Efficacy and safety of thrombolysis for acute ischemic stroke with atrial fibrillation: a meta-analysis

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Abstract

Background
The efficacy and safety of intravenous thrombolysis (IVT) in acute ischemic stroke with atrial fibrillation (AF) were controversial.

Methods
We performed a meta-analysis of all relevant studies retrieved by systematic searches of the, Embase, and Cochrane databases up to December 31, 2019. Modified Rankin Scale (mRS) scores 0–1 at 90 days, mRS 0–2 at 90 days, overall mortality, and symptomatic intracranial hemorrhage (sICH) incidence were collected as outcome measures. Fixed effects meta-analytical models were used, and between-study heterogeneity was assessed.

Results
A total of 8,509 patients were enrolled in eighteen studies. In AF IVT versus non-AF IVT studies, AF was associated with a significant decrease in the proportion of patients with mRS of 0–1 (24.1% vs. 34.5%; OR 0.57; 95% CI 0.50–0.65; \( P = 0.000 \)), mRS of 0–2 (33.6% vs. 47.8%; OR 0.50; 95% CI 0.44–0.57; \( P = 0.000 \)) and significant higher in mortality (19.4% vs. 11.5%; OR 2.05; 95% CI 1.79–2.36; \( P = 0.000 \)) and sICH incidence (6.4% vs. 4.1%; OR 1.60; 95% CI 1.27–2.01; \( P = 0.000 \)). In AF IVT versus AF non-IVT studies, thrombolysis carried a higher risk of sICH (5.7% vs. 1.6%; OR 3.44; 95% CI 2.04–5.82; \( P = 0.000 \)) instead of a better prognosis. Subgroup analysis in prospective studies also suggested a poorer functional prognosis and higher mortality in AF patients treated IVT compared with non-IVT.

Conclusion
Patients with AF had worse outcomes than those without AF after thrombolytic therapy. Patients with AF had a higher incidence of sICH after thrombolysis than those without thrombolysis.

Background
Atrial fibrillation (AF) is a major risk factor for cardioembolic stroke, which is responsible for up to one-third of ischemic stroke (IS) [1]. AF is associated with a 4–5 fold increased risk of IS [2], and AF-related strokes are more frequently fatal or disabling compared to those without a history of AF [3]. Intravenous thrombolysis (IVT) in acute IS patients within 4.5 hours of onset, is the main pharmacological therapy which can significantly improve functional outcome and reduce the risk of death and severe disability from stroke [4].
What is the efficacy and safety of thrombolysis in acute IS with AF? There are still different opinions on this subject. Compare IS patients with and without AF, most of the studies showed that patients without AF had better 90-day functional outcomes receiving thrombolytic therapy than those with AF [5-13], a few studies hold the opposite conclusion [14-15]. Most studies showed that higher mortality [5-12, 15-19] and sICH incidence [5, 7-12, 16-17, 19] in AF patients pretreated IVT than which of non-AF. Compare AF patients with and without IVT, some studies revealed IVT had a high proportion of excellent functional outcomes than non-IVT therapy [7, 9, 15, 20-21], however several other studies have done the opposite conclusion [5, 11]. In AF patients with IVT therapy, five studies showed lower mortality [7, 9, 15, 20-21] than non-IVT therapy. On the contrary, two studies displayed higher [5, 11]. Due to the results of the current literature were controversial, we performed a meta-analysis of all relevant studies on the efficacy and safety of thrombolytic therapy for acute IS with AF.

Methods

**Data sources and search strategy**

We used Pubmed, Embase and Cochrane electronic databases to identify all published studies assessing the efficacy and safety of thrombolytic therapy for acute IS with AF up to December 31, 2019. The search terms were ((stroke) OR (cerebrovascular disorders) OR (cerebral infarction) OR (brain infarction)) AND ((tissue plasminogen activator) OR (thrombolytic therapy) OR (thrombolysis)) AND (atrial fibrillation)). The search strategy had no language restrictions.

**Study selection**

Two reviewers (YZ Hu and CM Ji) independently conducted the study selection. Studies were considered potentially to be eligible for this systematic review if they met the following criteria: (1) comparing the efficacy and safety of thrombolysis in AF and non-AF patients. (2) comparing the efficacy and safety of AF patients treated IVT or not. (3) sufficient data on modified Rankin Scale (mRS) 0-1 and mRS 0-2, mortality, symptomatic intracranial hemorrhage (sICH) incidence were provided.

**Quality Assessment**

The quality of the cohort studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.
(NOS) [22]. This scale was recommended by the Cochrane Non-Randomized Studies Methods Working Group, and consisted of eight items that assessed patient selection, study comparability and outcome. Studies with scores of 0-3 were regarded as low quality, 4-6 as moderate quality, and 7-9 as high quality.

**Data extraction and outcome measures**

Two investigators (YZ Hu and CM Ji) independently extracted data on the study (authors, year of publication, design), population characteristics (number of patients, mean age, sex ratio, presence/absence of hypertension, diabetes mellitus and dyslipidemia, median baseline NIHSS score, onset to needle, mortality, incidence of sICH).

The primary efficacy endpoint was “excellent outcome” of mRS 0-1 at 90 days after stroke, and the secondary efficacy endpoint was “good outcome” of mRS 0-2 at 90 days after stroke. The primary safety endpoint was mortality, the secondary safety endpoint was sICH incidence.

**Statistical analysis**

The proportion of patients with mRS 0-1 and 0-2, mortality and sICH incidence were compared between AF IVT and non-AF IVT groups and (or) AF IVT versus AF non-IVT therapy. The data were analyzed by referring to the meta-analysis methods published by our research group [23]. The heterogeneity of the studies in our article were assessed by the $I^2$ test. The $I^2$ ranged from 0% to 100%, $I^2 >50\%$ indicated high heterogeneity. The funnel plot and Egger's test were used to assess publication bias in the meta-analysis. $P<0.05$ was considered as statistically significant publication bias. All statistical tests were performed using STATA 11.0.

**Results**

**Study characteristics**

We identified 1019 potentially relevant studies, with 994 excluded after screening for title and abstract. The remaining 25 studies were full-text retrieved for detailed evaluation. Based on the search criteria, a total of 18 studies reporting the efficacy and safety of thrombolysis for acute IS with AF were included in this study (Figure 1). Baseline characteristics of patients included in these studies were shown in Table 1 and Table 2. Eleven studies [6,8,10,12-14,16-19,24] compared IVT-treated AF to non-AF patients, two studies [20-21] compared IVT-treated to non-IVT in AF patients, and five studies [5,7,9,11,15] included two kinds of comparative data mentioned above.

**Table 1  Characteristics of studies comparing AF IVT with non-AF IVT**
| Study          | Study design | Comparison     | No. of patients | Mean age, y | Men (%) | Treatment | Hypertension (%) | Diabetes (%) |
|---------------|--------------|----------------|----------------|-------------|---------|-----------|----------------|--------------|
| Bluhmki 2009⁵  | RCT          | AF/non-AF      | 53/365         | NR          | NR      | rtPA 3-4.5h | 63.6/51.2       | 18.2         |
| Kimura 2009⁶  | prospective  | AF/non-AF      | 44/41          | 77.2/69.4   | 61.4/70.7 | rtPA <3h      | 70/64         | 16.2         |
| Awadh 2010⁷   | retrospective| AF/non-AF      | 74/154         | 76/66.4     | 40/59   | rtPA <4.5h   | NR            | NR           |
| Sanak 2010¹⁶  | retrospective| AF/non-AF      | 66/91          | 68.1/66.5   | 57.6/65.9 | rtPA <3h      | 72.7/38.5      | 13.6         |
| Zhang 2010⁷   | prospective  | AF/non-AF      | 22/31          | 68.3/60.7   | 40.9/74.2 | rtPA <4.5h   | NR            | NR           |
| Seet 2011⁸    | retrospective| AF/non-AF      | 76/138         | 78.9/71.5   | 42.1/53.6 | rtPA <3h      | 78.9/75.4      | 10.5         |
| Frank 2012⁹   | retrospective| AF/non-AF      | 639/2388       | 74.2/65.7   | 47.3/58.2 | rtPA <3h      | 71.1/61.6      | NR           |
| Padjen 2013¹⁰ | prospective  | AF/non-AF      | 155/579        | 76 /64      | 41.9 /55.6 | rtPA         | 80.0/62.3      | 20.0         |
| Saposnik 2013¹¹| prospective  | AF/non-AF      | 316/1373       | NR          | NR      | rtPA        | NR            | NR           |
| Sung 2013¹⁴   | retrospective| AF/non-AF      | 72/71          | 68.3/64.6   | 58.3/64.8 | rtPA <3h      | 79.2/77.5      | 27.8         |
| Al-Khaled 2014¹⁷| prospective  | AF/non-AF      | 387/620        | NR          | NR      | rtPA <4.5h   | NR            | NR           |
| Saarinen 2014¹⁸| retrospective| AF/non-AF      | 92/179         | 77 /69      | 46/55   | NR          | 74/63         | 32/1         |
| Tu 2015¹⁹     | prospective  | AF/non-AF      | 28/111         | 76.5/73     | 61/52   | rtPA <3h     | 64/64         | 21/2         |
| Zhao 2017¹²   | retrospective| AF/non-AF      | 30/93          | 69.8/63.5   | 46.7/67.7 | rtPA <4.5h   | 73.3/65.6      | 30.0         |
| Mehrpour 2019¹³| prospective  | AF/non-AF      | 24/94          | NR          | NR      | rtPA <4.5h   | NR            | NR           |
| Yang 2019¹⁵   | retrospective| AF/non-AF      | 47/56          | 71.2/60.4   | 34.0/80.4 | rtPA 3-9h    | 74.5/64.3      | 19.1         |

**Table 2** Characteristics of studies comparing IVT with non-IVT in AF patients
| Study          | Study design | Comparison        | No. of patients | age, y | Men (%) | Treatment | Hypertension (%) | Diabetes mellitus |
|---------------|--------------|-------------------|----------------|--------|---------|-----------|------------------|------------------|
| Bluhmki 2009  | RCT          | IVT/Non-IVT       | 53/55          | NR     | NR      | rtPA      | 3-4.5h           | NR               |
| Zhang 2010    | prospective  | IVT/Non-IVT       | 22/44          | 68.3/70.4 | 40.9/43.2 | rtPA <4.5h | NR               | NR               |
| Frank 2012    | retrospective| IVT/Non-IVT       | 639/992        | 74.2/73.9 | 47.3/47.6 | rtPA <3h  | NR               | NR               |
| Saposnik 2013 | prospective  | IVT/Non-IVT       | 316/1373       | NR     | NR      | rtPA      | NR               | NR               |
| Padjen 2014   | prospective  | IVT/Non-IVT       | 34/97          | 68/72  | 58.8/51.5 | rtPA <4.5h | 94.1/87.6        | 20.6/2.4         |
| Zhao 2016     | retrospective| IVT/Non-IVT       | 151/116        | 71.3/73.5 | 43.7/43.1 | rtPA <4.5h | 73.5/67.2        | 15.9/1.7         |
| Yang 2019     | retrospective| IVT/Non-IVT       | 47/31          | 71.2/74.7 | 34.0/58.1 | rtPA <3-9h | 74.5/93.4        | 19.1/3           |

mRS 0-1 at 90 days after stroke
Compared with non-AF patients, the proportion of patients with mRS 0-1 was significantly lower in IVT-treated AF patients (24.1% vs. 34.5%; OR 0.57; 95% CI 0.50-0.65; $I^2=71.0\%$; $P=0.000$) (Figure 2A). In contrast, there was no significant difference in the proportion of AF patients with a mRS of 0-1 between IVT and non-IVT therapy (24.0% vs. 21.4%; OR 1.0; 95% CI 0.84-1.18; $I^2=87.1\%$; $P=0.955$) (Figure 2B).

mRS 0-2 at 90 days after stroke
Compared with non-AF patients, a significantly lower proportion of IVT treated AF patients with mRS 0-2 (33.6% vs. 47.8%; OR 0.50; 95 % CI 0.44-0.57; $I^2=55.2\%$; $P=0.000$) (Figure 3A). The proportion of IVT treated AF patients with mRS 0-2 was lower than which of without thrombolytic therapy, but the difference did not reach statistical significance (31.0% vs. 32.5%; OR 0.86; 95% CI 0.74-1.00; $I^2=90.5\%$; $P=0.05$) (Figure 3B).

Mortality
A significantly higher proportion of IVT treated AF patients with mortality compared to non-AF patients (19.4% vs. 11.5%; OR 2.05; 95% CI 1.79-2.36; $I^2 = 44.1\%$; $P=0.000$) (Figure 4A). Mortality was no difference in AF patients between IVT and non-IVT (22.4% vs. 20.7%; OR 1.07; 95% CI 0.90-1.26; $I^2=71.7\%$; $P=0.446$) (Figure 4B).

sICH
The proportion of patients with sICH was significantly higher in IVT treated AF patients than non-AF patients (6.4% vs. 4.1%; OR 1.60; 95 % CI 1.27-2.01; $I^2= 0.0\%$; $P=0.000$) (Figure 5A). A significantly higher of sICH proportion in IVT treated AF patients compared to non-IVT therapy (5.7% vs. 1.6%; OR 3.44; 95% CI 2.04-5.82; $I^2=0.0\%$; $P=0.000$) (Figure 5B).

Subgroup analysis
Subgroup analysis was performed according to study design (Table 3). In both prospective and
retrospective AF IVT versus non-AF IVT studies, the functional outcomes of IVT patients with AF was worse than that of patients without AF ($P<0.001$), mortality ($P<0.001$) and sICH incidence ($P<0.05$) were also higher. On the other hand, in AF IVT and AF non-IVT prospective studies, the results suggested a poorer functional prognosis and higher mortality in AF patients treated thrombolytic therapy compared with non-thrombolysis ($P<0.05$), while in the retrospective studies, there were no statistically significant differences in these clinical outcomes. Both prospective and retrospective studies showed that risk of sICH was higher in AF IVT patients than AF non-IVT patients ($P<0.05$).

Table 3 Subgroup analyses of efficacy and safety of thrombolysis for acute IS with AF based on study design

| Study design | mRS 0-1 | Test of association | Heterogeneity |
|--------------|---------|---------------------|---------------|
|              | AF      | Non-AF              | OR (95 % CI)  | $p$ | $I^2$ (%) | $p$ |
| Retrospective(n=5) | 242/864 | 974/2746 | 0.68 (0.58-0.81) | <0.001 | 75.0 | 0.003 |
| Prospective(n=5) | 109/590 | 798/2389 | 0.41 (0.32-0.52) | <0.001 | 0.0 | 0.47 |
| IVT | Non-IVT | OR (95 % CI) | $p$ | $I^2$ (%) | $p$ |
| Retrospective(n=3) | 230/837 | 266/1139 | 1.20 (0.98-1.48) | 0.082 | 76.9 | 0.013 |
| Prospective(n=4) | 73/425 | 415/2048 | 0.71 (0.53-0.95) | 0.02 | 90.7 | <0.001 |

| Study design | mRS 0-2 | Test of association | Heterogeneity |
|--------------|---------|---------------------|---------------|
|              | AF      | Non-AF              | OR (95 % CI)  | $p$ | $I^2$ (%) | $p$ |
| Retrospective(n=6) | 349/930 | 1451/2837 | 0.55 (0.47-0.64) | <0.001 | 67.0 | 0.01 |
| Prospective(n=5) | 152/561 | 920/2118 | 0.42 (0.34-0.53) | <0.001 | 3.6 | 0.386 |
| IVT | Non-IVT | OR (95 % CI) | $p$ | $I^2$ (%) | $p$ |
| Retrospective(n=3) | 293/837 | 372/1139 | 1.08 (0.89-1.30) | 0.45 | 52.2 | 0.123 |
| Prospective(n=3) | 82/372 | 646/1993 | 0.58 (0.44-0.75) | <0.001 | 94.5 | <0.001 |

| Study design | Mortality | Test of association | Heterogeneity |
|--------------|-----------|---------------------|---------------|
|              | AF      | Non-AF              | OR (95 % CI)  | $p$ | $I^2$ (%) | $p$ |
| Retrospective(n=7) | 200/1022 | 375/3016 | 1.86 (1.53-2.25) | <0.001 | 56.8 | 0.031 |
| Prospective(n=7) | 393/2027 | 707/6136 | 2.29 (1.88-2.81) | <0.001 | 11.1 | 0.345 |
| IVT | Non-IVT | OR (95 % CI) | $p$ | $I^2$ (%) | $p$ |
| Retrospective(n=3) | 179/837 | 263/1139 | 0.92 (0.74-1.14) | 0.427 | 0.0 | 0.982 |
| Prospective(n=4) | 104/425 | 396/2048 | 1.32 (1.02-1.69) | 0.031 | 80.1 | 0.002 |

| Study design | sICH | Test of association | Heterogeneity |
|--------------|------|---------------------|---------------|
|              | AF      | Non-AF              | OR (95 % CI)  | $p$ | $I^2$ (%) | $p$ |
| Retrospective(n=7) | 44/1004 | 69/2991 | 1.62 (1.09-2.40) | 0.017 | 0 | 0.437 |
| Prospective(n=6) | 82/961 | 249/6070 | 1.59 (1.20-2.10) | 0.001 | 0 | 0.566 |
| IVT | Non-IVT | OR (95 % CI) | $p$ | $I^2$ (%) | $p$ |
| Retrospective(n=3) | 39/837 | 11/1139 | 4.22 (2.13-8.33) | <0.001 | 0.0 | 0.374 |
| Prospective(n=3) | 15/109 | 11/196 | 2.38 (1.02-5.54) | 0.044 | 0.0 | 0.812 |
Assessment of quality and publication bias

Most studies were of high quality, ranging from NOS 6 to 9 (Table 4). The mean NOS of all the included studies were 7. The funnel plot and Egger's test were performed to evaluate the publication bias of this meta-analysis. The Egger's test with the $P=0.783$, provided statistical evidence that there was no publication bias. Meanwhile, no significant publication bias was detected by Begg's funnel plot (Figure 6).

Table 4 Quality assessments of the included studies with the NOS

| Study               | Selection | Comparability | Outcome | Total score |
|---------------------|-----------|---------------|---------|-------------|
| Mehrpour et al 2019 | ****      | *             | **      | 7           |
| Yang et al 2019     | ****      | *             | ***     | 8           |
| Zhao et al 2017     | ***       | **            | **      | 7           |
| Zhao et al 2016     | ****      | **            | **      | 8           |
| Tu et al 2015       | ***       | **            | **      | 7           |
| Al-khaled et al 2014| ***       | *             | *       | 5           |
| Saarinen et al 2014 | ***       | **            | ***     | 8           |
| Padjen et al 2014   | ***       | **            | **      | 7           |
| Padjen et al 2013   | ****      | *             | ***     | 8           |
| Saposnik et al 2013 | ****      | *             | *       | 6           |
| Sung et al 2013     | ***       | **            | **      | 7           |
| Frank et al 2012    | ***       | *             | **      | 6           |
| Seet et al 2011     | ***       | **            | **      | 7           |
| Awadh et al 2010    | ****      | *             | **      | 7           |
| Sanak et al 2010    | ****      | **            | *       | 7           |
| Zhang et al 2010    | ***       | **            | **      | 7           |
| Bluhmki et al 2009  | ****      | **            | ***     | 9           |
| Kimura et al 2009   | ***       | *             | **      | 6           |

Discussion

Stroke patients with AF have been shown to have a poorer neurological outcome than stroke patients without AF [25]. AF appears to be an independent risk factor of in-hospital mortality, length of hospital stay, and increased treatment costs in stroke patients [26]. Kimura et al reported AF was independently associated with no early recanalization after IVT in acute IS [27]. A meta-analysis in 2016 done by Yue et al showed that AF was associated with poor outcomes in thrombolysed patients with acute IS [28]. With the increase of studies of thrombolysis in AF, we collected more evidence to compare the outcomes of thrombolysis in patients with AF and non-AF, and to compare the outcomes of thrombolytic and nonthrombolytic therapy in patients with AF. Thus we could obtain more comprehensive conclusions on the safety and efficacy of thrombolysis in patients with AF.

The final meta-analysis included eighteen studies. Sixteen studies compared thrombolytic outcomes in patients with and without AF. These studies encompassed 8509 patients and AF was 24.97%. Seven
studies compared the outcomes of IVT to non-IVT in AF patients. These studies consisted of 4449 patients, of which 28.36% receiving thrombolytic therapy. Among them, five studies included both comparisons. In AF IVT versus non-AF IVT studies, AF was associated with a significant decrease in the proportion of patients with mRS of 0–1, mRS of 0–2 at 90 days after stroke and significant higher in mortality and sICH incidence. In AF IVT versus AF non-IVT studies, thrombolysis carried a higher risk of sICH instead of a better prognosis. Subgroup analysis in prospective studies also suggested a poorer functional prognosis and higher mortality in AF patients treated IVT compared with non-IVT.

Heterogeneity existed in several statistical results in our study, for example, in mRS 0–1 at 90 days after stroke analysis, $I^2$ was 71.0%. By sensitivity analysis, heterogeneity was derived from two studies [14, 15]. The causes of heterogeneity in these two studies were analyzed, one study [14] included more severe stroke (NIHSS > 10) patients, one study [14] included patients with a longer thrombolysis time window (3–9 h) than the others. Excluding these two studies did not change the statistical results, but the heterogeneity had been greatly improved (OR 0.52; 95% CI 0.45–0.60; $I^2 = 30.6%; P = 0.000$).

There are several limitations in our research. First, there was only one RCT study in eighteen studies. Second, sample sizes of most studies were relatively small and varied between groups, which may limit analytical ability. Third, in the included studies, the time window of IVT was not uniform, some was less than 3 h, some was less than 4.5 h, and one was 3–9 h. Finally, detailed individual data were insufficient to identify subgroups according to age range, baseline NIHSS score, onset to needle and other clinical factors that may influence the efficacy and safety of thrombolysis in AF patients.

In conclusion, patients with AF had worse outcomes than those without AF after thrombolytic therapy. Patients with AF had a higher incidence of sICH after thrombolysis than those without thrombolysis. These conclusions required to be validated in randomized controlled trials.

Declarations

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Conflict of interest
There are no conflicts of interest for all the authors involved.

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Figures
Forrest plot of random-effects meta-analysis of IVT and mRS 0-1. Each study is represented by a point estimate of the OR and the accompanying 95% CIs. A: AF IVT versus non-AF IVT, $P=0.000$; B: AF IVT versus AF non-IVT, $P=0.955$. 

Figure 2
Forrest plot of random-effects meta-analysis of IVT and mRS 0-2. Each study is represented by a point estimate of the OR and the accompanying 95% CIs. A: AF IVT versus non-AF IVT, $P=0.000$; B: AF IVT versus AF non-IVT, $P=0.05$
Figure 4
Forrest plot of random-effects meta-analysis of IVT and mortality. Each study is represented by a point estimate of the OR and the accompanying 95% CIs. A: AF IVT versus non-AF IVT, \( P=0.000 \); B: AF IVT versus AF non-IVT, \( P=0.446 \)
Figure 5

Forrest plot of random-effects meta-analysis of IVT and sICH. Each study is represented by a point estimate of the OR and the accompanying 95% CIs. A: AF IVT versus non-AF IVT, P=0.000; B: AF IVT versus AF non-IVT, P=0.000
Figure 6

Funnel plot of publication bias in the meta-analysis. The largest studies are plotted near the average, and smaller studies are spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Deviation from this shape can indicate publication bias.