroke patients with AF might be associated with various physiopathological factors. It has been shown that, the collateral circulation self-established before thrombolysis could help to reduce the infarct size [30], decrease the flow and intensity of low perfusion, and protect the brain tissues [31]. However, with the respect of collateral circulation formation at the obstruction site, stroke patients with AF or arterial embolism are inferior to those patients induced by main aortic thrombosis [32]. Tu *et al.* [33, 34] have shown that, the severe hypoperfusion area is more obvious for the patients with AF, indicating that AF might be associated with larger emboliand reduced collateral circulation. However, Lou *et al.* [20] suggest that AF could increase their perfusion rate in the severe hypoperfusion area. In the stroke patients with AF, emboli could be easily and completely dissolved after thrombolysis, so that the entire hypoperfusion area (especially severe hypoperfusion area) would probably receive reperfusion, which might improve the outcomes within 3 m after thrombolysis. However, their results have also found that, AF could increase the PH hemorrhagic transformation, leading to a poor prognosis [20]. Therefore, it is still a controversial issue that whether AF in stroke patients subjected to thrombolysis is associated with more satisfactory early outcomes.

According to the NOS scale, the researches included in this study exhibited high overall quality. However, unsatisfactory results were obtained for the group comparability analysis in some studies. Potential confounding factors between the groups with and without AF have not been balanced in the comparison. Compared with the group without AF, the ages for the acute stroke patients with AF were always greater, usually with hypertension. Moreover, some of the stroke patients with AF had medication history of warfarin, and they might be associated with higher risks for TIA and stroke. In addition, these factors might also impact the correlation between AF and hemorrhage after thrombolysis, as well as the treatment prognosis. Further studies are still needed to address these issues.

In this meta-analysis, our results showed that, the AF types and the time point of thrombolytic therapy might also lead to differential clinical outcomes. A previous study has shown that, in patients with myocardial infarction, the hospital mortality for patients with chronic AF is significantly higher than those with newly diagnosed AF [35]. Moreover, Seet *et al.* [17] suggest that the incidence for hemorrhage after thrombolysis is elevated for the stroke patients accompanied with chronic AF, and the risk for adverse outcomes is increased alongwith the elongated AF duration. Chronic AF might lead to formation of larger emboli and induce greater infarction area, with increased resistance to thrombolysis. Zhang *et al.* [23] indicate that, in the acute ischemic stroke patients with AF, the thrombolytic therapy within 3 h after disease onset would result in good prognosis. Compared with the group without AF, thrombolysis during 3-4. 5 h after disease onset leads to relatively poor outcomes and increased risk of intracranial hemorrhage.

In conclusion, our results showed that, AF could impact the neurological function improvement in the early and late periods after thrombolysis in the acute stroke patients. Moreover, AF significantly elevated the incidences of intracranial hemorrhage and symptomat ichemorrhage after thrombolysis in stroke patients. Furthermore, AF was associated with increased mortality after thrombolysis in stroke patients. These findings suggest that AF might be risk factors for hemorrhage and poor prognosis after thrombolysis in acute ischemic stroke patients.

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Disclosure of conflict of interest

None.

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